doi.org/10.36721/PJPS.2025.38.5.REG.14853.1

Simo decoction in patients with early liver dysfunction after liver transplantation

Weihang Zhong, Haijin Lyu, Yuping Li and Jinfeng Zhuo*
Organ Transplantation Intensive Care Unit, Sun Yat-sen University Third Affiliated Hospital, Tianhe Road, Tianhe District, Guangzhou City, Guangdong, China.

Abstract: Simo decoction was used to treat patients with early liver dysfunction after liver transplantation (LT). We aimed to evaluate its effects on gastrointestinal and liver function. A total of 138 patients were divided into the control (Ctrl) group (standard care + placebo; n=69) or the experimental (Exp) group (standard care combined with Simo decoction; n=69). From postoperative day 1 to 5 (T1-T5), patients' liver and kidney function, blood glucose, blood ammonia, gastric residual volume, defecation time, enteral nutrition intake, adverse events and the co-administration of Simo decoction with tacrolimus were analyzed. Alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin and indirect bilirubin levels all showed decreasing trends, while creatinine, blood glucose and albumin remained stable. Compared with the Ctrl group, the Exp group demonstrated significantly lower blood ammonia levels during T1-T5, earlier defecation time and higher enteral nutrition intake at T4-T5. Although gastric residual volume was higher in the Exp group at T1, it was lower than the Ctrl group at T3-T5 without reaching statistical significance. Simo decoction demonstrated beneficial effects in improving gastrointestinal function and metabolic parameters following LT, facilitating toxin elimination and promoting gastrointestinal recovery, while showing no adverse effects on hepatic or renal function recovery.

Keywords: Simo decoction, LT, gastrointestinal function, liver function

Submitted on 15-07-2025 – Revised on 30-07-2025– Accepted on 15-08-2025

INTRODUCTION

LT is an important surgical method for the treatment of end-stage liver disease, which has achieved remarkable results in the field of organ transplantation (Meyers *et al*., 2023). So far, LT has been developed for nearly 60 years and it has been developed for more than 20 years in China (Koch *et al*., 2024). The survival rate of transplanted liver and patients after LT in China has gradually approached the world advanced level (Drefs *et al*., 2024). However, China's LT practice faces several challenges, including insufficient donor organ resources, suboptimal allocation systems and complex diagnostic, therapeutic and nursing processes for postoperative complications (Bruggenwirth *et al*., 2024; Kakiuchi *et al*., 2023; El-Deeb *et al*., 2024). Among these, post-transplantation complications significantly impact patient prognosis (Emara *et al*., 2023).

The common complications after LT include bleeding, thrombosis, liver failure, rejection and infection (Wali *et al.*, 2024). To solve the problem of liver source shortage, steatotic donor liver has become an important source to expand the liver source for transplantation (Rabinowich *et al.*, 2023). However, it has been found that complications such as primary liver graft nonfunction (PNF) and primary graft dysfunction (PGD) occur after LT with steatotic donor liver (Khajeh *et al*., 2019). PNF means that the transplanted liver function can't be completely recovered or even lost within 10 days after operation, with an incidence of 0.6 to 30% (Zhang *et al.*, 2024). PGD refers to abnormal liver function early after LT, including elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels. The incidence of PGD ranges from 18.3 to 29.5% (Harnoss *et al*., 2022), indicating that the incidence of early liver dysfunction is relatively high. The clinical manifestations of hepatic insufficiency vary in severity according to the degree of liver dysfunction (Pamecha *et al*., 2022). In the early stages, symptoms may be subtle, but as the condition progresses, digestive disturbances typically appear first. Common symptoms include anorexia, nausea, indigestion, fat intolerance and diarrhea (Zhang *et al*., 2023). Concurrently, gastrointestinal absorption and digestive functions become progressively impaired. Gastrointestinal dysfunction is not conducive to the absorption of nutrients and reduces the immunity of patients, which will lead to the increase of the probability and time of patients being admitted to the ICU and the infection rate and have adverse effects on the prognosis and survival rate of patients (LeFort *et al*., 2024). Therefore, improving gastrointestinal function and accelerating postoperative recovery are crucial in patient management.

Simo decoction belongs to the qi regulating agent in the traditional Chinese medicine prescription, which has the effect of invigorating qi. Moreover, Simo Decoction has a marked effect on improving digestive function. Zhang *et al.*, (2023) noted that Simo Decoction combined with western medicine is the most effective in improving gastrointestinal symptoms such as nausea and vomiting, anorexia and abdominal distension. Using rats as a model, Yan *et al.*, (2022) suggested that Simo decoction can improve gastric motility disorder in diabetic rats by increasing the level of substance P (SP), down regulation

**Corresponding author:* e-mail: rxlm136@163.com

of vasoactive intestinal polypeptide (VIP) and neuronal nitric oxide synthase (nNOS). In conclusion, Simo decoction has good application value in improving gastrointestinal function. Currently, Simo Decoction has been applied to improve postoperative gastrointestinal function in various conditions, including after colorectal cancer resection and hepatocellular carcinoma surgery (Yang *et al*., 2017; You *et al*., 2015). However, its effects on early liver dysfunction following LT have not yet been systematically investigated.

Based on this study, this study administered Simo Decoction combined with conventional nursing methods to LT patients for postoperative intervention. The objectives were to evaluate its effects on gastrointestinal function recovery and liver function changes, thereby providing a scientific basis for clinical strategies to reduce early liver dysfunction incidence after LT.

MATERIALS AND METHODS

Study subjects

A total of 138 subjects with early liver dysfunction after LT admitted to Sun Yat-sen University Third Affiliated Hospital from March 2022 to December 2023 were enrolled, 111 men and 27 women, 35 to 73 years old (52.33±13.22). The model for end-stage liver disease (MELD) score (Peschel *et al*., 2023) was between 2 and 49 points (39±3.33) and the acute physiology and chronic health evaluation 2 (APACHE 2) score (Yang *et al*., 2024) was between 4 and 42 points (16±1.36). This study employed a prospective, randomized, single-blind controlled design. Patients were randomly assigned to either the experimental (Exp) group or control (Ctrl) group using a random number table (n=69 per group) based on postoperative intervention methods. To minimize observer bias, data recorders responsible for subjective outcome assessments were independent from intervention administrators and remained blinded to group allocation (single-blind design). The Ctrl received routine nursing intervention after LT, while the Exp received Simo Decoction nursing intervention based on the Ctrl. Patients and their families were informed in detail and informed consent was obtained. In addition, the trial obtained the approval by the relevant medical ethics committee.

Inclusion criteria

(1) Patients underwent LT for the first time; (2) patients survived more than 30 days after LT; (3) patients received allogeneic LT; (4) patients had no mental disorders and could communicate normally with medical staff.

Exclusion criteria

(1) Patients with severe heart and renal insufficiency and abnormal blood system function; (2) patients with incomplete clinical general data and treatment data; (3) patients who dropped out of treatment.

Treatment methods

The Ctrl received routine immune rejection prevention and nutritional support after operation. subjects were instructed to take the immunosuppressant tacrolimus on time after operation (specification: 1mgx10 capsules x5 board/box Dosage form: hard capsule Approval number: H20084514 Manufacturer: Hangzhou Huadong Medicine Co., Ltd.), 0.1-0.15 mg/kg per day, twice a day. The dose was adjusted according to the blood drug concentration within 1 to 12 months after transplantation. The standard blood drug concentration was 5~20ng/mL. Nutritional support was provided mainly through nasogastric feeding tube according to the condition of subjects. To minimize placebo effects and achieve blinding at the patient level, the Ctrl group received a placebo solution carefully matched to Simo Decoction oral liquid in sensory characteristics (color, odor, taste and texture) but devoid of active ingredients. This placebo formulation was prepared using food-grade excipients and underwent rigorous sensory similarity evaluation (including independent assessment and blinded comparative testing) to ensure in distinguishability from Simo Decoction in appearance, taste and odor. Administration procedures were identical between groups to maintain patient blinding.

