



Effect of Tongfu traditional Chinese medicine preparation on patients with septic gastrointestinal dysfunction: a systematic review and meta-analysis

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Background: Tongfu traditional Chinese medicine (TCM) preparation is a common alternative therapy for clinical treatment of patients with septic gastrointestinal dysfunction. In recent years, a number of randomized controlled trials (RCTs) have been conducted to verify the effectiveness of Tongfu TCM preparation in the treatment of sepsis gastrointestinal dysfunction, but all of them have been small sample studies, and the research conclusions have been controversial. Here, this study conducted a meta-analysis on the clinical efficacy of the treatment of septic gastrointestinal dysfunction with TCM preparation, to produce a more objective and comprehensive systematic review to guide clinical application.

To evaluate the efficacy and safety of Tongfu traditional Chinese medicine (TCM) preparation in the treatment of patients with septic gastrointestinal dysfunction.

Methods: Randomized controlled trials (RCTs) of Tongfu TCM preparation in the treatment of septic gastrointestinal dysfunction published before February 2021 were searched for in the Chinese databases China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedical Literature Disk (CBMdisc), and Chongqing VIP (CQVIP), and English databases PubMed, Web of Science, EBSCO, and The Cochrane Library. Meta-analysis was performed using RevMan 5.3 software, and funnel plots were drawn to evaluate the bias of literatures.

Results: A total of 22 RCTs involving 1,558 patients were included. There were 772 patients in the control group and 786 in the trial group. Meta-analysis results showed that: gastrointestinal dysfunction score [mean difference (MD) = -0.50, 95% confidence interval (CI): -0.61 to -0.38], Acute Physiology and Chronic Health Evaluation II (APACHE II) score (MD = -3.30, 95% CI: -3.73 to -2.86), and mortality (MD = 0.34, 95% CI: 0.25-0.47) in the experimental group were significantly lower than those in the control group, and the difference was statistically significant ($P < 0.001$). The funnel plot results showed that there was little possibility of publication bias.

Discussion: Tongfu TCM preparation can effectively improve the gastrointestinal function of patients with sepsis gastrointestinal dysfunction, prevent the deterioration of the disease, and reduce the mortality; however, more evidence is required to substantiate these findings.

Keywords: Tongfu; Chinese medicine preparation; sepsis; gastrointestinal dysfunction; meta-analysis

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Introduction

Sepsis is a life-threatening impairment of organ function caused by the dysregulation of host response triggered by infection. In essence, it is a systemic inflammatory response of the body to various infectious factors. With the further development of sepsis, multiple organ dysfunction syndrome (MODS) may occur, which is one of the main causes of death in critically ill patients (1). According to statistics, about 31.5 million patients worldwide experience sepsis every year, and about 19.4 million patients manifest severe sepsis, among whom 5.3 million patients die (2). In recent years, despite some progress having been made in organ functional support technology and anti-infective treatment of sepsis, the mortality is still as high as 30–70%, bringing a huge burden to the global medical and health system and social economy (3).

Gastrointestinal dysfunction is one of the common complications in patients with sepsis, and they are of mutual influence and causation. At present, it is generally believed that the gastrointestinal tract not only initiates the occurrence of sepsis, but is also a victim of sepsis. When sepsis occurs, the intestine is one of the most vulnerable organs, which can lead to gastrointestinal dysfunction, such as uncontrolled inflammation, ischemia and hypoxia, reperfusion injury, immunosuppression and intestinal flora disorders. At the same time, when gastrointestinal dysfunction occurs, its mucosal barrier is damaged. There are a large number of bacteria and endotoxins in the intestine that spread through the mucosal barrier to the tissues outside the intestine—bacteria translocate, which further damages various organs and causes a second blow, so a vicious circle is formed. In addition, intestinal infection caused by gastrointestinal injury can also induce sepsis, and if severe, it can lead to multiple organ dysfunction and even death (4,5). Therefore, effective prevention and treatment of gastrointestinal dysfunction is one of the keys to reduce the mortality of patients with sepsis. Traditional Chinese medicine (TCM) holds that the function of the stomach and intestines can be maintained when the Qi descends unimpededly. If communication between the upper and lower Qi is obstructed, stasis of hollow organ (Fu)-Qi can lead to gastrointestinal dysfunction, such as abdominal distension, constipation, gastric retention, and even vomiting reflux and other manifestations. Symptoms of gastrointestinal dysfunction in sepsis are mostly caused by adverse rising of the stomach-Qi and obstruction of Fu-Qi. Based on the theoretical tenet that “the fluency of the six-Fu indicates its usability, the descending Qi reflects the

