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The efficacy of modified HuangLian JieDu decoction for early enteral nutrition in patients with sepsis

A randomized controlled study

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Abstract

Objective: This study aimed to evaluate the efficacy of modified HuangLian JieDu decoction (MHLJDD) as a supplementary medication for early enteral nutrition in septic patients.

Methods: This study was designed as a randomized controlled preliminary study. Septic patients were randomly divided into control (treated with the base treatment) and intervention (co-treated with MHLJDD and the base treatment) groups. The primary outcomes of this study were 60-day (d) mortality rate, length of mechanical ventilation (MV), and length of stay in the intensive care unit (ICU).

Results: Of the 86 included patients, 44 and 42 were allocated to the intervention and control groups, respectively. Lengths of MV and ICU stay were significantly shorter in the intervention group than in the control group (10.31 ± 3.92 d vs 8.66 ± 2.84 d, $P = .028$; and 11.88 ± 5.25 d vs 10.41 ± 3.14 d, $P = .029$; respectively). However, the difference in 60-d mortality rate between the 2 groups was not statistically significant (20.45% vs 38.10%, $P = .071$). The enteral-nutrition tolerance score of the control group was higher than that of the intervention group (6.81 ± 4.28 vs 4.68 ± 4.04, $P = .020$). Incidence of hyperglycemia and gastric retention (gastric residual volume > 250 mL) was higher in the control group than in the intervention group (59.52% vs 29.55%, $P = .005$; and 28.57% vs 11.36%, $P = .020$, respectively).

Conclusions: MHLJDD can shorten the MV and ICU stay of septic patients.

Abbreviations: AE = adverse event, ALB = albumin, EN = enteral nutrition, HLJDD = HuangLian JieDu decoction, ICU = intensive care unit, MHLJDD = modified HuangLian JieDu Decoction, MV = mechanical ventilation, PA = pre-albumin, SOFA = Sequential Organ Failure Assessment Score, TCM = traditional Chinese medicine, TF = transferrin.

Keywords: Chinese traditional medicine, enteral nutrition, HuangLian JieDu decoction, sepsis

1. Introduction

Sepsis is a systemic organ dysfunction and one of the most deadly hospital-acquired conditions.[1] Its burden is particularly high in intensive care units (ICUs).[2] Approximately 50 million cases of sepsis are recorded per year worldwide, with 11.0 million sepsis-related deaths, representing almost 20.0% of all global deaths.[3,4] Early enteral nutrition (EN) can protect the structural and functional integrity of the gastrointestinal mucosal barrier in septic patients,[5,6] shorten their hospital stay, reduce the associated medical costs[7] (especially those related to ICU stay), and improve the prognosis.[8]

The observations of Wang Jinda[9] have indicated that the high mortality rate in septic patients is related not only to the dysfunction of blood-coagulation mechanisms but also to acute gastrointestinal failure. According to the Zang-Fu (viscera) theory of traditional Chinese medicine (TCM), 6 Fu organs should be kept unobstructed. However, the functions of these

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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6 Fu organs are compromised in sepsis,[10] and restoration of gastrointestinal function should be one of the priorities in the treatment of septic patients.[11] Modern medicine also states that maintenance of a regular daily bowel movement and improvement of tolerance to EN can reduce the mortality rate of septic patients.[12]

Numerous studies have shown that HuangLian JieDu Decoction[13–16] (HLJDD) has various biological activities, such as anti-inflammatory, anti-bacterial, anti-endotoxic, and immunomodulatory activities. However, randomized-controlled-trial–derived evidence of successful use of HLJDD in septic patients is limited. This prospective randomized controlled study was designed to evaluate the clinical efficacy of modified HuangLian JieDu decoction (MHLJDD)-assisted early EN in septic patients. We hypothesized that the ability of MHLJDD to clear toxins, normalize body temperature, promote blood circulation, and remove blood stasis, as described in TCM,[11] can effectively improve the recovery of septic patients. It is known that HLJDD can reduce gastrointestinal mucosal damage, promote gastrointestinal peristalsis, stabilize intestinal flora, and reduce gastrointestinal nutritional intolerance,[13,14] and thus MHLJDD may help septic patients reach the goal of EN, improve their overall nutritional status, and shorten their mechanical ventilation (MV) and ICU stay.

