

Intensive goal-directed nutritional management improves outcomes in HBV related ACLF patients: a randomized controlled trial

Zhipeng Li

Third Affiliated Hospital of Sun Yat-sen University

Yeqiong Zhang

Third Affiliated Hospital of Sun Yat-sen University

Qiumin Luo

Third Affiliated Hospital of Sun Yat-sen University

Shengjiang Deng

Third Affiliated Hospital of Sun Yat-sen University

Wenxiong Xu

Third Affiliated Hospital of Sun Yat-sen University

Jia Chen

Third Affiliated Hospital of Sun Yat-sen University

Xin Song

Third Affiliated Hospital of Sun Yat-sen University

Xiyao Chen

Third Affiliated Hospital of Sun Yat-sen University

Chan Xie

Third Affiliated Hospital of Sun Yat-sen University

Liang Peng

`pliang@mail.sysu.edu.cn`

Third Affiliated Hospital of Sun Yat-sen University

Research Article

Keywords: hepatitis B virus, acute-on-chronic liver failure, intensive goal-directed nutritional management, quality of life, transplant-free mortality

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11131942/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background & Aims

Patients with acute-on-chronic liver failure (ACLF) are at high nutritional risk, which adversely influences prognosis. However, evidence supporting nutritional therapies in this population remains limited. We aimed to assess the safety and efficacy of intensive, goal-directed nutritional management in HBV-related ACLF (HBV-ACLF).

Methods

In this open-label, randomized controlled trial, 80 HBV-ACLF patients with Nutritional Risk Screening 2002 score ≥ 3 were randomized to receive either intensive goal-directed nutritional management (energy: $1.2 \times$ resting energy expenditure; protein: 1.2 g/kg/day, delivered through a stepwise protocol) or standard dietary advice. Primary endpoints were 30- and 90-day transplant-free mortality; secondary endpoints included safety, adverse clinical outcomes, liver severity scores, anthropometry, muscle function and quality of life.

Results

The modified intention-to-treat analysis included 78 patients (39 in each group). Compared with controls, intervention group reduced transplant-free mortality at day 30 (2.6% vs 20.5%) and day 90 (18.0% vs 38.5%), $p = 0.030$. In adjusted analyses, the survival benefit showed a consistent direction (adjusted HR 0.412, 95% CI 0.161–1.051, $p = 0.063$). The incidence of adverse clinical outcomes was lower in the intervention group at day 30 (23.7% vs 45.2%, $p = 0.060$) and day 90 (21.9% vs 70.8%, $p < 0.001$). The intervention group exhibited a more pronounced improvement in MELD score, COSSH-ACLF II score, anthropometric parameters, muscle function, and EQ-5D scores compared with controls ($p < 0.05$ for most comparisons).

Conclusions

Intensive goal-directed nutritional management improved short-term transplant-free mortality, hepatic function, muscle performance and quality of life in nutritionally at-risk HBV-ACLF patients. ACLF care may benefit from early, goal-directed nutritional intervention.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a severe clinical syndrome characterized by acute decompensation in patients with chronic liver disease, leading to high short-term mortality.^{1–3} Patients with ACLF are at exceptionally high nutritional risk, frequently presenting with malnutrition, frailty, and sarcopenia.^{1–3} Nutritional risk refers to the potential adverse impact of nutrition-related factors on clinical outcomes.^{4–5} These conditions not only impair quality of life but are also closely associated with increased rates of decompensation events and mortality in liver disease.^{6–8} Consequently, nutritional

therapy has received growing attention as a modifiable prognostic factor. Standardized management should include risk screening, assessment of malnutrition, and formulation of tailored intervention strategies.⁹

Despite guideline recommendations, nutritional management in ACLF remains challenging. Severe hepatic impairment often leads to sodium and water retention, resulting in weight gain that compromises the accuracy of weight-based nutritional assessment. Furthermore, rapid pathophysiological alterations during acute decompensation elevate the complexity and risks associated with nutritional intervention. Clinicians are often cautious about nutritional support, concerned that excessive intake may increase metabolic burden, precipitate or exacerbate hepatic encephalopathy, and worsen gastrointestinal symptoms, such as bloating or diarrhea. Therefore, achieving safe and effective nutritional support remains a key issue in ACLF care.

The Nutritional Risk Screening 2002 (NRS 2002) tool is the most widely used for risk identification, incorporating disease severity, nutritional impairment, and age.¹⁰ Because weight-based formulas often underestimate actual requirements in liver disease, indirect calorimetry (the gold standard) is recommended for measuring resting energy expenditure (REE) and setting precise energy targets.¹¹ Multiple guidelines recommend target-oriented nutritional strategies for ACLF, with daily energy intake of $1.0\text{--}1.4 \times \text{REE}$ and protein intake of $0.5\text{--}2.0 \text{ g/kg/day}$ to meet metabolic demands and improve outcomes^{1–3}. However, end-stage liver disease patients frequently fail to achieve these goals due to anorexia and impaired absorption,¹² making the choice of support route and optimization of strategies particularly important.

Conventional support follows a stepwise approach: oral feeding first, followed by enteral nutrition, and parenteral nutrition when necessary.¹³ Yet in ACLF, high risks of gastrointestinal bleeding and poor tolerance often limit enteral nutrition.¹⁴ Parenteral nutrition, in contrast, can more reliably meet nutritional targets, and current evidence suggests it does not increase mortality in critically ill patients.¹⁵ Thus, early supplemental parenteral nutrition may be considered when oral or enteral intake is insufficient.¹⁶

In China, hepatitis B virus (HBV) infection is the predominant cause of ACLF, but nutritional issues in this population remain underrecognized, and evidence for nutritional interventions in HBV-ACLF remains scarce. Previous studies on nutritional intervention for patients with liver failure have shown inconsistent results. Previous randomized controlled trials in alcohol-related liver disease failed to show survival benefit from nutritional interventions, largely due to poor tolerance of enteral feeding or inclusion of patients with end-stage cirrhosis^{14, 17}. However, some available studies suggest potential benefits^{18–20}. A randomized controlled trial demonstrated that late-evening snacks significantly improved energy metabolism;¹⁹ a cohort study showed that maintaining daily energy intake at $1.2 \times \text{REE}$ may enhance prognosis.²⁰ Regarding protein intake, higher doses ($\geq 2.2 \text{ g/kg/day}$) did not provide additional benefit compared with conventional levels ($\leq 1.2 \text{ g/kg/day}$).²¹

Based on these findings, we conducted a prospective randomized controlled trial in HBV-ACLF patients at nutritional risk (NRS-2002 ≥ 3). We hypothesized that an intensive, goal-directed nutritional management strategy targeting a daily intake of $1.2 \times \text{REE}$ and 1.2 g/kg protein, primarily using oral feeding with supplemental parenteral nutrition, would be safe and improve clinical outcomes compared to standard dietary advice.

MATERIAL AND METHODS

Study design and participants

This was an open-label, prospective, randomized, controlled trial conducted at Third Affiliated Hospital of Sun Yat-sen University. The study was approved by the Ethics Committee of Third Affiliated Hospital of Sun Yat-sen University (Approval No. II2023-242-03), registered at ClinicalTrials.gov (NCT06128421), and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal representatives. The full study protocol is available in Supplementary Appendix 1.

From December 2023 to March 2025, consecutive hospitalized patients with a clinical diagnosis of HBV-ACLF were screened for eligibility. The diagnosis of ACLF was strictly defined according to the Chinese Group on the Study of Severe Hepatitis B (COSSH) ACLF criteria,²² which apply to patients with chronic HBV infection (with or without established cirrhosis) presenting with acute hepatic deterioration accompanied by single or multiple organ failures.

The inclusion and exclusion criteria were the same as those in our previously published article.²³ In detail, the inclusion criteria were as follows: (1) Age from 20 to 60 years; (2) Positive hepatitis B surface antigen or HBV DNA for more than 6 months; (3) Serum total bilirubin level $\geq 12 \text{ mg/dL}$; (4) International normalized ratio (INR) ≥ 1.5 ; (5) Nutritional risk (NRS-2002 score ≥ 3); (6) Low-to-intermediate disease severity (COSSH-ACLF II score²⁴ < 8.4).