The Exp group received Simo Decoction nursing intervention in addition to standard immunosuppressive therapy and nutritional support. On the first day after operation, subjects were treated with Simo Decoction (specification: 10 mL*8, dosage form: oral liquid agent Approval number: Z20025044 Manufacturer: Hunan Hansen Pharmaceutical Co., Ltd.). The standard dosage was 20 mL three times daily, administered orally before meals. Based on individualized protocols established by attending physicians, different types of enteral nutrition solutions (Tp-Mct, TPF, TP) were selected according to patient tolerance, nutritional requirements and clinical status. Initiated at low rates (e.g., 20-30 mL/h), the infusion was gradually increased to the maximum tolerated level to meet caloric and protein needs. Simo Decoction dosage and administration frequency remained constant throughout treatment, though the course could be extended based on gastrointestinal symptom improvement, without dose adjustment. To ensure dosing consistency, all medication was prepared by designated staff following uniform prescriptions, with administration directly supervised by nursing personnel. Treatment was immediately discontinued and reasons documented if patients developed significant nausea/vomiting or became unable to take oral medication. All patients received medication and administration instructions from designated personnel following a standardized protocol, with dosing supervised by nursing staff to ensure consistent timing and dosage. Throughout the treatment period, all patients demonstrated excellent medication adherence without premature discontinuation or missed doses and no significant adverse effects were observed.

Laboratory tests

From the first postoperative day, 5 mL of fasting venous blood was drawn in the morning and centrifuged to obtain serum. Automatic biochemical analyzer (model: K-8800B Manufacturer: Shandong Yingtong Information Technology Co., LTD.) to perform liver function tests (including AST, ALT, total bilirubin (TBIL), direct bilirubin (DBILI), indirect bilirubin (IBILI), renal function indexes (including creatinine (Scr), albumin (Alb), blood glucose (BG) and blood ammonia were detected for five consecutive days.

Observation indicators

(1) To evaluate potential pharmacokinetic interactions between Simo Decoction and tacrolimus, the tacrolimus administration regimen (including initial dose and 1-3 day dosing) and the time required to achieve therapeutic blood concentration (target range: 5-20 ng/mL) were recorded for both patient groups.

(2) The changes of laboratory indicators: the results of AST, ALT, TBil, DBILI, IBILI, Scr, Alb, BG and blood ammonia in the Ctrl and the Exp were recorded and counted from the 1st to the 5th day after intervention (T1-5). The changes of liver function, renal function, BG and blood ammonia levels in the Ctrl and the Exp were compared and analyzed.

(3) Analysis of gastrointestinal function changes was conducted. Gastric residual volume (GRV) was objectively measured by aspirating gastric contents through a nasogastric tube prior to each scheduled enteral nutrition feeding or medication administration (typically every four hours). The aspirated volume, measured and recorded in milliliters (mL), served as an objective indicator of gastric content retention. The changes in GRV, enteral nutrition volume and total enteral nutrition were recorded and analyzed from day 1 to day 5 of intervention (T1 to T5). Enteral nutrition volume refers to the actual volume of nutritional solution administered via enteral tube on a given day, while total enteral nutrition represents the cumulative volume of all enteral nutrition solutions administered daily. Effective nutritional intake (ENI) was defined as the daily enteral nutrition volume minus the GRV on the same day. ENI was calculated using equation (1). Additionally, first defecation time (defined as the first postoperative bowel movement, recorded in days) was documented by nursing staff based on patient reports and nursing assessments.

$$Eni = V_{Ni(d)} - V_{Gf(d)} \quad (1)$$

In the above equation, $V_{Ni\ (d)}$ represents the intake volume of the nutritional solution, while $V_{Gf\ (d)}$ represents the gastric retention volume.

(4) During the intervention period, all patients were closely monitored for adverse reactions, with particular attention to Simo Decoction-related adverse events including nausea, vomiting, allergic reactions and drug interactions. All adverse events were assessed and documented by healthcare professionals to ensure timely identification and management of potential safety risks.

STATISTICAL ANALYSIS

Statistic Package for Social Science (SPSS) 19.0 (IBM, Armonk, NY, USA) was employed. Measurement data with normal distribution were presented as mean ± sd ($\bar{x}$±s) and one-way analysis of variance was employed. Count data were presented as case (%) and χ^2 test was adopted. To evaluate the correlation between the dosage of Simo Decoction and gastrointestinal function improvement, correlation analysis methods (such as Pearson correlation or Spearman rank correlation, depending on the data distribution) were employed for assessment. $P < 0.05$ was considered statistically meaningful.

RESULTS

Statistical analysis of general clinical data

According to statistics, there were 57 men (79.71%) and 12 women (20.29%) in the Ctrl and 55 men (82.61%) and 14 women (17.39%) in the Exp. The average age of the Ctrl was (49.49±10.5) years old and that of the Exp was (50.58±10.05). The average MELD score of the Ctrl was (25.06±13.38) points and that of the Exp was (23.41±12.57) points. The average score of APCHE 2 in the Ctrl was (13.41±6.49) and that in the Exp was (12.93±5.68). In the Ctrl, 16 cases (23.19%) were diagnosed as liver tumors, 19 cases (27.54%) as cirrhosis, 31 cases (44.93%) as liver failure and 3 cases (4.35%) as other liver diseases. In the Exp, 25 cases (36.23%) were diagnosed as liver tumors, 10 cases (14.49%) as cirrhosis, 32 cases (46.38%) as liver failure and 2 cases (2.90%) as other liver diseases. In the Ctrl, there were 33 cases (47.83%) taking Tp-Mct, 35 cases (50.72%) taking TPF and 1 case (1.45%) taking TP. In the Exp, there were 34 (49.28%), 35 (50.72%) and 0 (0%), respectively. Through statistical analysis, the distribution of gender (χ=0.190 P=0.663), average age (F=0.207 P=0.649), average MELD (F=0.149 P=0.7), average APCHE 2 score (F=0.597 P=0.441), underlying diseases (χ=4.985 P=0.173) and the distribution of postoperative enteral nutrition suspension (χ=1.015, P=0.602) in two groups were not visibly different ($P > 0.05$) (fig. 1 and 2).

Use of tacrolimus in two groups of patients

Fig. 3 shows a comparison of the use of Tacrolimus between the Ctrl and the Exp. The initial dose of Tacrolimus in the Ctrl was (1.95 ± 0.25) mg/kg, the first day was (3.54 ± 3.03) mg/kg, the second day was (5.91 ± 3.23) mg/kg, the third day was (7.91 ± 3.30) mg/kg and the time for Tacrolimus blood concentration to reach the standard was (5.93 ± 4.68) days. The initial dose of Tacrolimus for patients in the Exp was (1.99 ± 0.27) mg/kg, with a dose of (3.61 ± 3.21) mg/kg on the first day, (5.58 ± 2.71) mg/kg on the second day and (7.28 ± 2.56) mg/kg on the third day. The time for Tacrolimus blood concentration to reach the standard was (5.62 ± 3.36) days. After

statistical comparison, there was no significant statistical difference (P>0.05) between the two groups of patients in terms of the initial dose of Tacrolimus, the dose used on the first, second and third days and the time when Tacrolimus blood concentration reached the standard. This suggests that in this cohort, concurrent administration of Simo Decoction did not significantly alter either the dose requirement or the time needed to achieve therapeutic tacrolimus levels.

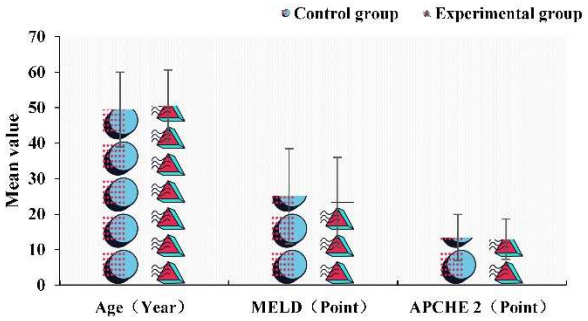

Fig. 1: Comparison of baseline characteristics (Age, MELD score, APACHE II score) between control (Ctrl, n=69) and experimental (Exp, n=69) groups. Data presented as mean ± SD. No significant intergroup differences were observed (P > 0.05).