2. Methods

2.1. Study design and subjects

This study was a randomized controlled trial (Clinical Trial Approval No.: ChiCTR 1900022600) and was approved by the Ethics Committee of Zhuji Hospital of Traditional Chinese Medicine (approval number: 2019ZQ044/2019.01.01). The informed consent signed by the legal representative of each patient was obtained before enrollment. The study included patients who were admitted to the ICU or emergency intensive care unit of Zhuji Hospital of Traditional Chinese Medicine between January 2019 and March 2021.

2.1.1. Inclusion criteria.

.1.2.1.1. Western-medicine diagnostic criteria. The western-medicine diagnosis was made according to the 3.0 Sepsis Diagnostic Criteria of 2016 (Singer et al, 2016), with the Sequential Organ Failure Assessment Score (SOFA) increased by ≥2 points.[17]

1.2.2.1. TCM diagnostic criteria. The TCM diagnosis was made according to the "Standards for the Diagnosis and Therapeutic Effect of Diseases and Syndromes of Traditional Chinese Medicine," stated by the State Administration of Traditional Chinese Medicine.[8] Heat-toxin syndrome is characterized by a persistently high body temperature and a crimson purple tongue, as the primary symptoms. Irritability, dizziness, nausea, and vomiting are secondary symptoms. Stasis syndrome is characterized by cyanosis, god-delirium, dark purple tongue, and astringent or late pulse, as the primary symptoms; shortness of breath, frailty, and macula fainting are secondary symptoms. Each syndrome can be diagnosed based on 1 primary symptom +1 sub-symptom.

2.1.2. Exclusion criteria. ICU stay <5 d; age ≤18 years; pregnant or breastfeeding women; has an advanced malignant tumor; Marshall score ≥20 points; history of surgery or primary injury in the gastrointestinal tract.

2.2. Randomization

After the hemodynamic indices of the selected patients were stable (mean arterial pressure [MAP] ≥ 65 mm Hg), the patients were randomly divided into 2 groups via a random-grouping method by using The Random Number Service (www.random.org), and 101 numbers were randomly divided into a control group and an intervention group in a 1:1 ratio. The random-assignment table was kept in 1 copy, and the random number and treatment information were assigned according to the order of patient inclusion. Blind statistical analysis was used in the data-summary stage.

2.3. Intervention

Patients were treated according to the International Consensus on the Definition of Sepsis and Septic Shock (Sepsis 3.0) of 2016.[17] The treatment included anti-infection therapy, fluid resuscitation, vasoactive drugs, blood glucose control, prevention of venous thrombus embolism, MV, renal replacement, maintenance of the water, electrolyte, and acid-base balance, and other treatment measures as required by the condition. Within 24 to 48 hour of admission to the ICU, if the hemodynamics of the patient were stable (MAP > 65 mm Hg, lactic acid < 4 mmol/L), the applied vasoactive drug dosage was gradually reduced, and noradrenaline < 0.2 μg/min/kg, early EN was introduced.[3]

2.3..1. Control group An indwelling nasogastric tube or nasointestinal tube was used to deliver the EN suspension (750 cal/500 mL, trade name "Nengquanli," Nutricia Pharmaceutical Co., Ltd.). The infusion method "Rennes" LINS-5 infusion pump (Shanghai Rennes Medical Equipment Co., Ltd.) was adopted. The nutrient preparation was maintained at 37 to 40 °C and infused continuously. The target cumulative calorie and protein were 20 to 25 kcal/kg·d and 1.2 to 2.0 g/kg·d, respectively, based on the ideal weight of a patient (kg) as follows: height (cm) – 100, target calorie supply was 25 kcal/kg·d, protein was 1.2 to 2.0 g/kg·d. The initial rate of the EN feeding was 10 to 15 mL/h. EN tolerance was evaluated every 6 hours, and gastric retention was extracted. If the EN was tolerated, the intestinal nutrition was increased by 10 to 25 mL/h every 4 to 8 hours. In the case of intolerance, the original rate was maintained or halved after symptomatic treatment. Supplemental parenteral nutrition was applied when 60% of the target calories were not reached after 5 d of treatment (in accordance with the draft of the EN process of the General Hospital of Nanjing Military Region [Qiu et al, 2011]).