The exclusion criteria were as follows: (1) Co-existing liver disease (other viral hepatitis, autoimmune liver disease, Wilson's disease, alcoholic liver disease.); (2) Hepatocellular carcinoma or other malignancy; (3) HIV infection; (4) Chronic kidney disease ($\text{eGFR} < 60 \text{ mL/min/1.73m}^2$); (5) Diabetes mellitus requiring pharmacological treatment; (6) Thyroid disease, (7) Unstable cardiopulmonary disease (NYHA class III-IV heart failure, severe COPD with home oxygen therapy, unstable coronary artery disease; well-controlled hypertension or atrial fibrillation without functional limitation were not excluded); (8) Neuromuscular diseases and serious psychiatric disease; (9) Acute cholecystitis, acute pancreatitis, biliary obstruction, short bowel syndrome, intestinal obstruction, inflammatory bowel disease; (10) Severe complications at enrollment: uncontrolled infection (septic shock), active gastrointestinal bleeding, overt hepatic encephalopathy grade III-IV, hepatorenal syndrome, (11) Gastrointestinal failure (defined as acute gastrointestinal injury grade III-IV per ESICM guidelines,²⁵ including intra-abdominal hypertension, abdominal compartment syndrome, or severe ileus/feeding intolerance (these conditions

are contraindications to enteral nutrition) ; (12) Pregnancy; (13) Body mass index (BMI) $\leq 18.5 \text{ kg/m}^2$ or $\geq 28 \text{ kg/m}^2$ (dry weight was estimated at baseline as the post-paracentesis weight for patients with tense ascites requiring large-volume paracentesis or as the stable, edema-free weight reported by the patient from the 2 weeks prior to admission.¹³); (14) Organ transplantation history, bed-ridden status; (15) Inability to tolerate oral nutrition and contraindications to parenteral nutrition; (16) Admission within the past week while already receiving enteral or parenteral nutrition; (17) Expected hospital length of stay < 3 days and expected residency in Guangdong Province < 90 days.

Patients were withdrawn if: (1) they voluntarily requested withdrawal; (2) clinical circumstances precluded continuation, such as lack of benefit from nutritional support in the intervention group;(3) in the control group, sustained inadequate oral intake of < 800 kcal/day for 5 consecutive days (as assessed by daily food intake records) required withdrawal and initiation of appropriate nutritional support per standard of care; (4) investigator judgement that withdrawal was appropriate.

Randomization and masking

Eligible patients were randomized 1:1 to the intervention or control group using a computer-generated randomization sequence. Following screening for eligibility and provision of informed consent, envelopes were opened in sequence by study staff to reveal the pre-generated allocation plan and assign each participant to their respective group. Due to the nature of the nutritional intervention, blinding of participants and care providers was not feasible. However, outcome assessors and data analysts were blinded to group allocation.

Intervention

Intensive goal-directed nutritional management

Baseline nutritional assessment: At baseline, comprehensive nutritional assessment included: NRS-2002 score; Anthropometry: mid-arm circumference (MAC), triceps skinfold thickness (TSF), mid-arm muscle circumference (MAMC); Handgrip strength (dominant hand, Jamar dynamometer, average of three trials); CT-derived skeletal muscle index at the third lumbar vertebra (L3-SMI); Dietary intake assessment via 24-hour recall; Serum albumin and prealbumin.

Intervention Group:

Energy target determination: REE was measured using the Express CCM metabolic cart (McCaffee, USA) under standardized conditions (morning, after an overnight fast, in a supine position, in a quiet environment). Nutrition targets were set at $1.2 \times \text{REE/day}$ for energy and 1.2 g/kg ideal body weight/day for protein (ideal body weight calculated as $\text{height in meters}^2 \times 22 \text{ kg/m}^2$).

Stepwise intensification protocol (10-day intervention) (Supplementary Fig. 1): The intervention followed a structured, three-step escalation protocol based on achievement of nutritional targets ($\geq 75\%$ of target was considered adequate, $< 75\%$ triggered escalation): Step 1 (Days 1–3): Intensive nutritional counseling. A dedicated dietitian provided daily counseling sessions, including individualized meal planning, education on high-energy foods, and strategies to overcome anorexia (small frequent meals, nutrient-dense snacks, late-evening carbohydrate-rich snack as recommended by ESPEN guidelines).¹³ Actual intake was reassessed every 24–48 hours via dietary recall and food diaries. Physical activity was encouraged as tolerated (bedside sitting, standing, and ambulation in the ward), but no structured exercise program was implemented.

Step 2 (Days 4–6): Initiation of oral nutritional supplements (ONS). If oral intake remained below 75% of the energy or protein target after 3 days of counselling, ONS were initiated. ONS used were standard, commercially available, high-protein formulas (Nutrison, manufactured by Nutricia; providing approximately 430 kcal and 15.9 g protein per 100g), administered as 2–3 divided doses between meals and as a late-evening snack. Dose was titrated based on gastrointestinal tolerance. Branched-chain amino acid-enriched formulas were not routinely used.

Step 3 (Days 7–10): Initiation of supplemental parenteral nutrition (SPN). If, after an additional 3 days (day 6 of intervention), intake was still below 75% of targets, SPN was initiated. SPN was administered via a peripherally inserted central catheter or peripheral line, providing glucose, lipids, or amino acids, prescribed to meet the remaining caloric and protein deficit.

Monitoring and Adjustment: The ONS and SPN regimens were jointly managed by study dietitians and physicians. Gastrointestinal tolerance (nausea, vomiting, diarrhea, bloating) and blood glucose were monitored daily. The intervention was adjusted as needed.

Post-intervention period (Days 11–90): After the 10-day intervention period, patients were encouraged to maintain a diet diary and continue aiming for their nutritional goals with routine outpatient dietary advice. Adherence to ONS and dietary recommendations was assessed at follow-up visits (day 30, day 90) via patient interview and review of dietary records.

Control Group:

Patients in the control group received a one-time session of standard dietary counselling from a dietitian at enrolment, which included advice on a balanced diet, the importance of small, frequent meals, and a late-evening snack. They were then allowed to eat according to their appetite and hospital meals without active monitoring or structured ONS/SPN as part of the study protocol. Hypoglycemia was managed with ≤ 800 kcal/day intravenous glucose (blood glucose < 10 mmol/L). If conditions such as gastrointestinal bleeding or hepatic encephalopathy arose requiring nutrition support, appropriate intervention was provided.²⁴

Outcomes

Primary outcomes were liver transplant-free mortality at 30 and 90 days after randomization.

Secondary outcomes included:

Safety: Incidence of adverse reactions potentially related to nutritional support, including gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal distension), hyperglycemia, catheter-related infections, and hepatic deterioration.

Adverse Clinical Outcomes: A composite of fluid and sodium retention requiring diuretic adjustment, gastrointestinal bleeding, septic shock, hepatic encephalopathy, hepatorenal syndrome, unplanned hospital readmission, and intensive care unit (ICU) transfer.

Liver Severity Scores: Changes in MELD score and COSHH-ACLF II score at day 30 and day 90.

Anthropometry and Function: MAC, TSF, handgrip strength (dominant hand, Jamar dynamometer), gait speed, Short Physical Performance Battery (SPPB) score,²⁷ Liver Frailty Index (LFI),²⁸ and L3-SMI assessed by computed tomography (at baseline, day 30, and day 90).

Quality of Life: European Quality of Life 5 Dimensions visual analogue scale (EQ-5D VAS) score.²⁹

Statistical analysis

The sample size was calculated in our previously published article,²³ which was estimated at least 60 patients (30 per group).

Analysis populations: Analyses followed the modified intention-to-treat (mITT) principle, including all randomized patients who received at least one component of the assigned intervention and had at least one post-baseline assessment. Patients undergoing liver transplantation were censored at the time of transplantation.

Assessment of baseline balance:

To quantitatively assess baseline comparability beyond p-values, we calculated standardized differences for all baseline variables. A standardized difference < 0.1 indicates good balance, 0.1–0.2 acceptable balance, and > 0.2 indicates potential imbalance requiring adjustment.

Survival analysis:

Unadjusted analysis: Time-to-event data (transplant-free survival) were analyzed using the Kaplan-Meier method and compared with the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using univariable Cox regression.

Adjusted analysis: Multivariable Cox proportional hazards regression for 90-day transplant-free mortality was performed, adjusting for pre-specified clinically relevant covariates: age, sex, adjusted BMI, baseline MELD score, serum sodium, infection at baseline, and cirrhosis status. These variables were selected based on clinical relevance and observed baseline imbalances. Results were presented as adjusted HR with 95% CI.