fluency of the ascending and descending Qi pathways”, the treatment principle is mainly to dredge the Fu (6). Among the traditional Chinese medicine preparations for intestinal tract, the main drug is rhubarb, which is aimed at dredging qi of Fu-organ and subsiding reverse function. At the same time, drugs such as strengthening the body's vitality, warming yang and benefiting qi, attacking blood stasis in the body, clearing away heat and detoxifying are added to prevent excessive diarrhea, which injures the body's stomach and causes the spleen and stomach to be cold. It is recommended to replenish the righteous qi and attack the pathogens at the same time, adjust the qi and restore it to a relatively coordinated state, so as to achieve the effect of gastrointestinal detoxification. A meta-analysis showed that traditional Chinese medicine preparations for intestinal tract can reduce the hospital mortality of ARDS patients, shorten the mechanical ventilation time and ICU hospital stay, and improve the respiratory mechanics parameters (7). However, we have not yet found a meta-analysis on the effect of general traditional Chinese medicine preparations on patients with sepsis and gastrointestinal dysfunction. In recent years, a number of randomized controlled trials (RCTs) have been conducted to verify the effectiveness of Tongfu TCM preparation in the treatment of sepsis gastrointestinal dysfunction, but all of them have been small sample studies, and the research conclusions have been controversial. In order to further clarify the effectiveness of Tongfu TCM preparation in the treatment of sepsis gastrointestinal dysfunction, this study conducted a systematic evaluation of published RCTs on Tongfu TCM preparation in the treatment of septic gastrointestinal dysfunction. This study provides a reference for the prospect and future research of Tongfu TCM preparation in the treatment of sepsis gastrointestinal dysfunction. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-2461>).

Methods

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) research type: randomized controlled trial in English and Chinese; (II) participants: patients over 18 years of age with septic gastrointestinal dysfunction; (III) interventions: experimental group: Traditional Western medicine treatment combined with Tongfu TCM preparation, including Tongfu TCM decoction or preparation. Control

group: Western medicine conventional treatment but not including TCM treatment; (IV) Outcome: Main outcome: Gastrointestinal dysfunction score. Secondary outcome: (i) Acute Physiology and Chronic Health Evaluation II (APACHE II) score; (ii) mortality.

The exclusion criteria were as follows: (I) case report, animal experiment, treatment experience, literature review, retrospective study; (II) patients with primary gastrointestinal diseases, such as primary gastrointestinal motility disorders, gastrointestinal bleeding, gastrointestinal tumors, or a history of gastrointestinal surgery; (III) republished literature; (IV) the full text was unable to be obtained; (V) the original research data could not be extracted or was missing.

Literature retrieval strategy

We searched for RCTs of Tongfu TCM preparation in the treatment of septic gastrointestinal dysfunction published before February 2021 in the Chinese databases China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedical Literature Disk (CBMdisc), and Chongqing VIP (CQVIP), and the English databases PubMed, Web of Science, EBSCO, and The Cochrane Library. At the same time, manual retrieval was carried out for references in the included literatures to maximize the obtainment of relevant literatures. The retrieval was carried out by combining Medical Subject Headings (MeSH) with free words. Chinese database search terms included the following: tongfu, tongxia, xiexia, xiafa, enema, rhubarb, mirabilite, chengqi soup, traditional Chinese medicine, Chinese herbal medicine, sepsis, multiple organ dysfunction, multiple organ failure, acute gastrointestinal injury/gastrointestinal dysfunction, and so on. English database search words included: Tongfu, relax bowel, purgation, purgative, enema, rhubarb, mirabilite, dachengqi decoction, Chinese medicine, herbal, sepsis, MODS, acute gastrointestinal injury/gastrointestinal dysfunction, and so on.