2.3..2. Intervention group Patients received MHLJDD in addition to the treatments applied to the control group. In accordance with the "Diagnosis of Traditional Chinese Medicine,"[18] 2 TCM physicians at the level of deputy director or above confirmed the TCM syndrome type and formulated the TCM syndrome differentiation and treatment prescriptions. In the treatment principle of clearing heat and detoxifying and promoting blood circulation, drugs were added and reduced with HLJDD as the main prescription. The composition of HLJDD is shown in Table 1. The YJD20-GL decocting machine (Beijing Donghuayuan Medical Equipment Co., Ltd.) was uniformly adopted to prepare MHLJDD. All the decoction preparations were prepared by decocting room to make 100 mL decoction, which was then divided into 2 to be administered as a 50-mL aliquot per morning and night.

2.4. Data collection

At the admission to the ICU, basic information about each patient, including age, gender, body mass index, basic disease conditions, source of infection, and reason for admission to the ICU, were collected, and the SOFA score within 24 hours was recorded.[19] Acute Physiology and Chronic Health Evaluation II Score (APACHE II) were recorded. Nutritional-risk screening (NRS-2002) score[20] and modified NUTRIC (mNUTRIC) score[21] were assessed simultaneously.

Table 1

The composition of modified HuangLian JieDu decoction.

English name	Chinese name	Plant part	Crude herbs (g)	Voucher number	Batch number	Place of origin
Coptis chinensis	Huang Lian	Rootstock	9	010111	200831	SiChuan
Scutellaria baicalensis	Huang Qin	Root	6	C-2106128	210530	Hebei
Phellodendron amurense	Huang Bai	Root	6	C-2102045	210128	SiChuan
Gardenia	Zhi Zi	Fruit	9	C-2102076	210202	Jiangxi
Paeonia suffruticosa Andrews	Mu Dan Pi	Root	9	C-2102040	210118	Anhui
Rehmannia glutinosa	Sheng Di Huang	Rootstock	6	010611	201116	Henan
Paeonia veitchii Lynch	Chi Shao	Root	6	201202	20122201	Shanxi
Citrus aurantium L	Zhi Ke	Fruit	6	210301	21030401	Jiangxi

2.5. Outcomes and follow-up

The primary outcome of this study was the 60-d mortality rate. The secondary outcomes were the lengths of MV and ICU stay.

1.2.5. Nutritional-process indices. The percentage of the patients receiving EN within 48 hours of enrollment; the percentage of the patients reaching 60% of the target calorie by day 4; the calories and proteins obtained in the first (1–7 d) and second (8–14 d) stages; and the time required to reach the target calorie were recorded.

2.2.5. Nutritional biochemical indices Blood was sampled on days 1, 3, 5, and 7 after admission to determine the serum levels of albumin (ALB), pre-albumin (PA), and transferrin (TF). The normal values of the indicators are 40 to 55 g/L (ALB), 200 to 400 mg/L (PA), and 2.20 to 4.0 g/L (TF).

The nutrition-related complications were expressed as the percentage of the patients who had hyper/hypoglycemia, upper gastrointestinal bleeding, or a gastric residual volume ≥250 mL.

The patients were followed up by 2 fixed nurses via telephone calls once a week for 60 d after initiating the treatment.

2.6. Clinical adverse events (AEs)

If any AE that significantly exacerbated the condition of any of the patients occurred during the study period, the researcher filled the "Adverse Effect" record form, and the patient was withdrawn from the study, treated as "lost to follow-up," and excluded from the analysis. General EN-related AEs were indicated using the EN tolerance score.

2.7. Sample size

The sample size was calculated using the PASS 15.0 software (NCSS Inc.) for a randomized controlled trial. The 60-d mortality rate was selected as the primary treatment-efficacy indicator, and the expected difference between the 2 groups was estimated at 10%. The sample size of each group was calculated to be 41 when α was 0.05, and the study power (1-β) was 80%.

2.8. Statistical analysis

All the statistical analyses were performed using the IBM SPSS Statistics software, version 21.0 (IBM, Armonk, NY). Quantitative data with a normal distribution were expressed as mean ± SD, and the independent sample *t* test was used for comparison between the 2 groups. Quantitative data that did not conform to a normal distribution were expressed as median (interquartile range), and Kruskal-Wallis rank-sum test was used for comparison between the 2 groups. Count data were expressed as the number of cases or percentage per category, and the χ^2 test was used for comparison between the 2 groups. The 60-d survival curve was plotted using the GraphPad 6.0c software. $P < .05$ was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

Of the 86 patients included in the final analysis, 44 were in the intervention group, and 42 were in the control group (Fig. 1). There were no significant differences in age, gender ratio, body weight, body mass index, ALB, or the ratio of NRS-2002 ≥3 and mNUTRIC ≥5 between the 2 groups ($P > .05$). APACHE II scores and SOFA were also comparable between the 2 groups at the time of inclusion ($P > .05$) (Table 2).