Subgroup analyses:

Pre-specified exploratory subgroup analyses were performed stratified by sex, baseline infection status, cirrhosis status, age, MELD score, serum sodium, and adjusted BMI.

Categorical variables were expressed as counts and percentages, compared using chi-square or Fisher's exact tests. Continuous variables were tested for normality using the Shapiro-Wilk test and were presented as mean $\pm$ standard deviation or median (interquartile range). Changes from baseline within groups were analyzed using paired t-tests or Wilcoxon signed-rank tests.

Randomization was not stratified due to the limited sample size; therefore, residual imbalance was addressed using multivariable adjustment.

A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Figures were generated with GraphPad Prism version 10.5.0 (GraphPad Software, San Diego, CA, USA).

The detailed study design, including predefined endpoints, intervention protocols, and sample size calculation, has been previously published. All analyses were performed in accordance with the prespecified protocol, and no major deviations from the original design were identified.

RESULTS

Patient population and flow

From December 2023 to March 2025, consecutive hospitalized patients with HBV-ACLF were screened for eligibility according to predefined inclusion and exclusion criteria (Figure. 1). A total of 110 patients met the eligibility criteria and were considered for enrollment. Among these, 27 patients declined participation and 3 were excluded due to withdrawal of consent prior to randomization. Finally, 80 patients were randomized in a 1:1 ratio to the intervention group ($n = 40$) or the control group ($n = 40$). During follow-up, one patient in the intervention group withdrew due to non-adherence, and one patient in the control group met a predefined withdrawal criterion (sustained oral intake < 800 kcal/day for 5 consecutive days) and subsequently received supplemental parenteral nutrition as standard care. The modified intention-to-treat (mITT) population therefore included 78 patients (39 in each group). Follow-up was complete for all patients at day 30 and day 90.

Of 518 patients screened, 408 were excluded, 110 patients met the inclusion criteria, while 27 refused to participate, 3 patients were excluded due to voluntary treatment withdrawal. Eighty patients were randomized; 2 were excluded post-randomization (1 withdrawal, 1 met withdrawal criteria), leaving 78 patients in the modified intention-to-treat analysis (39 per group).

Baseline characteristics

Baseline characteristics of the 78 patients were shown in Table 1. The average age was 43.8 years, and the majority were male (92.3%). 51.3% of the patients (40/78) were diagnosed with liver cirrhosis through imaging examinations (The CT or ultrasound examination indicated that the liver surface was not smooth, with an imbalance in proportions, enlarged spleen, portal hypertension, or esophageal and gastric varices.). At baseline, 10/78 (12.8%) patients were on antiviral therapy (entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide), well-balanced between groups (15.4% vs. 10.3%, $p = 0.498$). The time from hospital admission to initiation of nutritional intervention was similar between groups (4.51 ± 3.29 vs. 4.62 ± 4.68 days, $p = 0.911$).

Most variables showed acceptable balance. Several variables exhibited standardized differences exceeding 0.2: age (0.42), adjusted BMI (0.45), COSSH-ACLF II score (0.35), serum sodium (0.54), urea nitrogen (0.35), prealbumin (0.29), blood ammonia (0.47), CRP (0.26), L3-SMI (0.36), MAC (0.37), and TSF (0.45). The control group had lower serum sodium (135.97 vs. 138.05 mmol/L, standardized difference 0.54) and lower L3-SMI (47.78 vs. 50.22 cm²/m², standardized difference 0.36).

To assess the independent effect of the nutritional intervention, we performed multivariable Cox regression adjusting for prespecified prognostic factors (age, sex, MELD score, serum sodium, BMI, infection, and cirrhosis status), selected based on clinical relevance and established prognostic value in ACLF (Supplementary Table 1).

Table 1

Baseline characteristics of HBV-ACLF patients at enrollment. Values were expressed as mean $\pm$ SD, median (IQR), or n (%). Except for lower baseline serum sodium in the control group, there were no significant differences between groups in demographics, liver disease characteristics, or severity scores.

Age (year)	Intervention group (n = 39)	Control group (n = 39)	Standardized Difference	p value
	42.03 $\pm$ 8.48	45.51 $\pm$ 8.22	0.42	0.069
Male, n (%)	35 (89.7)	37 (94.9)	0.05	0.671
Cirrhosis, n (%)	18 (46.1)	22 (56.4)	0.12	0.307
Compensated Cirrhosis	8 (20.5)	8 (20.5)		
Decompensated Cirrhosis	10 (25.6)	14 (35.9)		
Antiviral therapy, n (%)	6 (15.4)	4 (10.3)	0.12	0.498
Days (admission to intervention)	4.51 $\pm$ 3.29	4.62 $\pm$ 4.68	0.03	0.911
Ascites, n (%)	19 (48.7)	24 (61.5)	0.14	0.565
Mild	10 (25.6)	11 (28.2)		
Moderate	1 (2.6)	9 (23.1)		
Severe	8 (20.5)	3 (7.7)		
Infection, n (%)	24 (61.5)	26 (66.7)	0.06	0.637
Adjusted BMI (kg/m ²)	23.04 $\pm$ 2.75	21.8 $\pm$ 2.76	0.45	0.051
MELD (point)	20.22 $\pm$ 3.48	21.13 $\pm$ 3.87	0.25	0.282
COSSH-ACLF IIs (point)	6.72 $\pm$ 0.55	6.92 $\pm$ 0.58	0.35	0.110
Serum Sodium (mmol/L)	138.05 $\pm$ 3.64	135.97 $\pm$ 4.02	0.54	0.019
Creatinine (μ mol/L)	54.14 $\pm$ 15.66	58.54 $\pm$ 20.13	0.24	0.284
Urea nitrogen (mmol/L)	3.74 $\pm$ 1.51	4.35 $\pm$ 1.95	0.35	0.126
Total Bilirubin (μ mol/L)	369.53 $\pm$ 123.55	357.56 $\pm$ 137.06	0.09	0.687
INR	1.98 $\pm$ 0.46	2.04 $\pm$ 0.44	0.13	0.535
Albumin (g/L)	34.93 $\pm$ 4.75	34.57 $\pm$ 5.21	0.07	0.752
Prealbumin (mg/L)	66.70 $\pm$ 21.77	61.45 $\pm$ 14.01	0.29	0.217
Blood Ammonia (μ mol/L)	22.51 $\pm$ 8.15	26.46 $\pm$ 8.63	0.47	0.061

Age (year)	Intervention group (n = 39)	Control group (n = 39)	Standardized Difference	p value
	42.03 ± 8.48	45.51 ± 8.22	0.42	0.069
CRP (mg/L)	13.50 ± 9.31	11.38 ± 7.12	0.26	0.306
Energy Requirement (kcal/day)	2128.08 ± 294.11	2035.41 ± 251.67	0.34	0.139
Baseline Energy Intake (kcal/day)	1324.18 ± 251.13	1289.3 ± 270.18	0.13	0.557
Protein Requirement (g/day)	75.66 ± 8.65	75.04 ± 7.92	0.08	0.744
Baseline Protein Intake (g/day)	43.56 ± 12.91	40.38 ± 12.87	0.25	0.279
L3-SMI (cm ² /m ²)	50.22 ± 7.87	47.78 ± 5.36	0.36	0.129
MAC (cm)	28.20 ± 3.05	27.13 ± 2.8	0.37	0.116
TSF (mm)	10.51 ± 5.54	8.32 ± 4.15	0.45	0.056
MAMC (cm)	24.91 ± 2.62	24.51 ± 2.42	0.16	0.492
Grip strength (kg)	30.43 ± 10.44	30.83 ± 8.78	0.04	0.86
Gait speed (m/s)	0.72 ± 0.14	0.71 ± 0.16	0.07	0.698
Chair stand test (s)	13.83 ± 3.34	14.52 ± 6.8	0.13	0.576
Balance test (s)	29.71 ± 1.23	29.81 ± 0.82	0.1	0.698
LFI (point)	3.99 ± 0.6	4.03 ± 0.59	0.07	0.813
SPPB (point)	9.67 ± 1.56	9.69 ± 1.54	0.01	0.958
EQ-5D VAS (point)	66.42 ± 13.39	65.00 ± 15.94	0.1	0.684

Footnote: HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; MELD, Model for End-stage Liver Disease; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B score; L3-SMI, Skeletal muscle index at the third lumbar vertebra; MAC, Mid-arm circumference; TSF, Triceps skinfold thickness; MAMC, Mid-arm muscle circumference; LFI, Liver frailty index; SPPB, Short Physical Performance Battery; EQ-5D VAS, European Quality of Life 5 Dimensions the visual-analogue scale.