Literature screening and data extraction

According to the inclusion and exclusion criteria, 2 researchers independently screened the literature, extracted the data, and filled in the information extraction form for cross-checking. If there was disagreement and it was unclear whether the literature should be included, resolution was sought through discussion or negotiation with a third

researcher. During literature screening, the title and abstract were read first. If the inclusion criteria were met, the full text was read to further determine inclusion. In the case of lacking important information, attempts were made to contact the original study author to provide additional information. Data extraction content included: (I) basic information of literature: title, first author, publication year, journal, and so on; (II) baseline characteristics and intervention measures of participants; (III) the key elements of literature quality evaluation; (IV) outcome indicators and outcome measurement data.

Literature quality assessment

The quality of the literature was independently evaluated by 2 investigators using the assessment tool of RCT risk of bias recommended by the Cochrane Manual, Version 5.3.0. After completion of the evaluation, the 2 researchers discussed and reached a consensus on the literature quality evaluation results. In case of disagreement, the 2 researchers engaged in discussion or negotiated with a third researcher to reach a consensus.

Statistical analysis

The software Rev Man 5.3 (ReviewManager 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaborative, 2014) was used for meta-analysis. Weighted number difference (MD) OR standard mean difference (SMD) were used as effect indexes for measurement data, and relative risk (RR) or odds ratio (OR) were used as effect indexes for enumeration data. Point estimates and 95% confidence interval (CI) were given for each effect size. The chi-square (χ^2) test was used to determine whether there was statistical heterogeneity among the included study results, and I^2 test was used to determine the magnitude of heterogeneity. If $P > 0.1$ and $I^2 < 50\%$, no statistical heterogeneity was considered, and a fixed-effect model was selected for meta-analysis. If $P < 0.1$ and $I^2 > 50\%$, statistical heterogeneity was considered, and further analysis of the source of heterogeneity was needed. After excluding the influence of obvious clinical heterogeneity, a random-effects model was selected for meta-analysis. When the clinical heterogeneity between the 2 studies is large, only descriptive analysis will be undertaken. To evaluate the effects of different observation time on pooled estimates, we performed a subgroup analysis stratified by observation time for outcomes with enough included studies. In this

work, a sensitivity analysis will be performed to assess the robustness of the results. In this work, we will conduct sensitivity analysis on gastrointestinal dysfunction score, APACHE II score, and mortality by changing different effect models and statistical methods. The difference between the re-obtained effects and the original effects will be compared. If the results of the Meta analysis cannot be substantially changed, it indicates that the stability and reliability of the Meta analysis are relatively good. When the number of included studies was ≥ 10 , funnel plots were used to determine whether there was publication bias. A P value < 0.05 was considered statistically significant.

Results

Literature retrieval results

A preliminary examination of 815 relevant literatures was conducted, including 778 studies in Chinese and 37 in English. After deletion of duplicate literatures by NoteExpress, 417 studies remained. According to the screening criteria, we read the titles and abstracts, which led to the exclusion of 311 literatures due them being reviews, animal experiments, and inconsistent with the topic, and initially included 106 literatures. After re-screening by reading the full text, 84 articles that did not meet the inclusion criteria were excluded, including repeated publication, non-RCTs, non-sepsis gastrointestinal dysfunction, non-Tongfu-type TCM preparations or Tongfu-type TCM preparations combined with other TCM treatment measures. A total of 22 articles were finally included. The flow chart of literature screening is shown in *Figure 1*.

The basic characteristics of the included studies and the results of bias risk assessment

The basic characteristics of the included studies are shown in *Table 1*. The results of bias risk assessment are shown in *Table 2*.