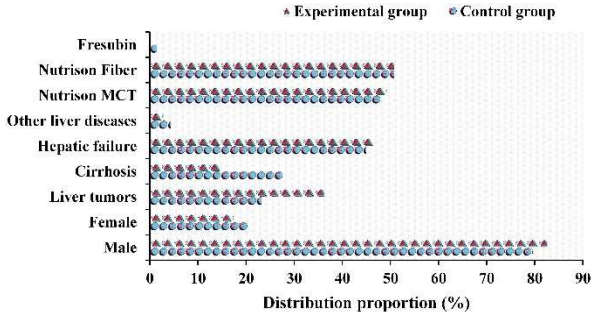

Fig. 2: Distribution of preoperative sex, underlying liver disease types, and initial postoperative enteral nutrition formulations in Ctrl (n=69) and Exp (n=69) groups. No significant intergroup differences (P > 0.05).

Changes of liver function in the Ctrl

Fig. 4 illustrates the changes of AST, ALT, TBil, DBILI and IBILI levels in the Ctrl at T1-T5. From T1 to T5, AST, ALT, DBILI and IBILI in the Ctrl were gradually decreased and TBil also suggested a decreasing trend from T1 to T4, but exhibited a slight increase at T5. However, in general, TBil was lower as against T1 and T2.

Changes in liver function levels in the Exp

Fig. 5 illustrates that from T1 to T5, AST, ALT, TBil, DBILI and IBILI of the Ctrl were all in a state of gradual decrease.

Changes of renal function, BG and blood ammonia levels in the Ctrl

Fig. 6 illustrates that Scr of the subjects in the Ctrl was basically stable from T1 to T4 and it was visibly reduced at T5. There was no significantly change in Alb level from T1 to T5. The BG at T1-T2 decreased slightly. The level of blood ammonia decreased gradually from T1 to T5.

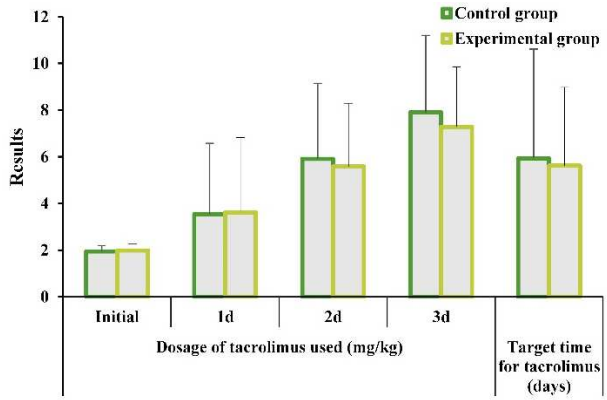

Fig. 3: Comparison of tacrolimus dosing (initial dose and days 1-3 postoperative) and time to achieve therapeutic concentration (5-20 ng/mL) between groups. Data as mean ± SD. No significant differences (P > 0.05).

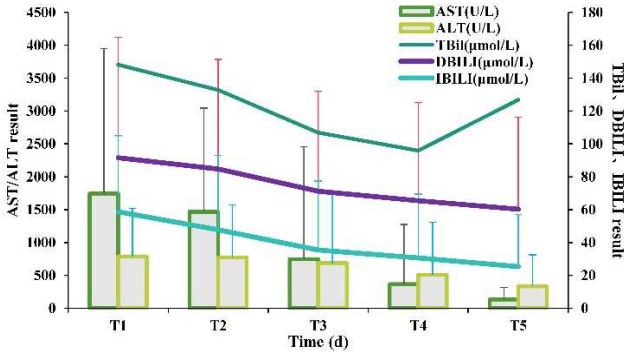

Fig. 4: Serial changes in liver function parameters (AST, ALT, TBil, DBil, IBil) from postoperative days 1-5 (T1-T5) in Ctrl group (n=69). Data as mean ± SD. Note mild TBil rebound at T5.

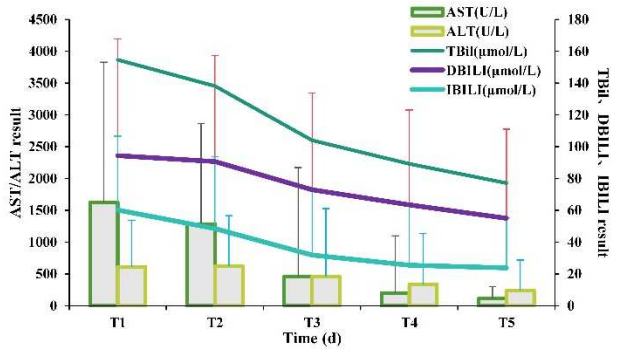

Fig. 5: Temporal trends of liver function markers (AST, ALT, TBil, DBil, IBil) during T1-T5 in Exp group (n=69). Data as mean ± SD.

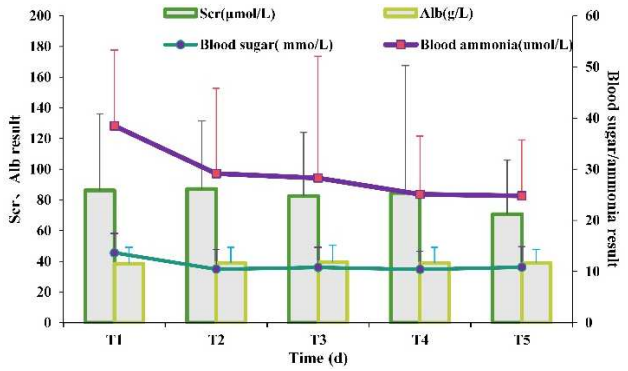

Fig. 6: Postoperative trends of renal function (Scr), blood glucose (BG), albumin (Alb), and blood ammonia in Ctrl group (n=69) across T1-T5. Data as mean ± SD.

Changes in renal function, BG and blood ammonia levels in the Exp

Fig. 7 illustrates there was a small decrease in Scr from T1 to T5 in the Exp. Alb level had no significantly change at T1-T5. The BG of T1-T2 decreased slightly. The level of blood ammonia decreased gradually from T1 to T5.

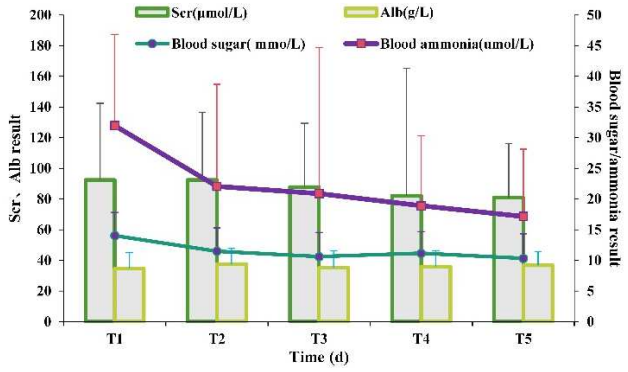

Fig. 7: Dynamic changes of Scr, BG, Alb, and blood ammonia levels in Exp group (n=69) during T1-T5. Data as mean ± SD.

Contrast of liver and kidney function, BG and blood ammonia levels of subjects at T1-T5

To evaluate the effects of Simo Decoction on liver and kidney function, BG and blood ammonia, the levels of AST, ALT, TBil, DBILI, IBILI, Scr, Alb, BG and blood ammonia were compared from T1 to T5. After statistical comparison and analysis, it was found that there were no significantly statistical distinctions in AST, ALT, TBil, DBILI, IBILI, Scr and BG levels between the Ctrl and the Exp at T1-T5 ($P > 0.05$). At T1, T3 and T4, Alb of the Exp was significantly lower than the Ctrl group (P=0.004, 0.003, 0.041<0.05), suggesting transient hypoalbuminemia occurred in the Simo Decoction group at these specific time points. No significant differences in Alb levels were observed between the two groups at either T2 or T5 ($P > 0.05$). At T1-T5, the blood ammonia level in the Exp was significantly lower than the Ctrl group (P=0.005, 0.004, 0.022, 0.001, 0.000<0.05) (fig. 8).

Changes in gastric retention, nutritional solution and total enteral nutrition volume in the Ctrl patients

The changes in gastric retention, nutritional solution and total enteral nutrition volume in the Ctrl patients are depicted in fig. 9. From T1 to T5, there was a gradual increase in the nutritional solution and total enteral nutrition volume in the Ctrl group patients, while gastric retention showed a gradual decrease.