Nutritional intervention implementation and target attainment

The intensive goal-directed nutritional management was effectively implemented as planned (Fig. 2). Individual patient-level changes from baseline to day 10 (Fig. 2A-B) showed that the majority of intervention patients increased their energy and protein intake, whereas intake declined or remained unchanged in most control patients. Compared with controls, patients in the intervention group achieved significantly higher mean daily energy intake (1666 ± 246 vs. 1260 ± 258 kcal/day, mean difference 373 kcal/day, 95% CI 274–471, $p < 0.001$) and protein intake (62 ± 23 vs. 42 ± 21 g/day, mean difference 16 g/day, 95% CI 10–22, $p < 0.001$) (Fig. 2C-D). At day 10, the proportion of patients achieving full energy targets ($\geq 90\%$ of prescribed) was higher in the intervention group than in controls (30.8% vs. 12.8%, $p = 0.052$), as was protein target attainment (35.9% vs. 15.4%, $p = 0.036$) (Fig. 2E).

The route of nutritional support also differed markedly: in the intervention group, 27 patients (69.2%) received oral nutritional supplements (ONS) and 2 (5.1%) required supplemental parenteral nutrition (SPN); none required enteral nutrition via nasogastric tube. In contrast, only 5 patients (12.8%) in the control group received ONS (self-initiated or prescribed by non-study clinicians), and one patient was withdrawn due to persistently inadequate oral intake and subsequently received SPN.

Transplant-free mortality

Two patients from each group underwent liver transplantation during the 90-day follow-up (all censored at transplantation). Kaplan-Meier survival curves for 90-day transplant-free survival were presented in Fig. 3. The log-rank test demonstrated a statistically significant improvement in survival in the intervention group compared with the control group ($p = 0.030$). The transplant-free mortality was significantly lower in the intervention group at day 30 [2.6% (1/39) vs 20.5% (8/39), absolute risk reduction 17.9% (95% CI, 4.2% to 31.6%); unadjusted HR 0.31 (95% CI 0.11–0.89)]. This survival benefit persisted at day 90 [18.0% (7/39) vs 38.5% (15/39), absolute risk reduction 20.5% (95% CI, 2.5% to 38.5%); unadjusted HR 0.42 (95% CI 0.19–0.93)].

Adjusted survival analysis

To account for potential confounding due to baseline imbalances between groups (Table 1), we performed multivariable Cox regression analysis for 90-day transplant-free mortality. Variables included in the model were prespecified based on clinical relevance and observed baseline differences: age (> 40 vs. ≤ 40 years), sex, MELD score (> 20 vs. ≤ 20), serum sodium (> 135 vs. ≤ 135 mmol/L), adjusted BMI (> 24 vs. ≤ 24 kg/m²), infection at baseline, and cirrhosis status.

As shown in Supplementary Table 1, the adjusted hazard ratio for the nutritional intervention was 0.412 (95% CI 0.161–1.051, $p = 0.063$). While the point estimate suggests a clinically meaningful 59% relative risk reduction, the confidence interval crossed 1.0 and the p-value did not reach the conventional threshold for statistical significance. This attenuation compared with the unadjusted analysis (HR 0.384, 95% CI 0.156–0.942, $p = 0.037$) is likely attributable to the modest sample size and the inclusion of multiple covariates, which reduced statistical power. Notably, the direction and magnitude of the treatment effect remained consistent, supporting the robustness of the primary finding.

Subgroup analyses

As shown in Supplementary Table 2, the treatment effect consistently favored the intervention across most subgroups. The hazard ratio reached statistical significance in male patients (HR 0.374, 95% CI 0.144–0.975, $p = 0.044$) and patients aged > 40 years (HR 0.311, 95% CI 0.111–0.863, $p = 0.025$). Point estimates also favored the intervention in patients with infection (HR 0.440), cirrhosis (HR 0.408), MELD > 20 (HR 0.417), and serum sodium > 135 mmol/L (HR 0.376), although confidence intervals crossed 1.0 due to limited sample size. Tests for interaction were not significant for any comparison (all p for interaction > 0.16), indicating no evidence of differential treatment effects across subgroups. The apparent lack of benefit in the small subgroup of patients aged ≤ 40 years (HR 1.409, 95% CI 0.128–15.543) should be interpreted with caution given the very few events and wide confidence interval.

These findings suggest that early, goal-directed nutritional intervention reduced short-term mortality in patients with HBV-ACLF who were at nutritional risk.

Safety of nutritional intervention

The intensive goal-directed nutritional management was well-tolerated (Supplementary Table 3). The incidence of gastrointestinal symptoms was comparable between groups (19/39 [48.7%] vs 18/39 [46.2%], $p = 0.821$). Rates of catheter-related infections (3 vs. 2, $p = 1.0$) and significant hyperglycemia (2 vs. 2, $p = 1.0$) were low and not different between groups. No episode of hepatic encephalopathy was attributed to the nutritional intervention. No severe nutrition-related adverse events occurred.

Adverse clinical outcomes

The incidence of adverse clinical outcomes was shown in Table 2. It was numerically lower in the intervention group at day 30 (9/38 [23.7%] vs 14/31 [45.2%], $p = 0.060$) and significantly lower at day 90 (7/32 [21.9%] vs 17/24 [70.8%], $p < 0.001$).

The reduction was primarily driven by significant decreases in: Fluid and sodium retention requiring diuretic adjustment (day 90: 21.9% vs. 58.3%, $p = 0.005$), Unplanned hospital readmission (day 90: 12.5% vs. 45.8%, $p = 0.005$). Other complications (GI bleeding, HE, HRS, septic shock) were numerically lower in the intervention group but did not reach statistical significance.

Table 2
The incidence of adverse clinical outcomes at 30-and 90-day.

30-Day adverse clinical outcomes	Intervention group	Control group	p value
	9/38(23.7%)	14/31 (45.2%)	0.060
Fluid and sodium retention	9/38 (23.7%)	9/31 (29%)	0.615
Gastrointestinal bleeding	0	0	-
Hepatic encephalopathy	0	1/31 (3.2%)	0.449
Hepatorenal syndrome	1 /38 (2.6%)	2/31 (6.5%)	0.584
Septic shock	0	1/31 (3.2%)	0.449
ICU admission	0	1/31 (3.2%)	0.449
Unplanned hospitalization	2/38 (5.3%)	4/31 (12.9%)	0.397
90-Day adverse clinical outcomes	7/32 (21.9%)	17/24 (70.8%)	< 0.001
Fluid and sodium retention	7/32 (21.9%)	14/24 (58.3%)	0.005
Gastrointestinal bleeding	0	1/24 (4.2%)	0.429
Hepatic encephalopathy	0	0	-
Hepatorenal syndrome	0	1/24 (4.2%)	0.429
Septic shock	0	0	-
ICU admission	0	0	-
Unplanned hospitalization	4/32 (12.5%)	11/24 (45.8%)	0.005

Footnote: Adverse clinical outcomes included fluid retention, gastrointestinal bleeding, septic shock, hepatic encephalopathy, hepatorenal syndrome, unplanned readmission, and ICU transfer. Percentages were calculated using the number of patients alive at each time point as the denominator. Adverse clinical outcomes included fluid retention, gastrointestinal bleeding, septic shock, hepatic encephalopathy, hepatorenal syndrome, unplanned readmission, and ICU transfer.

Liver failure severity scores

Both MELD and COSSH-ACLF II scores improved significantly more in the intervention group over time (Supplementary Table 4, Fig. 4A-B). The mean reduction in MELD score from baseline was greater in the intervention group at day 30 (-2.12 ± 8.03 vs 2.46 ± 8.92 , between-group difference -4.59 (95% CI -9.02 to -0.16 , $p = 0.043$), and day 90 (-9.93 ± 5.24 vs -5.81 ± 7.64 , between-group difference -4.12 (95% CI -7.91 to -0.34), $p = 0.033$). Similarly, COSSH-ACLF II scores decreased more in the intervention arm at all time points (day 30 -0.73 ± 0.87 vs 0.09 ± 1.21 , between-group difference -0.83 (95% CI -1.39 to $-$

0.28), $p = 0.005$; day 90: -1.70 ± 0.72 vs -1.05 ± 0.98 , between-group difference -0.65 (95% CI -1.15 to -0.15), $p = 0.031$).