Meta-analysis results

Gastrointestinal dysfunction score

Among the included literatures, 15 reported the effects of Tongfu TCM preparations on the scores of gastrointestinal dysfunctions in patients with sepsis (8-11,13-16,21-23,25-27,29). A total of 1,214 participants

were included, including 616 in the experimental group and 598 in the control group. The results of meta-analysis showed that the score of gastrointestinal dysfunction in the experimental group was significantly lower than that in the control group (random-effects model, MD = -0.50, 95% CI: -0.61 to -0.38, $P < 0.001$). Subgroup analysis was conducted according to different observation time, and the results showed that no matter whether the intervention lasted for 3, 7, or 14 days, the score of gastrointestinal dysfunction in the experimental group was significantly lower than that in the control group, with statistically significant differences (*Figure 2*).

APACHE II score

Among the included literatures, 15 reported the effects of Tongfu TCM preparations on APACHE II score of patients with septic gastrointestinal dysfunction (9-16,21-23,25-27,29). A total of 1,461 participants were included, including 740 in the experimental group and 721 in the control group. The results of meta-analysis showed that the APACHE II score of the experimental group was significantly lower than that of the control group, and the difference was statistically significant (fixed effect model, MD = -3.30, 95% CI: -3.73 to -2.86, $P < 0.001$). Subgroup analysis was conducted according to different observation times, and the results showed that no matter whether the intervention lasted for 3, 5, 7, or 14 days, the APACHE II score of the experimental group was significantly lower than that of the control group, with statistically significant differences (*Figure 3*).

Mortality

Among the included literatures, 12 reported the effect of Tongfu TCM preparations on the mortality rate of patients with septic gastrointestinal dysfunction (10,11,13,16,18-22,24,27,29). A total of 997 participants were included, including 507 in the experimental group and 490 in the control group. The results of meta-analysis showed that the mortality of the experimental group was significantly lower than that of the control group, and the difference was statistically significant (fixed effect model, MD = 0.34, 95% CI: 0.25-0.47, $P < 0.001$). Subgroup analysis was conducted according to different observation time, and the results showed that the mortality of the experimental group was significantly lower than that of the control group at 14 or 28 days after intervention, with statistically significant differences (*Figure 4*).