Changes in gastric retention, nutritional solution and total enteral nutrition volume in the Exp patients

Fig. 10 illustrates the changes in gastric retention, nutritional solution and total enteral nutrition volume in the Exp patients at T1, T2, T3, T4 and T5. From T1 to T5, there was a gradual increase in the nutritional solution and total enteral nutrition volume in the Exp patients, while gastric retention also showed a gradual decrease.

Contrast of gastrointestinal function in subjects at T1-T5

The study analyzed the role of Simo Decoction in the recovery of gastrointestinal function in patients by comparing gastric retention, enteral nutrition solution usage, total enteral nutrition volume and defecation time in the Ctrl and Exp groups at T1 to T5. The results showed that at T1, gastric retention in the Exp (194.64±206.81 mL) was significantly higher than in the Ctrl (115.51±98.69 mL) (P<0.05). However, with the extension of the intervention period, gastric retention decreased overall in both groups. Specifically, the Exp showed a continuous downward trend, while the Ctrl exhibited an increase in gastric retention from T1 to T3 and a decrease from T4 to T5. Moreover, at T3 to T5, gastric retention in the Exp was lower than in the Ctrl, although the difference was not significant (P>0.05). Regarding enteral nutrition solution volume, it was higher in the Exp than in the Ctrl at T1-T3, but without statistical differences (P>0.05). However, at T4 (928.31±405.19 mL) and T5 (1068.33±407.42 mL), the volume of enteral nutrition solution used in the Exp was higher than in the Ctrl (755.94±433.34 mL, 825.22±375.36 mL) ($P < 0.05$). Calculated effective intake showed no significant difference between the Ctrl and Exp groups at T1-T3 (P>0.05). However, at T4 (850.71±462.31 mL) and T5 (993.77±455.88 mL), the effective intake in the Exp was significantly higher than in the Ctrl (643.19±458.15 mL, 730.43±411.24 mL) ($P < 0.05$). At T1-T5, the total amount of tube feeding in the Exp was slightly higher as against the Ctrl ($P > 0.05$). The defecation time of the Exp was (4±1.63) d and that of the Ctrl was (4.59±1.16) d. The defecation time of the Exp was visibly shorter than the Ctrl ($P < 0.05$) (table 1).

The correlation between Simo Decoction intake and gastric function recovery in the Exp patients

The study analyzed the gastric retention and effective intake of patients in each group when the intake of Simo Decoction was 1-6 doses, 7-12 doses and >12 doses (fig. 11).