3.2. Primary outcome

The 60-d mortality rate in the intervention group was lower than that in the control group, but the difference was not statistically significant (20.45% vs 38.10%, $P = .071$). There was no statistically significant difference in the 60-d survival curve between the 2 groups. The duration of MV was significantly shorter in the intervention group than in the control group (10.31 ± 3.92 d vs 8.66 ± 2.84 d, $P = .028$). The ICU stay in the intervention group was significantly shorter than that in the control group (11.88 ± 5.25 d vs 10.41 ± 3.14 d, $P = .029$) (Table 3 and Fig. 2).

3.3. Secondary outcomes

The median duration to reach the target calorie was significantly shorter in the intervention group than in the control group (7 d vs 4.5 d, $P = .019$). The proportion of the patients reaching ≥60% of the target cumulative calorie by day 4 was significantly higher in the intervention group than in the control group (88.64% vs 69.05%, $P = .049$). During the second stage (8–14 d), the caloric (1083.67 ± 321.27 vs 1354.80 ± 297.26, $P < .001$) and protein (40.88 ± 9.53 vs 46.55 ± 10.08, $P = .009$) intakes were significantly higher in the intervention group than in the control group. The ALB after 5 d of treatment in the intervention group was significantly higher than that in the control group (33.59 ± 3.10 vs 31.97 ± 3.18, $P = .019$). The ALB, PA, and TF after 7 d of treatment in the intervention group were significantly higher than those in the control group (43.65 ± 3.64 vs 40.41 ± 6.16, $P = .004$; 243.34 ± 58.22 vs 204.01 ± 78.68, $P = .010$; and 2.57 ± 0.80 vs 2.16 ± 0.62, $P = .010$; respectively) (Table 4).

3.4. EN complications

EN-related AEs were evaluated based on the EN tolerance score. The EN tolerance score of the control group was higher than that of the intervention group (6.81 ± 4.28 vs 4.68 ± 4.04,