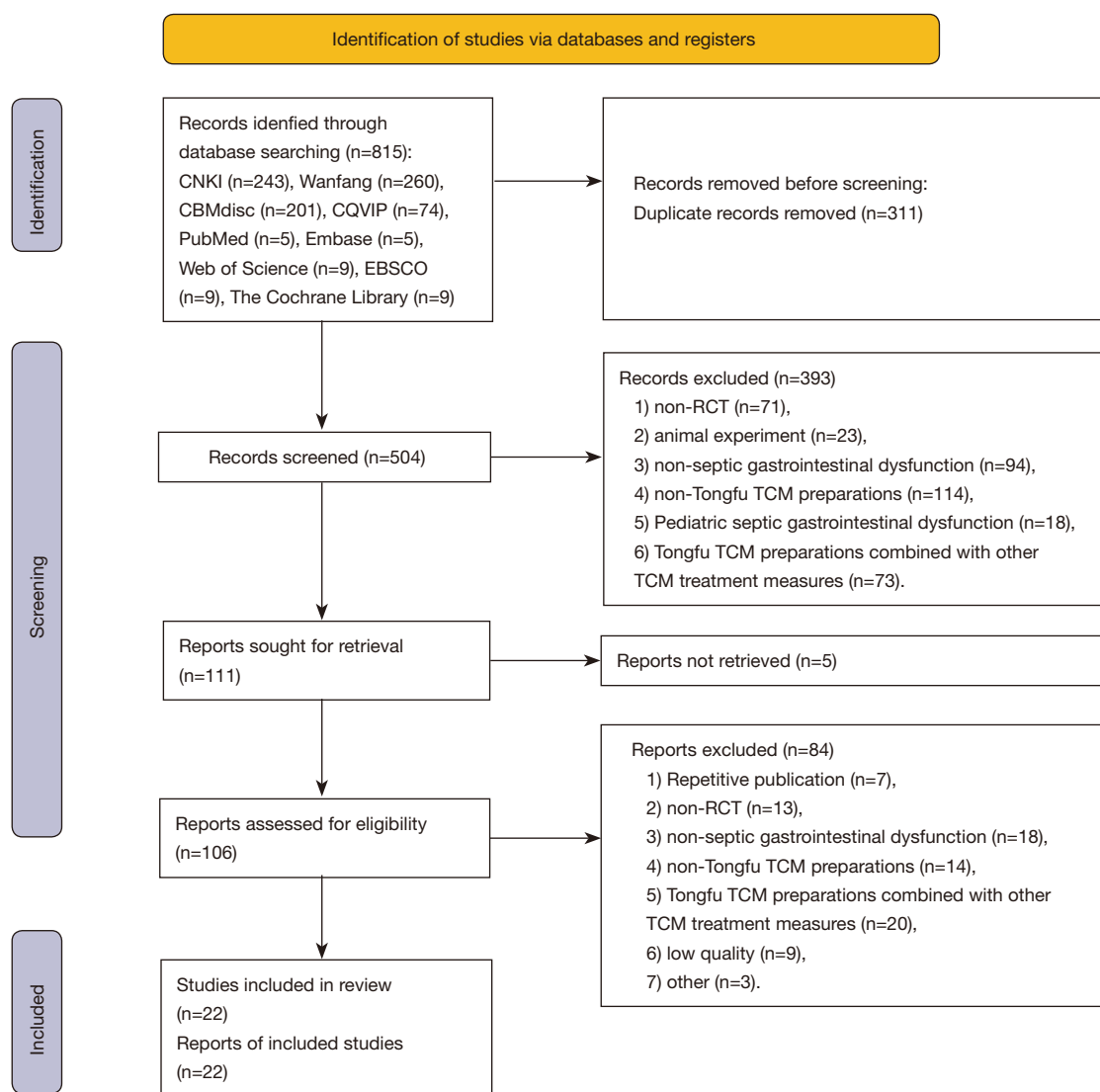


Figure 1 The flow chart of literature screening and results. RCT, randomized controlled trial; TCM, traditional Chinese medicine.

Sensitivity analysis and publication bias

Sensitivity analysis

The sensitivity analysis of gastrointestinal dysfunction score, APACHE II score, and mortality was carried out using the transformation effect model and different statistical methods. The results of the meta-analysis showed that the OR value, 95% CI, and P value were very similar before and after the sensitivity analysis, except for the statistical method before and after the APACHE II score conversion. Other results did not change significantly, suggesting that

the stability and reliability of the results were relatively good (Table 3).

Publication bias

Outcome indicators of ≥ 10 included literatures, such as gastrointestinal dysfunction score, APACHE II score, and case fatality rate, were evaluated by funnel plots. The funnel plot was inverted and fundamental symmetrical, and the distribution of each study site was relatively uniform, suggesting that there was little possibility of publication bias (Figures 5-7).