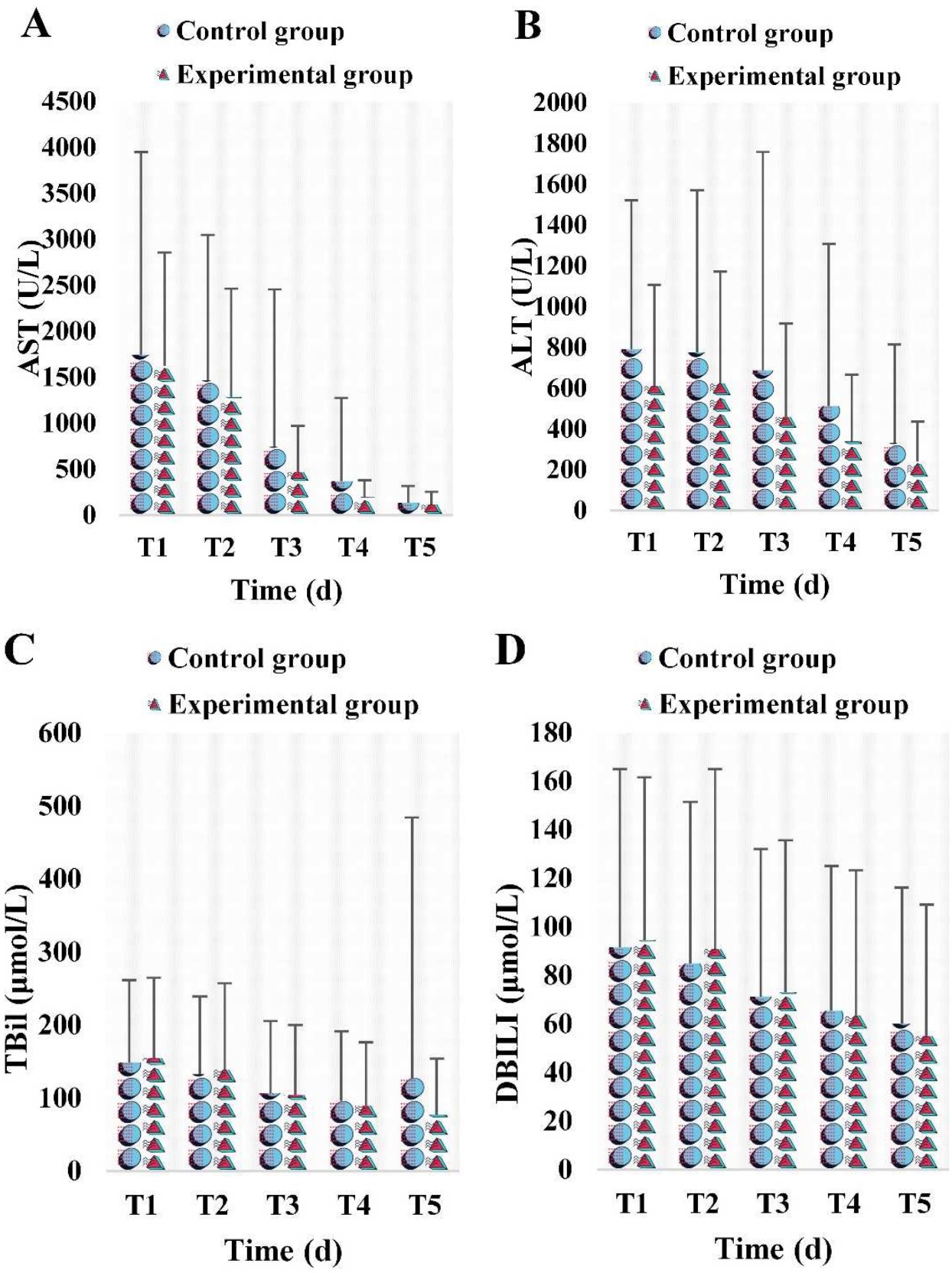

Fig. 8 is continue…

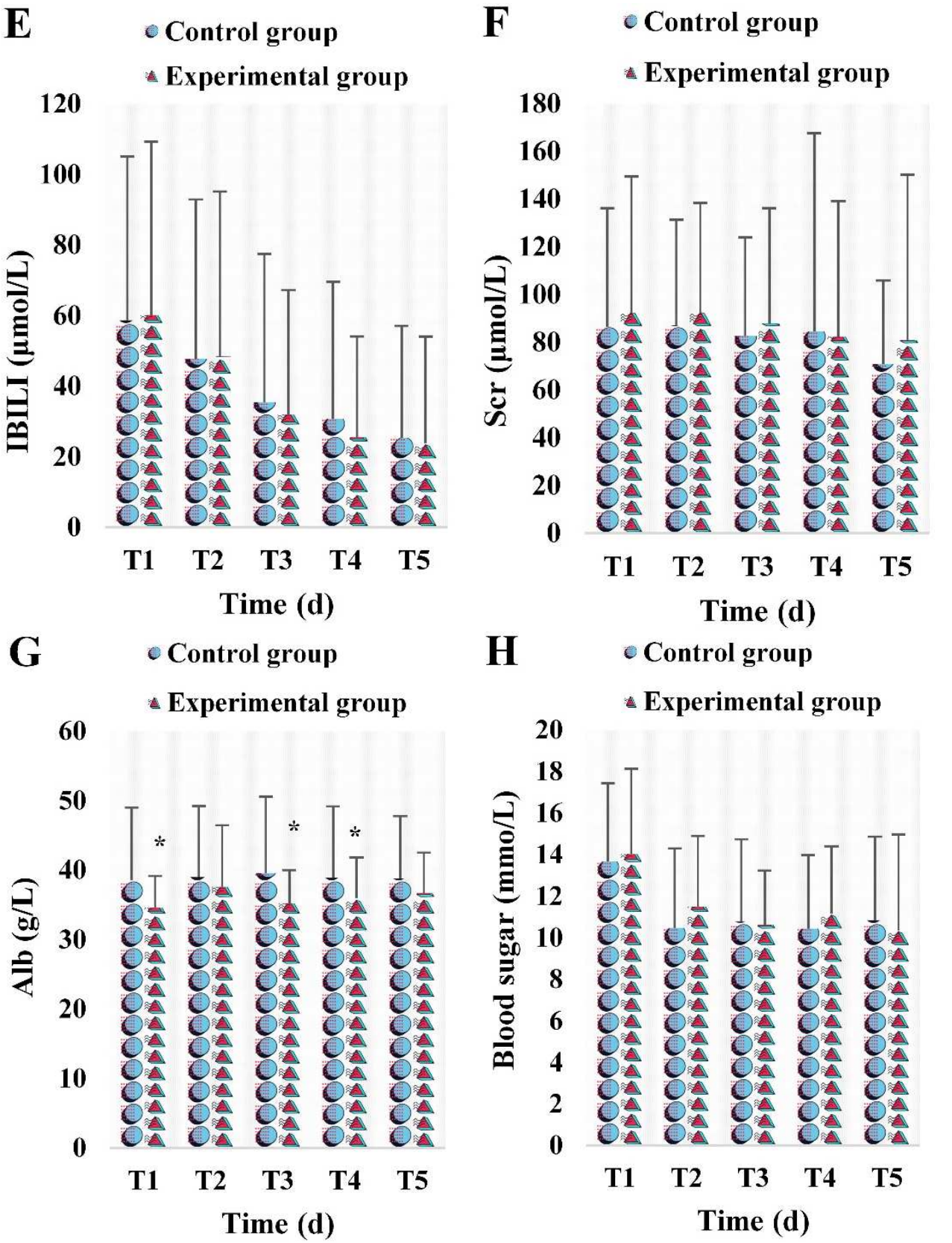

Fig. 8 is continue…

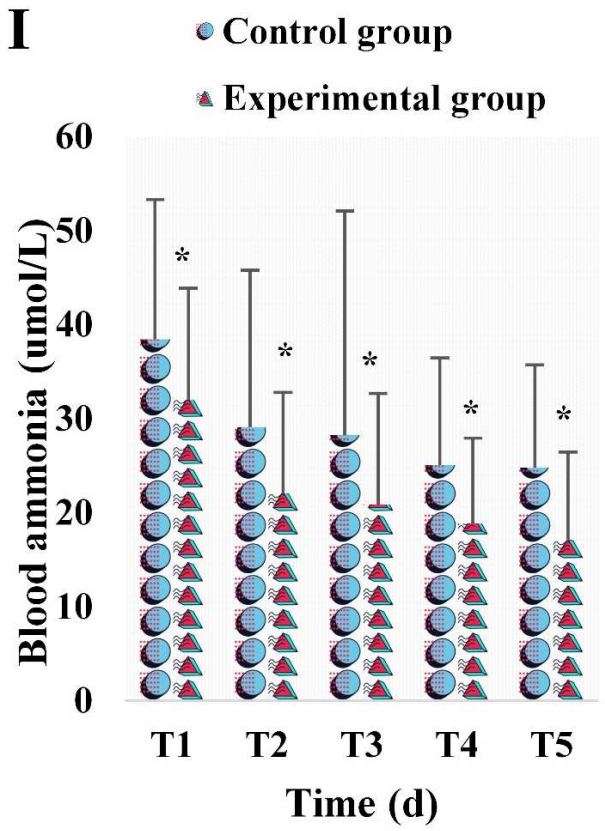

Fig. 8: Comparative analysis of key laboratory parameters between groups at T1-T5: (A) AST, (B) ALT, (C) TBil, (D) DBil, (E) IBil, (F) Scr, (G) Alb, (H) BG, (I) blood ammonia (Ctrl vs. Exp, n=69 each). Data as mean ± SD. *P < 0.05 vs. Ctrl. Note: Significantly lower Alb in Exp group at T1/T3/T4 and consistently reduced ammonia levels (T1-T5).

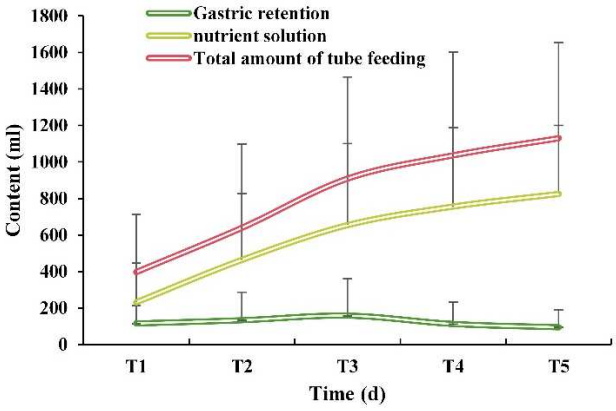

Fig. 9: Temporal patterns of gastric residual volume (GRV), administered enteral nutrition volume, and total enteral nutrition intake in Ctrl group (n=69) during T1-T5. Data as mean ± SD.

The gastric retention for intake of 1-6 doses, 7-12 doses and >12 doses of Simo Decoction were (380±83.27) mL, (625.16±97.85) mL and (692±123.34) mL, respectively. The effective intake was (3512.5±308.38) mL, (2753.54±337.02) mL and (2850.55±337.08) mL, respectively. Statistical analysis revealed no significant difference in gastric retention and effective intake among the groups with intake of 1-6 doses, 7-12 doses and >12 doses (P>0.05).

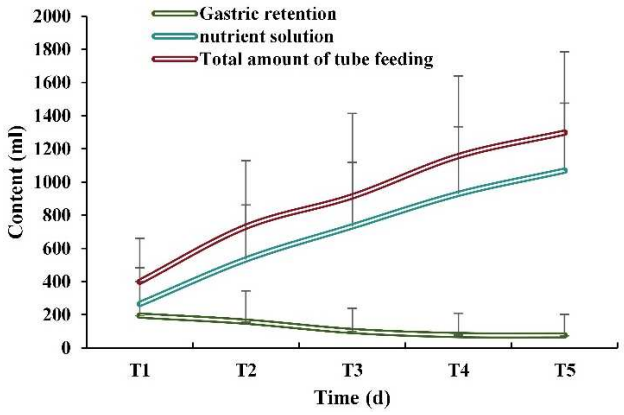

Fig. 10: Progression of GRV, enteral nutrition delivery, and cumulative nutrition intake in Exp group (n=69) across T1-T5. Data as mean ± SD.

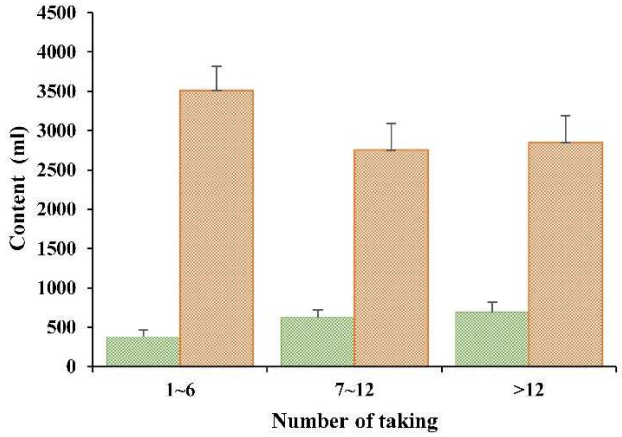

Fig. 11: Stratified analysis of GRV and effective nutritional intake (ENI) by cumulative Simo Decoction dose subgroups (1-6 doses, 7-12 doses, >12 doses) in Exp group (n=69). Data as mean ± SD. No significant dose-dependent effects (P > 0.05).

Safety evaluation

The adverse events were systematically monitored and recorded in both patient groups. The Exp group (Simo Decoction intervention group, n=69) reported 5 cases (7.25%) of mild nausea, all of which were sufficiently minor to require neither drug discontinuation nor special treatment. In the Ctrl group (standard care group, n=69), 3 cases (4.35%) of mild nausea were observed. The difference in nausea incidence between groups was not

statistically significant (χ^2=0.72, P=0.40). Furthermore, no Simo Decoction-related severe allergic reactions, drug interactions, or other serious adverse events were identified in the Exp group (table 2). All adverse events were promptly managed during the intervention period without affecting patients' continued treatment.