Functional recovery and quality of life

The intervention group demonstrated superior recovery in muscle function and physical performance (Supplementary Table 4, Fig. 4C-F). Handgrip strength increased in the intervention group but declined in the control group (mean change at day 30: $+4.06 \pm 5.13$ kg vs. -1.86 ± 5.99 kg; between-group difference 6.04 kg (95% CI 1.87 – 10.21), $p = 0.006$; at day 90: 7.93 ± 4.50 kg vs -0.19 ± 7.68 kg, between-group difference 8.13 kg (95% CI 1.83 – 14.42), $p = 0.015$). Gait speed and SPPB scores also improved significantly more in the intervention group ($p < 0.05$ at day 90). L3-SMI, assessed by CT, declined in both groups at day 30, consistent with acute-phase catabolism. By day 90, a trend towards recovery was observed in the intervention group while decline continued in controls (4.12 ± 9.12 vs -4.43 ± 5.78 cm²/m², between-group difference 8.57 (95% CI -0.71 to 17.88), $p = 0.067$).

Quality of life

EQ-5D VAS scores improved markedly in the intervention group compared to controls. The between-group difference in mean change from baseline was significant at day 30 (20.00 ± 3.96 vs 4.82 ± 5.71 , $p = 0.033$). At day 90 it was improved and remained significant (32.88 ± 3.23 vs 18.2 ± 6.03 points, $p = 0.038$) (Supplementary Table 4, Supplementary Fig. 2).

DISCUSSION

This randomized controlled trial in nutritionally at-risk patients with HBV-ACLF demonstrates that intensive, goal-directed nutritional management is safe and significantly reduces 30- and 90-day transplant-free mortality. In adjusted analyses accounting for baseline imbalances, the survival benefit showed a consistent direction (adjusted HR 0.412) but the p -value did not reach the conventional threshold for statistical significance ($p = 0.063$), likely due to limited sample size. Nevertheless, the consistency of findings across unadjusted, adjusted, and subgroup analyses supports the robustness of the observed benefit. Although the adjusted analysis did not reach statistical significance, the consistency across multiple analyses supports a likely true effect, which should be confirmed in larger trials. The intervention also led to greater improvements in liver function scores, muscle strength, physical performance, and quality of life, alongside a reduction in composite adverse clinical outcomes. These findings provide the first randomized evidence in HBV-ACLF and underscore the critical role of proactive nutritional management in this vulnerable population. Nutritional support may improve outcomes through multiple mechanisms, including preservation of skeletal muscle mass (thereby enhancing ammonia detoxification), modulation of systemic inflammation, and maintenance of gut barrier integrity.

The survival benefit observed in our trial contrasts with several previous randomized controlled trials in which intensive nutritional support failed to improve hard outcomes in severe liver disease.

Understanding the reasons for these divergent findings is essential for interpreting our results and guiding future research. Moreno et al.¹⁴ found that adding intensive enteral nutrition to corticosteroids did not improve 6-month survival in patients with severe alcoholic hepatitis. The intervention, delivered via nasogastric tube for 14 days targeting 30–40 kcal/kg/day, was poorly tolerated: 48.5% of patients experienced premature tube withdrawal, and the median feeding duration was only 5 days. This highlights a fundamental limitation of fixed-dose enteral regimens in acutely ill patients with liver disease—poor adherence negates any potential benefit. Similarly, Dupont et al.¹⁷ reported that a 4-week course of enteral nutrition followed by oral supplements did not improve 1-year survival in patients with alcoholic cirrhosis and jaundice. Importantly, this population had advanced, end-stage cirrhosis (81.8% Child-Pugh C), and the control group's spontaneous oral intake (~25 kcal/kg/day) was already close to the intervention target, leaving little room for improvement. This suggests that nutritional intervention may be ineffective when applied too late in the disease course, after irreversible organ failure has developed.

The positive findings of our study likely stem from several key differentiators in both patient population and intervention strategy. First, we specifically targeted patients with early-to-intermediate stage HBV-ACLF (COSSH-ACLF II score < 8.4) and excluded those with advanced organ failures (grade III-IV ascites, overt HE, HRS) or contraindications to oral intake. This contrasts with the aforementioned trials that included patients with more advanced, often irreversible, disease where the window for nutritional repletion may have closed. Second, our intervention was individualized and goal-directed, using measured REE to set precise energy targets and a stepwise intensification protocol to achieve them. By combining counseling, ONS, and timely SPN, we overcame the common barrier of inadequate oral intake. This dynamic approach ensured that the majority of patients met their nutritional goals. Third, we utilized SPN when oral/enteral routes were insufficient, a pragmatic escalation that allowed us to safely and reliably meet targets without relying on a potentially poorly tolerated nasogastric tube. Fourth, the intervention was embedded within a framework of intensive monitoring and reassessment, which may have facilitated earlier detection of complications and improved overall care. We acknowledge that the increased interaction and monitoring inherent to the intervention may have contributed to better outcomes beyond nutritional intake alone. However, this reflects the real-world implementation of goal-directed nutritional care.

In contrast to our approach, the only prior RCT in HBV-ACLF—which tested a late-evening snack dominated by low-protein, high-carbohydrate content—did not show a mortality benefit, likely due to insufficient intervention intensity.¹⁹

Our results align with recent positive trials of intensive nutrition in other populations. A goal-oriented individualized nutrition reduced 30-day mortality from 10% to 7% in malnourished medical inpatients,³⁰ consistent with our reduction from 20.5% to 2.6% at day 30, with a larger effect size. Potential explanations include (i) the high-risk nature of HBV-ACLF with profound baseline malnutrition and metabolic stress, amplifying early-intervention benefits, and (ii) reinforcement of target attainment beyond the initial intervention period. Likewise, a recent RCT in alcohol-related ACLF reported markedly

lower 90-day mortality with intensive nutrition (8.6% vs 42.9%).³¹ Both that study and ours showed significantly greater improvements in MELD and COSSH-ACLF II versus controls, supporting a favorable prognostic effect of individualized nutrition.

Overall adverse clinical outcomes were significantly reduced in the intervention group, with a particularly pronounced effect observed at 90 days (21.9% vs 70.8%, $p < 0.001$). This reduction was primarily driven by significant decreases in fluid and sodium retention and unplanned hospitalizations. Although individual complications such as hepatic encephalopathy, hepatorenal syndrome, and septic shock did not reach statistical significance—likely due to limited power—the consistent directional effect collectively contributed to improved clinical trajectories. These findings align with previous studies suggesting that intensive goal-directed nutritional may mitigate complications and reduce readmissions in patients with advanced liver disease.

Regarding body composition and function, prior RCTs showed that targeted nutrition improves handgrip strength and anthropometry in severely malnourished transplant candidates and in cirrhosis with minimal encephalopathy,^{32–33} aligning with our findings. Both groups exhibited L3-SMI decline at day 30—consistent with unavoidable acute-phase catabolism—yet by day 90, the control arm declined further while the intervention arm showed a rebound trend ($p = 0.067$), paralleling sustained gains in handgrip strength, gait speed, and SPPB.³⁴ Quality of life improved significantly in the intervention group at day 30; although between-group differences were not significant at day 90, a favorable trend persisted.

This study has several limitations. First, it was conducted as a single-center, open-label trial, which limits external validity and highlights the need for multicenter larger sample validation. However, the intervention was standardized, outcome assessors and data analysts were blinded, and the consistent effect across multiple objective endpoints (mortality, MELD, L3-SMI) reduces the likelihood that bias alone explains the findings. Second, for safety considerations, we excluded patients with advanced organ failures (overt HE, HRS, uncontrolled infection), diabetes, and extremes of BMI. Therefore, our findings apply only to early-stage HBV-ACLF patients who can tolerate oral intake and should not be extrapolated to more advanced disease or those with significant comorbidities. Whether a similar strategy benefits sicker populations requires separate investigation. Third, mechanistic analyses were not performed, leaving the impact of nutritional intervention on energy metabolism, immune regulation, and the gut microbiome unresolved. Future multicenter studies with broader patient populations, functional endpoints, and mechanistic exploration are warranted.