Table 1 Basic characteristics of included studies

Included studies (year)	Sample (C/T)	Gender (M/F)		Age (C/T, year)	APACHE II score (C/T, score)	Gastrointestinal function score (C/T, score)	Intervention	
		C	T				C	T
Zheng Fu, 2007, (8)	30/30	13/17	16/14	-	-	1.43±0.57/1.40±0.56	RT + glycerin enema	RT + Rhubarb liquorice soup RE
Xin Wang, 2007, (9)	19/21	11/8	15/6	62±15/59±16	18.73±1.44/17.95±2.14	2.42±0.76/2.38±0.47	RT + rectal NS infusion	RT+ Rectal infusion Yiqi tongfu decoction Qihuang concentrated liquid
Meili Duan, 2009, (10)	96/112	69/27	77/35	70.2±11.5/66.5±13.9	22.2±7.7/22.3±7.8	1.52±0.71/1.79±0.79	RT + mosapride PO/NF	RT+ Tongfu Granules PO/NF
Xi Chen, 2010, (11)	30/30	19/11	20/10	66.00±15.75/69.93±14.90	21.23±6.96/24.40±7.99	1.56±1.01/1.49±1.06	RT+ placebo PO/NF	RT+ Tongfu Granules PO/NF
Lan Li, 2012, (12)	49/49	-	-	-	23.3±10.7/23.9±9.6	-	RT+ rectal NS infusion	RT+ Tongfu and adjusting lung prescription
Wenjing Li, 2012, (13)	40/40	24/16	22/18	72.95±11.07/71.98±11.72	22.48±1.93/22.43±1.91	2.00±0.60/1.98±0.66	RT	RT+ banxia xiexin tang jiajian decoction
Chunmei Zhang, 2014, (14)	30/30	16/14	13/17	71.87±7.28/69.70±8.32	19.23±3.21/20.77±4.61	1.40±0.56/1.43±0.57	RT+ purified water NF	RT+Tongji and Gongxia Traditional Chinese Medicine
Zhengyun Tian, 2015, (15)	30/30	18/12	17/13	57.03±11.51/56.77±10.63	19.83±4.43/20.03±4.65	2.00±0.69/1.97±0.76	RT	Tiaoqi Tongfu and Xieme traditional prescription PO/NF
Yufeng Luo, 2015, (16)	30/30	16/14	13/17	51.28±14.05/51.51±13.96	20.52±6.18/20.03±7.72	2.37±0.62/2.28±0.43	RT + mosapride	RT + Flavoured rhubarb aconite soup PO/NF
Xiaodan Zheng, 2015, (17)	32/32	17/15	14/18	56.75±11.98/54.75±11.73	22.47±4.05/23.12±5.06	1.91±0.78/2.00±0.80	RT	RT + Tongjie oral solution PO/NF
Chunyan Jiang, 2015, (18)	40/40	35/5	34/6	83.93±4.51/84.69±3.92	15.52±3.40/16.33±2.35	-	RT	RT + Tongfu Granules
Qianying Wang, 2015, (19)	29/31	-	-	-	-	-	-	-
Dan Huang, 2016, (20)	34/33	-	-	67.59±18.01/69.97±11.15	20.35±5.08/23.15±6.03	1.41±0.70/1.85±1.00	RT	RT + Tongfu and Jiedu prescription granules PO/NF
Xusheng Wang, 2017, (21)	60/60	33/27	38/22	56.23±3.14/57.16±2.78	17.98±4.61/18.27±3.71	2.29±0.73/2.45±0.43	RT	RT + rhubarb aconite soup PO/NF

Table 1 (continued)

Table 1 (continued)

Included studies (year)	Sample (C/T)	Gender (M/F)		Age (C/T, year)	APACHE II score (C/T, score)	Gastrointestinal function score (C/T, score)		Intervention	
		C	T			C	T	C	T
Feibo Huang, 2018, (23)	24/25	13/11	12/13	66.67±11.43/63.80±12.79	-	1.92±0.97/1.84±0.97	RT	RT + Yiqi Wenyang Tongfu prescription PO/NF	
Zhiling Gao, 2018, (24)	35/35	25/10	24/11	73.72±10.81/74.58±10.66	-	-	RT	RT + Yiqi Tongfu prescription PO/NF	
Zengfeng Huang, 2019, (25)	30/30	17/13	18/12	56.70±9.10/57.30±8.60	25.10±6.20/25.30±6.00	2.40±0.60/2.30±0.70	RT	RT + Yiqi Huoxue Tongfu granules PO/NF	
Ke Sun, 2019, (26)	43/43	25/18	23/20	54.95±5.28/55.02±5.31	-	2.12±0.42/2.16±0.41	RT	RT + Tongfu Huayu soup PO/NF	
Fengqin Wei, 2019, (27)	25/25	14/11	13/12	74.28±5.29/74.76±4.26	19.24±5.32/20.56±4.51	2.44±0.71/2.60±0.58	RT	RT + Rhubarb aconite and small Chengqi soup PO/NF	
Weiwei Gao, 2019, (28)	29/30	15/14	17/13	72.14±10.43/72.33±10.72	-	-	RT	RT + Zenge Tongfu Zhuyu prescription enema	
Dan Guo, 2020, (29)	37/30	21/16	20/17	62.55±9.79/62.49±9.85	23.25±5.47/23.20±5.57	1.97±0.89/2.00±0.91	RT	RT + Tongfu and Jiedu prescription PO/NF	

RT, routine treatment; NS, normal saline; PO, per os; NF, nasal feeding; RE, retention enema.