DISCUSSION

With the increasing maturity of liver and kidney transplantation technology in China, the number of organ donation and transplantation in China has reached the second level in the world by 2020 (Rawashdeh *et al*., 2023). In China, the number of diagnosed patients per year is about 400,000 (Sun *et al*., 2024; Liu *et al*., 2024). LT has become a standard treatment for end-stage liver diseases, including hepatocellular carcinoma and cirrhosis. Particularly for early-stage liver cancer patients who meet specific criteria, LT significantly improves survival outcomes (Sanchez-Garcia *et al*., 2024; Toshida *et al*., 2024). However, due to the long operation time and trauma of LT and the need to completely block the portal vein and inferior vena cava for total hepatectomy, the body enters the anhepatic phase. The anhepatic phase will make the blood of the intestine and lower limbs unable to return to the heart, causing systemic blood circulation disorders and indirectly leading to kidney and gastrointestinal tract damage (Lazzarotto-da-Silva *et al*., 2024; Lee *et al*., 2022). In addition, a large amount of liquid drug infusion during surgery, such as anesthesia, can also lead to the disorder of internal environment and gastrointestinal function, which leads to a longer recovery time of intestinal function after surgery. Postoperative gastrointestinal dysfunction often impairs nutrient absorption and digestion, consequently hindering liver function recovery after LT. This study examined the efficacy of Simo Decoction in improving gastrointestinal function and monitored subsequent liver function changes in LT patients.

Simo Decoction has the effects of promoting qi, reducing adverse reactions, eliminating accumulation and relieving pain and has obvious effects in improving digestive function (He *et al*., 2020. Common aucklandia root has the effect of promoting qi and relieving pain, strengthening the spleen. Pharmacological studies have shown that the decoction can promote gastrointestinal peristalsis and relieve the spasm of small intestinal smooth muscle (Elhawary *et al*., 2021; Zeng *et al*., 2020). Orange fruit has the effect of regulating qi, relieving distension. It contains citric acid substances, which can promote gastric secretion and improve digestive function (Zhao *et al*., 2024). Arecoline in areca seed can stimulate the choline receptor, promote the secretion of saliva, sweat glands and other glands and increase gastrointestinal peristalsis (Yao *et al*., 2023). Combined spicebush root has the effect of promoting qi and relieving pain. It contains volatile oil, which has a two-way regulation effect on gastrointestinal smooth muscle, which can stimulate gastrointestinal smooth muscle and inhibit smooth muscle. It can promote the secretion of digestive juice (Lai *et al*., 2021). In conclusion, Simo Decoction mainly improves gastrointestinal function, mainly by promoting gastric secretion and enhancing gastrointestinal peristalsis to accelerate gastrointestinal emptying. In this study, the gastric retention in the Exp at T1 was significantly higher than that in the Ctrl (P<0.05). This discrepancy was unexpected. Given that the Simo Decoction intervention was initiated on postoperative day 1, the observed difference at this time point is unlikely to be directly attributable to pharmacological effects. Instead, it may more plausibly reflect inherent instability during the early postoperative phase, baseline heterogeneity among patients, or transient random fluctuations. However, with the extension of intervention time, the gastric retention in the Exp gradually decreased, while in the Ctrl, gastric retention increased from T1 to T3 and decreased from T4 to T5. Moreover, at T3 to T5, the gastric retention in the Exp was lower than that in the Ctrl, but without significant differences (P>0.05).

Additionally, the defecation time of patients in the Exp was significantly shorter than that in the Ctrl (P<0.05). Consequently, the primary evidence supporting the beneficial role of Simo Decoction in gastrointestinal function recovery principally includes the Exp group demonstrated significantly enhanced enteral nutrition tolerance at T4 and T5 timepoints (reflected by increased volumes of both administered enteral nutrition and effective nutritional intake), a consistent trend of lower gastric residual volumes compared to controls beginning at T3 and earlier time to first defecation. These collective findings suggest its potential promotive effects on postoperative gastrointestinal function recovery. Xiao *et al*., (2020) confirmed that there was no significantly distinction between Simo Decoction and domperidone suspension in promoting the post-pyloric placement of spiral nasointestinal tubes. This indicates that Simo Decoction has the effect of promoting gastric motility. In addition, studies have found that the use of enteral nutrition and the intake of effective nutrition gradually increased in both the Ctrl and the Exp, while the use of enteral nutrition and the intake of effective nutrition in the Exp were significantly higher than those in the Ctrl at T4 and T5 (P<0.05). The amount of enteral nutrition solution needs to be increased gradually after surgery and attention should be paid to the recovery of gastrointestinal function of patients. The faster the gastrointestinal emptying is, the higher the dose and infusion rate of enteral nutrition solution will be increased (Song *et al.,* 2022). Therefore, Simo Decoction can promote the recovery of gastric function faster.

The study also evaluated the use of Tacrolimus, changes in liver function, kidney function, blood glucose and blood ammonia levels in two groups of patients during the

Table 1: Comparison of gastric retention, nutritional solution, effective intake, total enteral nutrition volume and defecation time between the two groups of patients at T1 to T5

Observation project		Ctrl (n=69 cases)	Exp (n=69 cases)	t	P
Gastric retention (mL)	T1	115.51±98.69	194.64±206.81	2.868	0.005*
	T2	133.26±153.79	158.12±186.06	0.855	0.394
	T3	158.12±202.33	101.81±136.30	-1.917	0.058
	T4	112.75±119.50	77.61±131.30	-1.644	0.102
	T5	94.78±95.70	75.66±126.89	-0.997	0.321
Dosage of enteral nutrition solution (mL)	T1	230.65±215.64	265.07±218.61	0.931	0.353
	T2	463.33±362.86	533.38±328.48	1.189	0.237
	T3	653.99±445.69	732.32±387.46	1.102	0.272
	T4	755.94±433.34	928.31±405.19	2.414	0.017*
	T5	825.22±375.36	1068.33±407.42	3.645	0.000*
Effective nutrient intake (mL)	T1	115.14±238.00	70.43±306.54	-0.957	0.34
	T2	330.07±397.00	375.27±425.92	0.645	0.52
	T3	495.87±510.82	630.51±452.01	1.64	0.103
	T4	643.19±458.15	850.71±462.31	2.648	0.009*
	T5	730.43±411.24	993.77±455.88	3.563	0.001*
Total amount of tube feeding (mL)	T1	396.14±315.29	398.19±263.27	0.041	0.967
	T2	638.84±458.90	730.24±398.57	1.249	0.214
	T3	908.55±556.98	912.9±499.69	0.048	0.962
	T4	1036.28±565.44	1156.21±485.35	1.337	0.183
	T5	1130±524.05	1297.83±487.08	1.949	0.053
Defecation time (d)		4.59±1.16	4±1.63	-2.474	0.015*

Table 2: Incidence and statistical analysis of adverse events in Exp and Ctrl group patients

Types of adverse events	Exp (n=69)	Ctrl (n=69)	χ^2	*P*
Mild nausea	5 (7.25%)	3 (4.35%)	0.72	0.40
Vomiting	0 (0%)	1 (1.45%)	1.00	0.32
Allergic reaction	0 (0%)	0 (0%)	—	—
Drug interactions	0 (0%)	0 (0%)	—	—
Others	0 (0%)	0 (0%)	—	—

intervention period and evaluated the effects of taking Simo Decoction on Tacrolimus use, liver function, kidney function, blood glucose and blood ammonia levels after LT. The results showed that there was no significant statistical difference (P>0.05) in the initial dose of Tacrolimus, the dosage used on days 1-3 and the time to meet blood concentration standards, as well as the AST, ALT, TBil, DBILI, IBILI, Scr and blood glucose levels of postoperative intervention on days T1, T2, T3, T4 and T5 between the two groups of patients. These results indirectly suggest that under the study conditions, Simo Decoction did not induce clinically significant pharmacokinetic interactions affecting tacrolimus exposure. However, formal drug-drug interaction studies remain necessary to definitively exclude potential interactions. Additionally, a mild rebound in TBil was observed in the Ctrl group at T5. Although the magnitude was small and not statistically significant between groups, it may have originated from natural laboratory variability, interindividual differences in bile drainage, or potential early signals of graft function changes. Given its limited magnitude and absence of intergroup significance, this change holds minimal clinical relevance in the current study context. Nevertheless, it underscores the need for continued postoperative liver function monitoring, particularly beyond the study observation period. Furthermore, the analysis revealed significantly lower Alb levels in the Exp group versus controls at T1, T3 and T4 (P<0.05). This finding of transient hypoalbuminemia warrants attention. The clinical significance of Alb is one of the important indicators reflecting the normal liver function (Xu *et al.,* 2020) and the normal level is between 35 and 55 g/L, while the Alb level of the subjects at T1-T5 was 35 to 39 g/L. The statistically significant yet transient decline observed in the Exp group during the early postoperative period suggests potential effects on albumin synthesis or distribution. Possible mechanisms include inflammation-induced increases in capillary permeability, alterations in fluid compartmentalization, or potential modulation of acute-phase protein synthesis by Simo Decoction or its bioactive constituents. While the clinical relevance of this modest reduction remains unclear in this short-term study, particularly given the absence of overt complications such as edema, it underscores the importance of enhanced monitoring of nutritional status and fluid balance during the initial postoperative period in patients receiving Simo