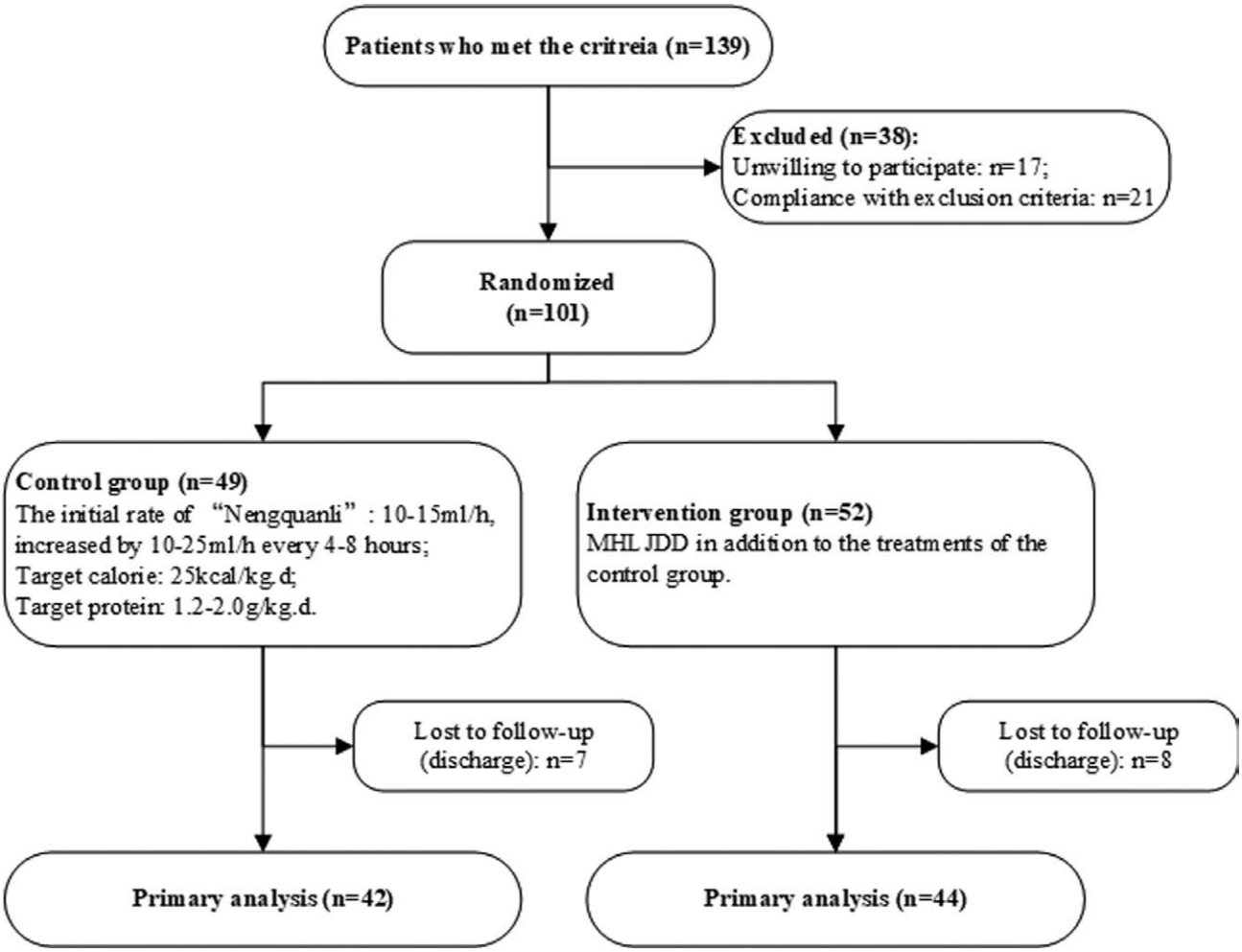

Figure 1 . Flowchart demonstrating the process of inclusion of septic patients to the study.

Table 2

Baseline characteristics of sepsis patients.

Characteristic	Control group (n = 42)	Intervention group (n = 44)	*P* value
Age, yr, mean ± SD	74.93 ± 10.44	72.11 ± 10.62	.219
Gender (male), n (%)	34 (80.95)	32 (72.73)	.367
APACHE II, mean ± SD	21.38 ± 5.42	21.68 ± 5.85	.806
SOFA score, mean ± SD	7.14 ± 4.04	7.60 ± 3.40	.560
Weight, kg, mean ± SD	65.35 ± 12.02	66.68 ± 11.93	.609
Body mass index, kg/m^2, mean ± SD	22.19 ± 3.54	21.41 ± 3.23	.288
Albumin, g/L, mean ± SD	29.65 ± 4.68	28.01 ± 4.15	.088
SOFA score infection site of sepsis, n (%)			.741
Respiratory system	24 (57.14)	20 (45.45)	
Digestive system	7 (16.67)	10 (22.73)	
Urinary system	4 (9.52)	6 (13.64)	
Blood infection	3 (7.14)	6 (13.64)	
Craniocerebral infection	2 (4.76)	1 (2.27)	
Other infections	2 (4.76)	1 (2.27)	
NRS-2002 ≥ 3, n (%)	38 (86.36)	36 (81.81)	.397
Modified NUTRIC ≥ 5, n (%)	37 (88.10)	33 (75.00)	.119
ALB, g/L, mean ± SD	28.35 ± 3.60	29.19 ± 2.87	.234
PA, mg/L, mean ± SD	89.06 ± 46.08	82.61 ± 42.37	.501
TF, g/L, mean ± SD	1.92 ± 0.17	1.83 ± 0.35	.201

ALB = albumin, APACHE = Acute Physiology and Chronic Health Evaluation, NRS = nutritional risk screening, PA = prealbumin, SD = standard deviation, SOFA = sequential organ failure assessment, TF = transferrin.

P = .020). Nevertheless, the prevalence of EN-related AEs was higher in the control group than in the intervention group. For instance, incidence of hyperglycemia and gastric retention (GRV > 250 mL) was higher in the control group than in the intervention group (59.52% vs 29.55%, *P* = .005; and 28.57% vs 11.36%, *P* = .020; respectively) (Table 5).

Table 3

Comparison of primary outcomes in patients with sepsis.