CONCLUSION

Intensive, goal-directed nutritional management significantly lowers short-term mortality, improves liver function, preserves muscle mass and function, and reduces adverse clinical outcomes in early-stage HBV-ACLF patients at nutritional risk. The survival benefit is likely mediated through both improved nutritional intake and enhanced monitoring. Early nutritional risk screening and goal-directed intervention

should be integrated into routine HBV-ACLF care. These findings fill a key evidence gap and provide a foundation for updating clinical guidelines.

Abbreviations

ACLF: Acute-on-chronic liver failure; BMI: Body mass index; COSSH: Chinese Group on the Study of Severe Hepatitis B; COSSH-ACLF IIs: COSSH-ACLF II scores; EN: Enteral nutrition; EQ-5D VAS: European Quality of Life 5 Dimensions visual analogue scale; HBV: Hepatitis B virus; HBV-ACLF: Hepatitis B virus-related ACLF; ICU: Intensive care unit; LFI: Liver frailty index; INR: International normalized ratio; L3-SMI: Skeletal muscle index at the third lumbar vertebra; MAC: Mid-arm circumference; MELD: Model for End-Stage Liver Disease; mITT: Modified intention-to-treat; NRS 2002: Nutritional Risk Screening 2002; ONS: Oral nutritional supplements; PN: Parenteral nutrition; REE: Resting energy expenditure; SPN: Supplemental parenteral nutrition; SPPB: Short Physical Performance Battery; TSF: Triceps skinfold thickness

Declarations

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest disclosure

All other authors declare no conflicts of interest.

Funding statement

This study was supported by grants from the Major Special Projects for Four Major Chronic Diseases (Grant No. 2024ZD0526202), the Key Projects of Guangzhou Science and Technology Program (Grant Nos. 2023B03J1287 and 2023B01J1007), and the Five-Year Plan Project of the Third Affiliated Hospital of Sun Yat-Sen University (Project No. 2023W106).

Ethics approval statement

The study was approved by the Ethics Committee of Third Affiliated Hospital of Sun Yat-sen University (Approval No. II2023-242-03), and conducted in accordance with the Declaration of Helsinki.

Patient consent statement

Written informed consent was obtained from all participants or their legal representatives.

Registration of Clinical Trials

This study was registered prospectively at ClinicalTrials.gov (NCT06128421).

Acknowledgement

All authors thank all the participants who took part in the study.

Author contributions

Study design and supervision were performed by Zhipeng Li, Chan Xie and Liang Peng. Material preparation, data collection and analysis were performed by Zhipeng Li, Yeqiong Zhang, Qiumin Luo, Shengjiang Deng. The first draft of the manuscript was written by Zhipeng Li. Patient selection and inclusion, follow-up, data collection, and manuscript revision were performed by Zhipeng Li, Yeqiong Zhang, Qiumin Luo, Shengjiang Deng, Wenxiong Xu, Jia Chen, Xin Song, and Xiyao Chen. Statistical analysis was performed by Zhipeng Li, Yeqiong Zhang and Qiumin Luo. All authors reviewed, commented on, and approved the final manuscript.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on acute-on-chronic liver failure. *J Hepatol* 2023;79:461-491.
2. Karvellas CJ, Bajaj JS, Kamath PS, et al. AASLD Practice Guidance on Acute-on-chronic liver failure and the management of critically ill patients with cirrhosis. *Hepatology* 2023; 79: 1463-1502.
3. Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association, Severe Liver Disease and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. [Guidelines for diagnosis and treatment of liver failure (2024 version)]. *Zhonghua Gan Zang Bing Za Zhi* 2025;33:18-33.
4. Chinese Society of Hepatology, Chinese Medical Association, Chinese Society of Gastroenterology, Chinese Medical Association. [Clinical guidelines on nutrition in end-stage liver disease]. *Zhonghua Gan Zang Bing Za Zhi* 2019;27:330-342.
5. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr* 2017;36:49-64.
6. Lai JC, Tandon P, Bernal W, et al. Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021;74:1611-1644.
7. Mangana Del Rio T, Sacleux SC, Vionnet J, et al. Body composition and short-term mortality in patients critically ill with acute-on-chronic liver failure. *JHEP Rep* 2023;5:100758.
8. Perdiguero GG, Spina JC, Martínez J, et al. Enhancing ACLF prediction by integrating sarcopenia assessment and frailty in liver transplant candidates on the waiting list. *JHEP Rep* 2024;6:100985.
9. Cederholm T, Bosaeus I. Malnutrition in Adults. *N Engl J Med* 2024;391:155-165.

10. Kondrup J, Allison SP, Elia M, et al. ESPEN guidelines for nutrition screening 2002. *Clin Nutr*.2003;22:415-421.
11. Limon-Miro AT, Jackson CD, Eslamparast T, et al. Predicted estimates of resting energy expenditure have limited clinical utility in patients with cirrhosis. *J Hepatol* 2022;77:98-107.
12. Palmese F, Bolondi I, Giannone FA, et al. The Analysis of Food Intake in Patients with Cirrhosis Waiting for Liver Transplantation: A Neglected Step in the Nutritional Assessment. *Nutrients* 2019;11. doi: 10.3390/nu11102462.
13. Bischoff SC, Bernal W, Dasarathy S, et al. ESPEN practical guideline: Clinical nutrition in liver disease. *Clin Nutr* 2020;39:3533-3562.
14. Moreno C, Deltenre P, Senterre C, et al. Intensive Enteral Nutrition Is Ineffective for Patients With Severe Alcoholic Hepatitis Treated With Corticosteroids. *Gastroenterology* 2016;150:903-910.e8.
15. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014;371:1673-1684.
16. Reignier J, Gaillard-Le Roux B, Dequin PF, et al. Expert consensus-based clinical practice guidelines for nutritional support in the intensive care unit: the French Intensive Care Society (SRLF) and the French-Speaking Group of Pediatric Emergency Physicians and Intensivists (GFRUP). *Ann Intensive Care* 2025;15:99.
17. Dupont B, Dao T, Joubert C, et al. Randomised clinical trial: enteral nutrition does not improve the long-term outcome of alcoholic cirrhotic patients with jaundice. *Aliment Pharmacol Ther* 2012;35:1166-1174.
18. Chang Y, Liu QY, Zhang Q, et al. Role of nutritional status and nutritional support in outcome of hepatitis B virus-associated acute-on-chronic liver failure. *World J Gastroenterol* 2020;26:4288-4301.
19. Hou W, Li J, Lu J, et al. Effect of a carbohydrate-containing late-evening snack on energy metabolism and fasting substrate utilization in adults with acute-on-chronic liver failure due to Hepatitis B. *Eur J Clin Nutr* 2013;67:1251-1256.
20. Liu X, Kong M, Hua X, et al. Effects of an individualised nutritional intervention on the prognosis of patients with liver failure. *Asia Pac J Clin Nutr* 2022;31:215-221.
21. Heyland DK, Patel J, Compher C, et al. The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial. *Lancet* 2023;401:568-576.
22. Wu T, Li J, Shao L, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. *Gut* 2018;67:2181-2191.
23. Li Z, Luo Q, Wang P, et al. Efficacy and safety of individual nutrition support in patients with hepatitis B virus-related acute-on-chronic liver failure at nutrition risk: a study protocol for a randomised controlled clinical trial. *BMJ Open* 2024;14:e088832.
24. Li J, Liang X, You S, et al. Development and validation of a new prognostic score for hepatitis B virus-related acute-on-chronic liver failure. *J Hepatol* 2021;75:1104-1115.