Decoction therapy. Notably, Simo Decoction demonstrated no adverse effects on tacrolimus absorption or efficacy, postoperative renal function recovery, or glycemic control. In summary, although the intervention did not significantly impede recovery of hepatocellular injury markers (ALT, AST) or cholestasis indicators (bilirubin), the observed transient hypoalbuminemia suggests a subtle, time-limited influence on hepatic synthetic function during the early postoperative phase that warrants further investigation in subsequent studies.

Therefore, Simo Decoction does not affect the recovery of liver function after LT. The blood ammonia level of the Exp was significantly lower than the Ctrl group at T1-T5 ($P < 0.05$). Clinical studies have confirmed that after LT, the body will have metabolic abnormalities or decrease in liver function, which will lead to increased blood ammonia levels in the liver (Wang *et al.,* 2021; Sugahara *et al.,* 2021). Simo Decoction can increase the body's metabolism by effectively promoting gastrointestinal peristalsis, thereby promoting the elimination of toxins from the body (Qiang and Yuanshui, 2020). Therefore, Simo Decoction can reduce the blood ammonia level and promote the recovery of the body after surgery.

However, it should be noted that although Simo Decoction demonstrated certain advantages in reducing blood ammonia levels, it failed to show statistically significant improvements in key liver function parameters reflecting hepatocellular injury (ALT, AST) or cholestasis (TBil). This observation somewhat limits its potential as a hepatoprotective intervention, a consideration that warrants further analysis in subsequent studies. Furthermore, subgroup analysis of different cumulative dose ranges (1-6 doses, 7-12 doses, >12 doses) revealed no significant differences in gastric residual volume or effective nutritional intake. The absence of a clear dose-response relationship may be attributed to either the relatively fixed and narrow dosing regimen adopted by most patients, or the complex multifactorial nature of postoperative gastrointestinal function recovery.

CONCLUSION

In conclusion, the administration of Simo Decoction in patients with early postoperative liver dysfunction following LT effectively improved gastrointestinal function (as evidenced by reduced gastric residual volumes over time, shorter time to first defecation and enhanced enteral nutrition tolerance in later phases), promoted gastrointestinal recovery and enhanced metabolic clearance (reflected by decreased blood ammonia levels) without adversely affecting the recovery of liver function (assessed via ALT, AST and TBil) or renal function. However, whether the gastrointestinal function will affect the recovery of liver function after LT has not been studied in this article and further improvement is still needed.

Ethical approval

This study was approved by the ethics committee of Sun Yat-sen University Third Affiliated Hospital (Approval No. SY-22-03). Signed written informed consents were obtained from the patients and/or guardians.

Author's contributions

Weihang Zhong and Jinfeng Zhuo designed the study and performed the experiments, Haijin Lyu collected the data, Yuping Li analyzed the data, Weihang Zhong and Jinfeng Zhuo prepared the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the 2022 nursing scientific research fund project (project number: 2022HLMS08) project name: four grinding soup oral liquid is applied to the study of the early liver transplantation in patients with hepatic insufficiency.

Conflict of interests

The authors declared no conflict of interest.

REFERENCES

Bruggenwirth I, Lantinga VA, Lascaris B, Thorne AM, Meerdink M, de Kleine RH, Blokzijl H, van den Berg AP, Reyntjens K, Lisman T, Porte RJ and de Meijer VE (2024). Prolonged hypothermic machine perfusion enables daytime liver transplantation - an IDEAL stage 2 prospective clinical trial. *Eclinicalmedicine*, **68**: 102411.

Drefs M, Schoenberg MB, Borner N, Koliogiannis D, Koch DT, Schirren MJ, Andrassy J, Bazhin AV, Werner J and Guba MO (2024). Changes of long-term survival of resection and liver transplantation in hepatocellular carcinoma throughout the years: A meta-analysis. *Ejso-Eur. J. Surg. Onc.*, **50**(3): 107952.

El-Deeb MA, Okba A, El-Meteini M, Ahmed EE, Mohamed RS, Mamdouh R and Maged M (2024). Impact of serum IL 10 on prediction of early allograft rejection in liver transplantation. *Egypt. J. Immunol.*, **31**(1): 162-173.

Elhawary EA, Mostafa NM, Labib RM and Singab AN (2021). Metabolomic profiles of essential oils from selected rosa varieties and their antimicrobial activities. *Plants-Basel*, **10**(8): 1721

Emara MM, Elsedeiq M, Abdelkhalek M, Yassen AM and Elmorshedi MA (2023). Norepinephrine boluses for the prevention of post-reperfusion syndrome in living donor liver transplantation: A prospective, open-label, single-arm feasibility trial. *Indian J. Anaesth.*, **67**(11): 991-998.

Harnoss JM, Cai J, Hinterkopf S, Radhakrishnan P, Schmitt A, Dupovac M, Nees LK, Strowitzki MJ, Taylor CT and Schneider M (2022). Prolyl hydroxylase inhibition mitigates allograft injury during liver transplantation. *Transplantation*, **106**(10): e430-e440.

He Z, Hu L and Chen C (2020). Response to the letter: Comment on "simo decoction versus domperidone suspension for post-pyloric spiral nasoenteric tube placement: A multicenter, randomized, non-inferiority trial". *Clin. Nutr.*, **39**(12): 3847-3848.

Kakiuchi T, Nosho T, Oka M and Tashiro K (2023). Hyperammonemia in a carbamoyl-phosphate synthetase 1 deficiency recipient after living-donor liver transplantation from a carrier donor: a case report. *Front Med-Lausanne*, **10**: 1327854.

Khajeh B, Dashti-Khavidaki S, Nasiri-Toosi M, Mohammadi K and Jafari A (2019). Effects of pre-transplant L-carnitine supplementation on primary graft dysfunction in liver transplant recipients: A pilot, randomized, placebo-controlled clinical trial. *Res. Pharm. Sci.*, **14**(6): 504-514.

Koch PF, Ludwig K, Krenzien F, Hillebrandt KH, Schoning W, Pratschke J, Raschzok N, Sauer IM and Moosburner S (2024). miRNA as potential biomarkers after liver transplantation: A systematic review. *Transplant Rev-Orlan*, **38**(2): 100831.

Lai H, Yang Z, Lou Z, Li F, Xie F, Pan W, Xu C, Zhang L, Zhang S, Zhang L and Huang M (2021). Root extract of *Lindera aggregata* (Sims) kosterm. Modulates the Th17/treg balance to attenuate DSS-induced colitis in mice by IL-6/STAT3 signaling pathway. *Front. Pharmacol.*, **12**: 615506.

Lazzarotto-da-Silva G, Santos LM, Lucena I, Rabolini BB, Hallal CP, Feier FH, Grezzana-Filho T, Chedid MF, Leipnitz I, Chedid AD, de Araujo A, Alvares-da-Silva MR and Kruel C (2024). Celiac trunk stenosis by median arcuate ligament in orthotopic liver transplantation: a potential hidden foe to the biliary tree. *Hpb*, **26**(1): 137-144.