Table 2 Risk of bias assessment for included studies

Included studies (year)	Random method	Allocation concealment	Blinding method	The integrity of the data (exit/lost to follow-up)	Selectively report research results	Other sources of bias
Zheng Fu, 2007, (8)	Unclear	Unclear	No	Unclear	Unclear	Unclear
Xin Wang, 2007, (9)	Unclear	Unclear	No	Unclear	Unclear	Unclear
Meili Duan, 2009, (10)	BRE	Unclear	No	Unclear	Unclear	Unclear
Xi Chen, 2010, (11)	CTM	Unclear	Double blind	Unclear	Unclear	Unclear
Lan Li, 2012, (12)	RNT	Unclear	No	Unclear	Unclear	Unclear
Wenjing Li, 2012, (13)	Unclear	Unclear	Single blind	Unclear	Unclear	Unclear
Chunmei Zhang, 2014, (14)	Computer	Unclear	No	Unclear	Unclear	Unclear
Zhengyun Tian, 2015, (15)	RNT	Unclear	No	Unclear	Unclear	Unclear
Yufeng Luo, 2015, (16)	RNT	Unclear	No	Unclear	Unclear	Unclear
Xiaodan Zheng, 2015, (17)	Unclear	Unclear	No	Unclear	Unclear	Unclear
Chunyan Jiang, 2015, (18)	RNT	Unclear	Double blind	Unclear	Unclear	Unclear
Qianying Wang, 2015, (19)	RNT	Unclear	No	Unclear	Unclear	Unclear
Dan Huang, 2016, (20)	RNT	Unclear	Single blind	Unclear	Unclear	Unclear
Xusheng Wang, 2017, (21)	RNT	Unclear	No	Unclear	Unclear	Unclear
Xionghui Li, 2017, (22)	Unclear	Unclear	No	Unclear	Unclear	Unclear
Feibo Huang, 2018, (23)	RNT	Unclear	No	Unclear	Unclear	Unclear
Zhiling Gao, 2018, (24)	SAS programming	An opaque envelope	No	Unclear	Unclear	Unclear
Zengfeng Huang, 2019, (25)	Unclear	Unclear	No	Unclear	Unclear	Unclear
Ke Sun, 2019, (26)	RNT	Unclear	No	Unclear	Unclear	Unclear
Fengqin Wei, 2019, (27)	Unclear	Unclear	No	Unclear	Unclear	Unclear
Weiwei Gao, 2019, (28)	RNT	Unclear	No	Unclear	Unclear	Unclear
Dan Guo, 2020, (29)	RNT	Unclear	No	Unclear	Unclear	Unclear

BRE, block random envelope method; RNT, random number table; CTM, coin toss method.

Discussion

Methodological quality of the included literatures

This study systematically analyzed RCTs on the effects of Tongfu TCM preparations on patients with septic gastrointestinal dysfunction. The literature quality was evaluated according to the RCT bias risk assessment tool recommended by the Cochrane Manual Version 5.3.0, which revealed that the overall literature quality needed to be improved. Prominent problems in research design included: in the generation of random assignment sequence, most of the studies did not give specific random methods; allocation scheme concealment was ignored in all study

designs, which could lead to selective bias; no studies had truly achieved the double-blind method between participants and interventionists, which may have resulted in measurement bias; most of the studies did not directly describe the situation of withdrawal or loss of follow-up, which may have led to loss of follow-up bias; most of the studies did not report the relevant information of adverse reactions, so safety analysis could not be conducted; the result report was not standardized; all the included studies were Chinese studies, which affected the generalizability of the analyzed results. These problems exist widely in TCM clinical studies, which affect the reproducibility and authenticity of the conclusions to some extent, and have