Characteristic	Control group (n = 42)	Intervention group (n = 44)	*P* value
Mechanical ventilation time (d), mean ± SD	10.31 ± 3.92	8.66 ± 2.84	.028
Length of stay in ICU (d), mean ± SD	11.88 ± 5.25	10.41 ± 3.14	.029
60-day mortality rate, n (%)	16 (38.10)	9 (20.45)	.071

ICU = intensive care unit, SD = standard deviation.

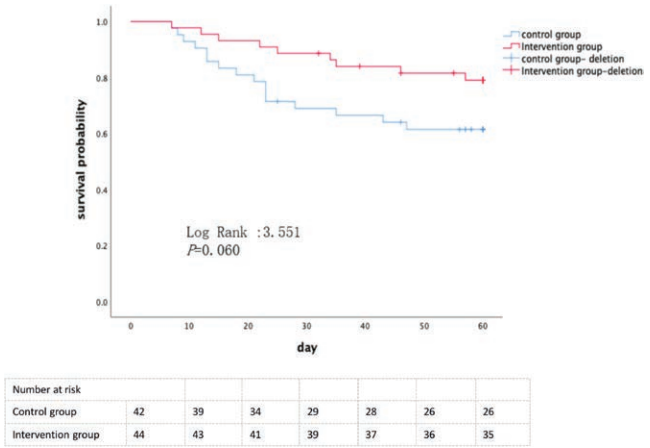

Figure 2 . Comparison of the 60-d survival curves of the 2 groups.

Research and Application of HuangLian JieDu decoction,"[23] HLJDD normalizes body temperature and detoxifies and cools the blood. Studies have shown that HLJDD not only alleviates the clinical symptoms in mice with ulcerative colitis and improves the associated damage in the colon but also restores the intestinal microflora homeostasis by inhibiting the growth of intestinal pathogens and preventing the decrease in the numbers of beneficial bacteria.[24,25] HLJDD can inhibit the inactivation of NF-κB and MAPKs and the degradation of IκBα in lipopolysaccharide-stimulated RAW24.7 cells in addition to the inactivation of MAPKs and the Lyn pathway in the antigen-pathway. Moreover, it exerts anti-inflammatory and anti-oxidant effects by inhibiting allergic reactions and production of inflammatory mediators.[26] Additionally, HLJDD has been shown to improve acute ulcerative colitis in mice by modulating the NF-κB and Nrf2 signaling pathways and enhancing intestinal-barrier function.[27]

The 2017 guidelines of the European Society of Intensive Care Medicine recommend initiating EN in critically ill patients within 24 to 48 h of admission to the ICU.[28] However, due to

Table 4

Nutritional process and nutritional biochemical indexes of sepsis patients.

Characteristic	Control group (n = 42)	Intervention group (n = 44)	*P* value
Time to start EN feeding (d), median (IQR)	3 (1, 4)	2 (1, 3)	.297
Time to reach target calorie (d), median (IQR)	7 (3, 10)	4.5 (1-7.75)	.019
The proportion of EN within 48 h, n (%)	36 (85.71)	38 (86.36)	.822
Proportion of reaching 60% of the target calorie on the 4th day, n (%)	29 (69.05)	39 (88.64)	.049
Average daily intake of calories from day 1 to day 7, mean ± SD	735.48 ± 285.44	834.32 ± 290.91	.116
Average daily protein intake from day 1 to day 7, mean ± SD	32.52 ± 8.38	35.52 ± 8.37	.086
Average daily intake of calories from day 8 to day 14, mean ± SD	1083.67 ± 321.27	1354.80 ± 297.26	≤.001
Average daily protein intake on from day 8 to day 14, mean ± SD	40.88 ± 9.53	46.55 ± 10.08	.009
ALBT1, mean ± SD	31.80 ± 3.01	31.49 ± 2.63	.615
ALBT2, mean ± SD	31.97 ± 3.18	33.59 ± 3.10	.019
ALBT3, mean ± SD	40.41 ± 6.16	43.65 ± 3.64	.004
PAT1, mean ± SD	142.00 ± 46.80	142.23 ± 28.53	.977
PAT2, mean ± SD	176.47 ± 69.37	196.77 ± 66.06	.169
PAT3, mean ± SD	204.01 ± 78.68	243.34 ± 58.22	.010
TFT1, mean ± SD	2.04 ± 0.48	1.95 ± 0.13	.232
TFT2, mean ± SD	2.14 ± 0.69	2.38 ± 0.40	.056
TFT3, mean ± SD	2.16 ± 0.62	2.57 ± 0.80	.010

ALB = albumin, EN = enteral nutrition, IQR = interquartile range, PA = prealbumin, SD = standard deviation, T1 = 3rd day after treatment, T2 = 5th day after treatment, T3 = 7th day after treatment, TF = transferrin.