25. Reintam Blaser A, Malbrain ML, Starkopf J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. *Intensive Care Med* 2012;3:384-394.
26. Schuetz P, Fehr R, Baechli V, et al. Design and rationale of the effect of early nutritional therapy on frailty, functional outcomes and recovery of malnourished medical inpatients trial (EFFORT): a pragmatic, multicenter, randomised-controlled trial. *Int J Clin Trials* 2018;5:142-150.
27. Essam Behiry M, Mogawer S, Yamany A, et al. Ability of the Short Physical Performance Battery Frailty Index to Predict Mortality and Hospital Readmission in Patients with Liver Cirrhosis. *Int J Hepatol* 2019;2019:8092865.
28. Lai JC, Covinsky KE, Dodge JL, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017;66:564-574.
29. Gormley MA, Akiyama MJ, Rennert L, et al. Changes in Health-related Quality of Life for Hepatitis C Virus-Infected People Who Inject Drugs While on Opioid Agonist Treatment Following Sustained Virologic Response. *Clin Infect Dis* 2022;74:1586-1593.
30. Schuetz P, Fehr R, Baechli V, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet* 2019;393:2312-2321.
31. Giri P, Taneja S, Sahni N, et al. Outpatient intensive nutrition therapy improves survival and frailty in males with Alcohol related ACLF - Randomised controlled trial. *Clin Gastroenterol Hepatol* 2025; 23:1164-1173.e2.
32. Chapman B, Wong D, Sinclair M, et al. Reversing malnutrition and low muscle strength with targeted enteral feeding in patients awaiting liver transplant: A randomised controlled trial. *Hepatology* 2024;80:1134-1146.
33. Maharshi S, Sharma BC, Sachdeva S, et al. Efficacy of Nutritional Therapy for Patients With Cirrhosis and Minimal Hepatic Encephalopathy in a Randomised Trial. *Clin Gastroenterol Hepatol* 2016;14:454-460.e3.
34. Geng N, Kong M, Zhang J, et al. Dynamic skeletal muscle loss and its predictive role on 90-day mortality in patients with acute-on-chronic liver failure. *Front Nutr* 2025;12:1446265.

Figures

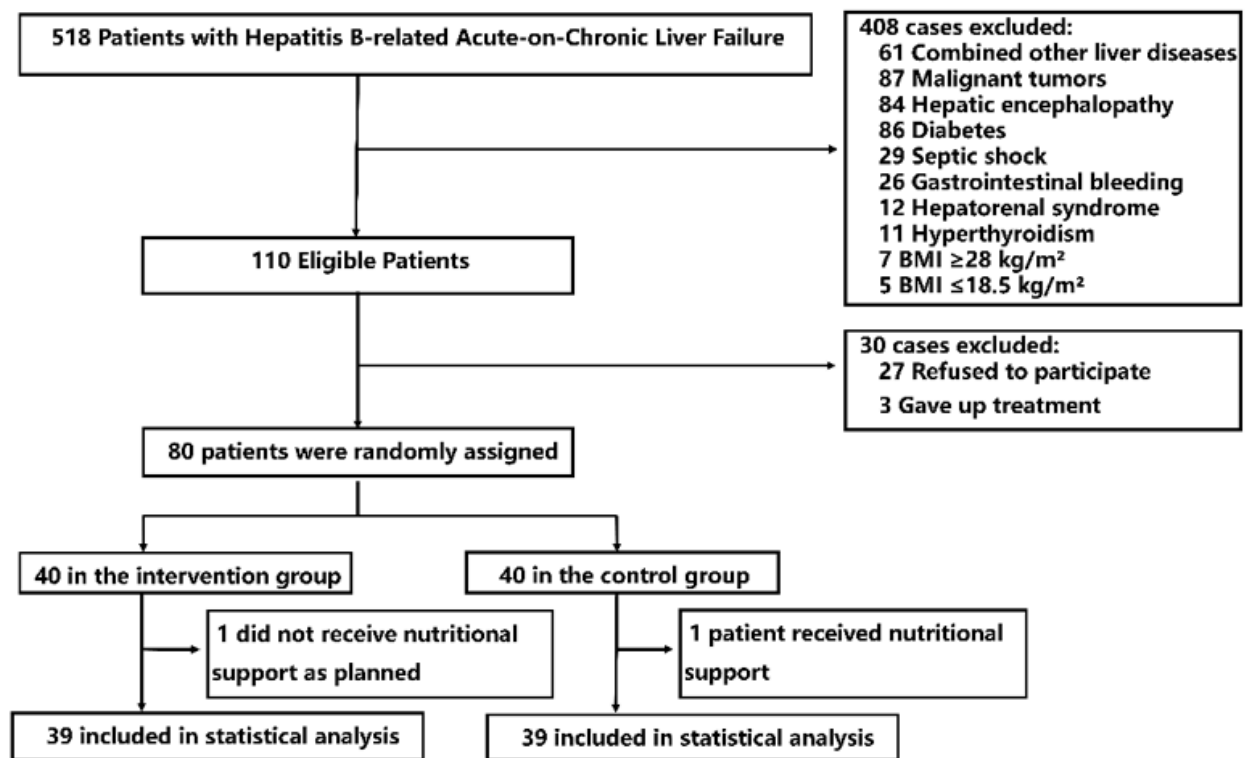


Figure 1

CONSORT flow diagram of patient enrolment and randomization.

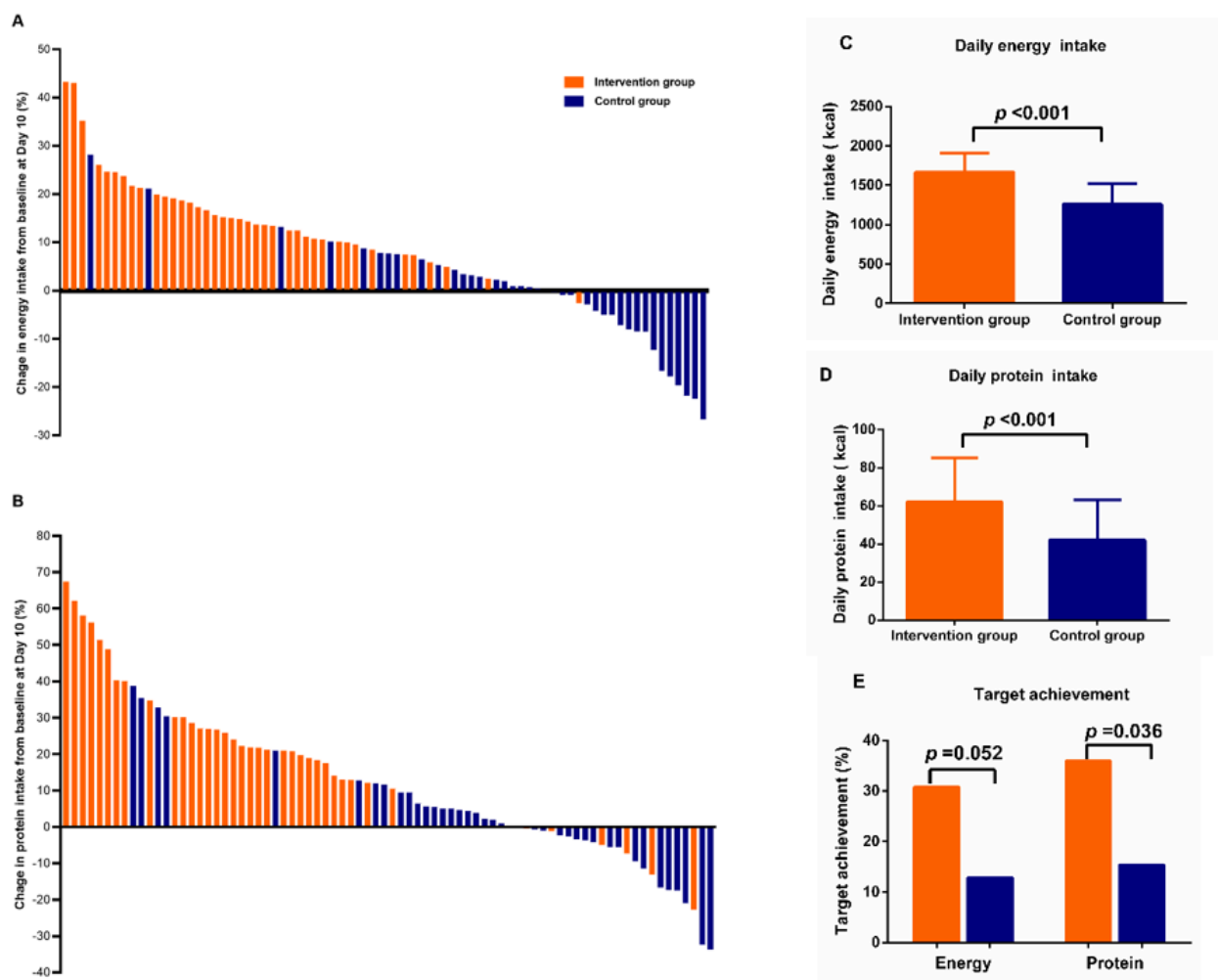


Figure 2

Nutritional intake during the 10-day intervention period. (A) Individual changes in daily energy intake from baseline to day 10, expressed as percentage change. Each bar represents one patient. Dark green bars, intervention group; light green bars, control group. (B) Individual changes in daily protein intake from baseline to day 10. (C) Comparison of mean daily energy intake between groups (intervention: 1666 ± 246 kcal/day; control: 1260 ± 258 kcal/day; $p < 0.001$). (D) Comparison of mean daily protein intake between groups (intervention: 62 ± 23 g/day; control: 42 ± 21 g/day; $p < 0.001$). (E) Proportion of patients achieving full nutritional targets ($\geq 90\%$ of prescribed) at day 10, showing higher attainment in the intervention group for both energy (30.8% vs. 12.8%, $p = 0.052$) and protein (35.9% vs. 15.4%, $p = 0.036$). Data are presented as mean ± SD (C–D) or percentages (E). P-values were calculated using Student's t-test (C–D) or chi-square test (E).