Lee RA, Goldman J, Haidar G, Lewis J, Arif S, Hand J, La Hoz RM, Pouch S, Holaday E, Clauss H, Kaye KS and Nellore A (2022). Daptomycin-resistant *Enterococcus bacteremia* is associated with prior daptomycin use and increased mortality after liver transplantation. *Open Forum Infect Di.*, **9**(3): ofab659.

LeFort KR, Rungratanawanich W and Song BJ (2024). Contributing roles of mitochondrial dysfunction and hepatocyte apoptosis in liver diseases through oxidative stress, post-translational modifications, inflammation and intestinal barrier dysfunction. *Cell. Mol. Life Sci.*, **81**(1): 34.

Liu Q, Yan X, Li R, Yuan Y, Wang J, Zhao Y, Fu J and Su J (2024). Polyamine signal through hcc microenvironment: A key regulator of mitochondrial preservation and turnover in TAMs. *Int. J. Mol. Sci.*, **25**(2):

Meyers M, Demetter P, De Roo A, Pezzullo M, Jungels C, Brichard B, De Magnee C, De Krijger RR and Verset G (2023). Primary extrarenal rhabdoid tumour of the liver: a case report and literature review. *Acta. Gastro-Ent. Belg.*, **86**(4): 555-562.

Pamecha V, Pattnaik B, Sinha PK, Patil NS, Sasturkar SV, Mohapatra N, Kumar G, Choudhury A and Sarin SK (2022). Early allograft dysfunction after live donor liver transplantation: It's time to redefine? *J. Clin. Exp. Hepatol.*, **12**(1): 101-109.

Peschel G, Weigand K, Grimm J, Muller M and Buechler C (2023). Serum omentin-1 is correlated with the severity of liver disease in patients with chronic hepatitis C. *World J. Hepatol.*, **15**(12): 1315-1324.

Qiang H and Yuanshui S (2020). Comment on "Simo decoction versus domperidone suspension for post-pyloric spiral nasoenteric tube placement: A multicenter, randomized, non-inferiority trial". *Clin. Nutr.*, **39**(5): 1625.

Rabinowich L, Katchman H, Halaila A, Imam A, Issachar A and Braun M (2023). [CHALLENGES IN LIVER TRANSPLANT 2023]. *Harefuah*, **162**(9): 568-574.

Rawashdeh B, Alryalat SA, Kim J, Eriksen C, Abu AM, Prasad R and Cooper M (2023). The leading transplantation journals: A trend analysis, 2011-2021. *J. Transplant*, **2023**: 8858320.

Sanchez-Garcia J, Lopez-Verdugo F, Shorti R, Krong J, Kastenberg ZJ, Walters S, Gagnon A, Paci P, Zendejas I, Alonso D, Fujita S, Contreras AG, Botha J, Esquivel CO and Rodriguez-Davalos MI (2024). Three-dimensional liver model application for liver transplantation. *Transplantation*, **108**(2): 464-472.

Song M, Zhao P and Hu W (2022). Application effect of intra-abdominal pressure monitoring system in early enteral nutrition nursing of ICU patients. *Contrast Media Mol. I.*, **2022**: 3545278.

Sugahara G, Yamasaki C, Yanagi A, Furukawa S, Ogawa Y, Fukuda A, Enosawa S, Umezawa A, Ishida Y and Tateno C (2021). Humanized liver mouse model with transplanted human hepatocytes from patients with ornithine transcarbamylase deficiency. *J. Inherit. Metab. Dis.*, **44**(3): 618-628.

Sun L, Wan AH, Yan S, Liu R, Li J, Zhou Z, Wu R, Chen D, Bu X, Ou J, Li K, Lu X, Wan G and Ke Z (2024). A multidimensional platform of patient-derived tumors identifies drug susceptibilities for clinical lenvatinib resistance. *Acta. Pharm. Sin. B.*, **14**(1): 223-240.

Toshida K, Itoh S, Toshima T, Yoshiya S, Goto R, Mita A, Harada N, Kohashi K, Oda Y and Yoshizumi T (2024). Clinical significance of mechanistic target of rapamycin expression in vessels that encapsulate tumor cluster-positive hepatocellular carcinoma patients who have undergone living donor liver transplantation. *Ann Gastroent Surg*, **8**(1): 163-171.

Wali JA, Abdelmonem M, Nguyen A, Shan H, Pandey S and Yunce M (2024). Incidence of formation of anti-D between patients with and without a history of solid organ transplant. *Vox Sang.*, **119**(4): 363-367.

Wang T, Gong J, Chen Z, Huang C, Yu J, Guo Z and He X (2021). The role of spontaneous portal-systemic shunts in liver transplantation: Case report and literature review. *Ann. Palliat. Med*, **10**(7): 8365-8370.

Xiao Y, He Z, Long Y, Chen W, Chen D, Chi R, Ye H,

Deng X, Lv B, Sun C, Hu B, Nie Z, Gu S and Chen C (2020). Simo decoction versus domperidone suspension for post-pyloric spiral nasoenteric tube placement: A multicenter, randomized, non-inferiority trial. *Clin. Nutr.*, **39**(8): 2406-2412.

Xu F, Cheng R, Miao S, Zhu Y, Sun Z, Qiu L, Yang J and Zhou Y (2020). Prior toxoplasma gondii infection ameliorates liver fibrosis induced by *Schistosoma japonicum* through inhibiting th2 response and improving balance of intestinal flora in mice. *Int. J. Mol. Sci.*, **21**(8): 2711.

Yan C, Dai C, Liu N, Qian W, Yang P and Hou X (2022). Effects of Simo decoction on gastric motility of diabetic rats. *Neurogastroent. Motil.*, **34**(12): e14450.

Yang L, Yang J, Zhang X, Ye X, Liu Y, Wei B and Wang J (2024). Predictive value of soluble CD40L combined with APACHE II score in elderly patients with sepsis in the emergency department. *BMC Anesthesiol.*, **24**(1): 32.

Yang Y, Zuo HQ, Li Z, Qin YZ, Mo XW, Huang MW, Lai H, Wu LC and Chen JS (2017). Comparison of efficacy of simo decoction and acupuncture or chewing gum alone on postoperative ileus in colorectal cancer resection: A randomized trial. *Sci. Rep-Uk.*, **7**: 37826.

Yao N, Feng L, Jiang W, Wu P, Ren H, Shi H, Tang L, Li S, Wu C, Li H, Liu Y and Zhou X (2023). An emerging role of arecoline on growth performance, intestinal digestion and absorption capacities and intestinal structural integrity of adult grass carp (*Ctenopharyngodon idella*). *Anim. Nutr.*, **15**: 173-186.

You XM, Mo XS, Ma L, Zhong JH, Qin HG, Lu Z, Xiang BD, Wu FX, Zhao XH, Tang J, Pang YH, Chen J and Li LQ (2015). Randomized clinical trial comparing efficacy of simo decoction and acupuncture or chewing gum alone on postoperative ileus in patients with hepatocellular carcinoma after hepatectomy. *Medicine*, **94**(45): e1968.

Zeng C, Luo S, Feng S, Chen T, Zhou L, Yuan M, Huang Y, Liao J and Ding C (2020). Phenolic composition, antioxidant and anticancer potentials of extracts from rosa banksiae ait. flowers. *Molecules*, **25**(13): 3068.

Zhang T, Gao H, Fan Y, Chen S, Li Y, Liu R, Li T and Yin C (2023). Gut microbiota disorder induces liver dysfunction in polycystic ovary syndrome rats' model by regulating metabolite rosmarinic acid. *Life Sci.*, **330**: 121912.

Zhang Y, Dong H, Zhang X and Wang J (2024). Use total portosystemic shunt to rescue an emergency PNF with intractable hypotension: A case report. *Medicine*, **103**(1): e36687.

Zhang YX, Zhang YJ, Miao RY, Fang XY, Wei JH, Wei Y, Lin JR and Tian JX (2023). Effectiveness and safety of traditional Chinese medicine decoction for diabetic gastroparesis: A network meta-analysis. *World J. Diabetes*, **14**(3): 313-342.

Zhao Q, Liu J, Chen L, Gao Z, Lin M, Wang Y, Xiao Z, Chen Y and Huang X (2024). Phytomedicine Fructus Aurantii-derived two absorbed compounds unlock antidepressant and prokinetic multi-functions via modulating 5-HT(3)/GHSR. *J. Ethnopharmacol.*, **323**: 117703.