3.5. Clinical AEs

No serious AE related to the study occurred during the study.

4. Discussion

The results of this study showed that MHLJDD can shorten MV and ICU stay and reduce the prevalence of EN-related AEs in septic patients.

In TCM, sepsis belongs to the category of "febrile diseases." Domestic scholars have carried out numerous animal experiments and clinical studies on TCM treatment of sepsis and demonstrated satisfactory results.[22] According to "Modern

acute gastrointestinal paralysis in septic patients, feeding intolerance, gastric reflux, and aspiration, complicated by aspiration pneumonia, may occur and affect the prognosis.[29] Additionally, it is difficult to reach the target EN feeding volume in septic patients staying in the ICU. In this study, the patients fed with MHLJDD, compared with the control group, demonstrated significant improvement in EN complications, such as intolerance to EN, gastric retention, and hyperglycemia, consistent with the results of Chen et al[24]. Other studies have shown[30,31] that in patients with MV in the ICU, 100% target caloric intake is not sufficient to significantly improve the life quality or functional outcome, or to increase the survival rate after 6 months,

Table 5

Nutrition-related complications in sepsis patients.

Characteristic	Control group (n = 42)	Intervention group (n = 44)	*P* value
Enteral nutrition tolerance score, mean ± SD	6.81 ± 4.28	4.68 ± 4.04	.020
Hyperglycemia, n (%)	25 (59.52%)	13 (29.55%)	.005
Hypoglycemia, n (%)	3 (7.14%)	5 (11.36%)	.760
Gastric residual volume (GRV > 250 mL), n (%)	12 (28.57%)	5 (11.36%)	.045
Upper gastrointestinal bleeding, n (%)	3 (7.14%)	4 (9.09%)	.717

SD = standard deviation.

compared with the levels acquired via 70% caloric intake. In the presented study, although MV and ICU stay were shorter in the intervention group than in the control group, the 60-d mortality rates and survival curves were not significantly different between the 2 groups. Nevertheless, significantly more patients achieved the early EN goal in the intervention group than in the control group. In the intervention group, the proportion of patients reaching 60% of the target calories by day 4 was higher, the time to reach the target calories during the early stage was shorter (4.5 d vs 7 d), and the accumulated proteins and calories during days 8 to 14 were more than in the control group. Consequently, the nutritional biochemical indices, such as ALB, PA, and TF, in the intervention group on day 7 were higher than those in the control group, and MV and ICU stay were significantly shorter in the intervention group than in the control group. Although these differences did not significantly influence the 60-d mortality rate, the intervention group had a trend of higher survival than the control group (Fig. 2), which might be related to the sample size, underlying conditions of the patients, or propensity of the patients to return to ICU after their initial discharge.

The immune defense and recovery ability of septic patients are severely impaired, and improvement of nutrition highly facilitates recovery from this disease even though the effect on long-term prognosis may be limited. Although we did not find a statistically significant difference between the 60-d mortality rates of the 2 groups, clinical practice has changed and there is increasing awareness of the necessity to prescribe sufficient nutritional support for critically ill patients.

This study has some limitations. As TCM treatment is based on syndrome differentiation, the treatment measures were changeable, and the treatment process was complicated, thus it is difficult to unify the results. The composition of TCM prescriptions is complex. Their exact mechanism of action is not fully understood, and the active ingredients of the drugs are not fully uncovered. In patients with critical illness, dietary management, intestinal microecology, and immune inflammatory mechanism all interact and work together. EN management was the only subject of this study. Another drawback of this study is the small sample size. The causal inference for the TCM intervention should be better informed with real-world data. Next, we can analyze the data of Zhang et al,[32] and with EHR big data, we can have thousands of patients with longitudinal data, which can help this TCM intervention.

5. Conclusions

MHLJDD facilitates septic patients to achieve the target EN, improves their overall nutritional status, and shortens their MV and ICU stay.

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