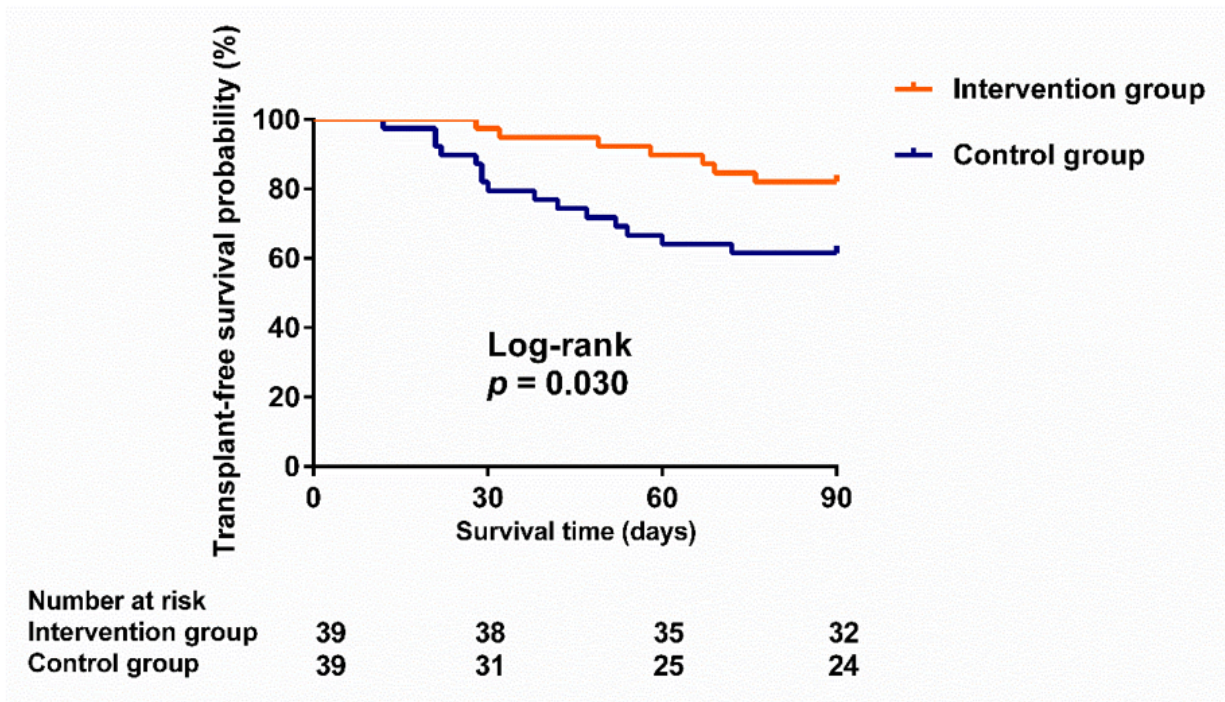


Figure 3

Transplant-free survival at 90 days Unadjusted Kaplan-Meier curves for 90-day transplant-free survival. The intervention group showed significantly lower mortality compared with controls (log-rank $p=0.030$). Patients undergoing liver transplantation were censored at the time of transplantation. Number at risk shown below.

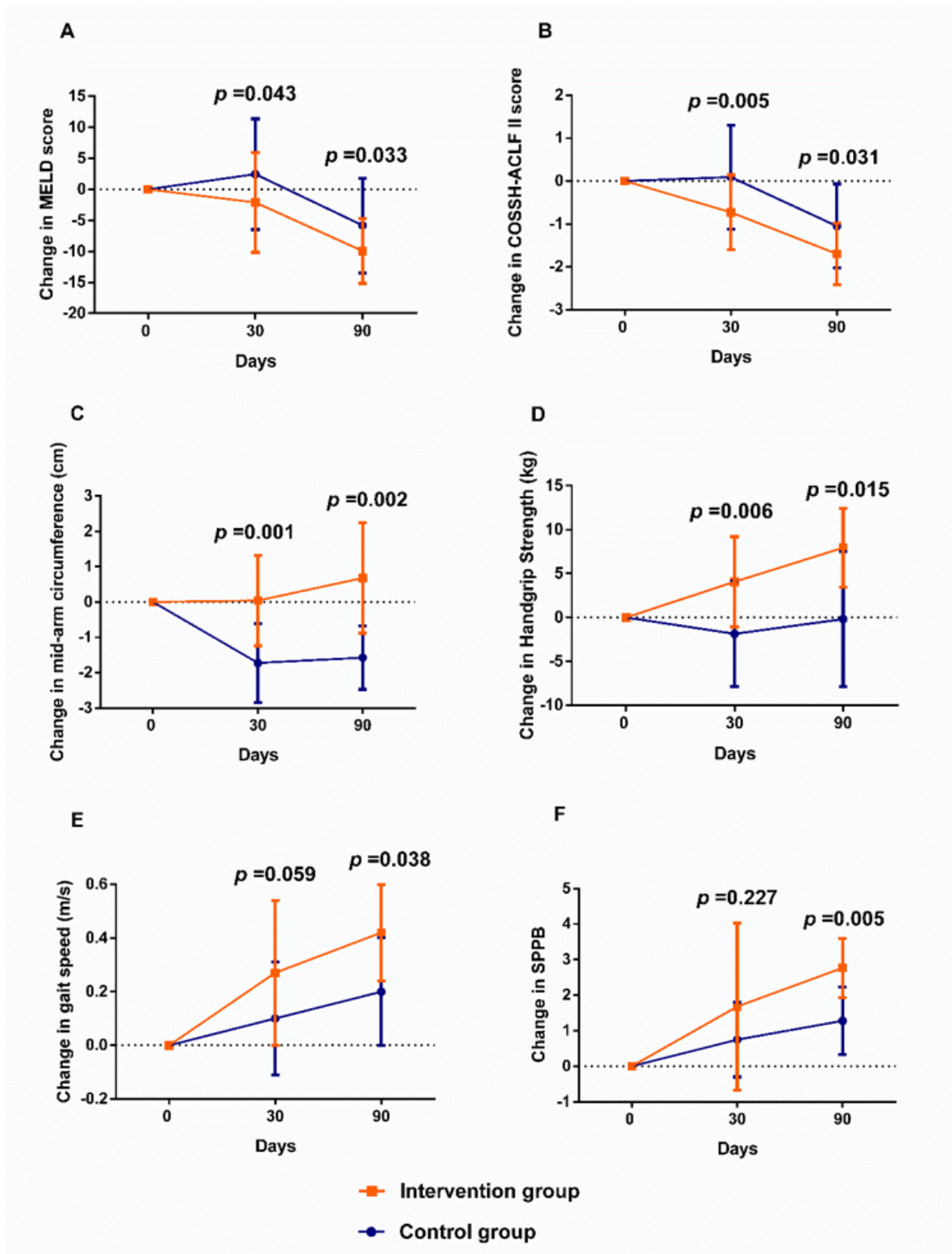


Figure 4

Changes in liver disease severity and physical function over time. Changes from baseline to day 30 and 90 in (A) MELD score, (B) COSSH-ACLF II score, (C) Mid-Arm Circumference, (D) Handgrip strength, (E) Gait speed, and (F) SPPB score. Values are presented as mean $\pm$ SD. Values are presented as mean $\pm$ SD. Between-group comparisons were performed using linear mixed-effects models for repeated measures.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryFigures.docx](#)