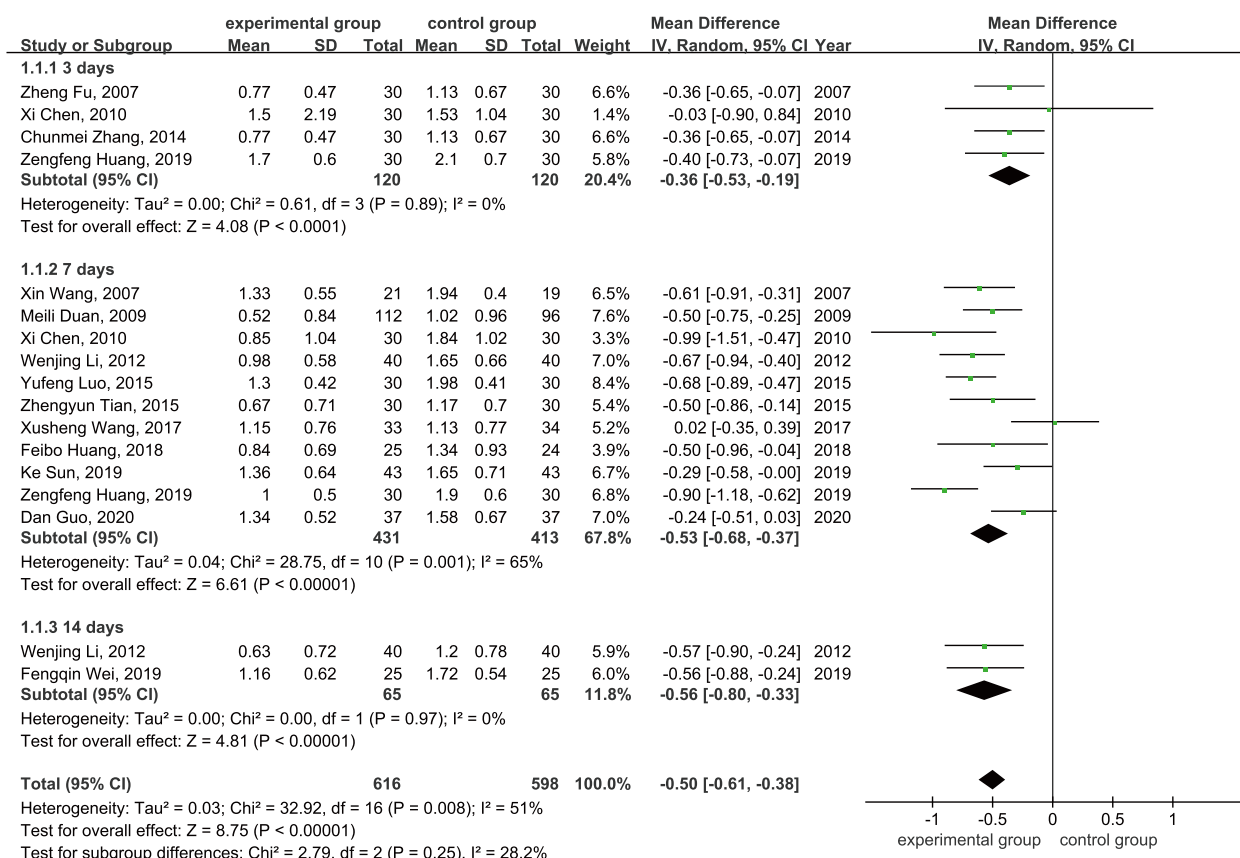


Figure 2 Influence of Tongfu TCM preparation on gastrointestinal dysfunction scores of patients with sepsis. TCM, traditional Chinese medicine; CI, confidence interval; SD, standard deviation.

been highlighted by international evidence-based medicine academics.

Effect of Tongfu TCM preparation on patients with septic gastrointestinal dysfunction

Pathogenic toxin can cause reverse and disordered qi movement in patients with sepsis; as a result, the spleen loses its ability in ascending clear, the stomach loses its ability in descending turbidity, and the lungs lose their ability in purification and descending. The lungs and the large intestine are both superficies and interior for each other. The lungs are zang-viscera, and the intestine is a fu-viscera; they are both superficies and interior for each other and can affect each other. When the lung qi descends, the transportation function of the intestines is normal; when the lung qi is reversed and ascends, the intestine experiences qi constipation and excessive heat, leading to the accumulation of pathogenic toxin, which will turn into

heat to consume and injure fluids; finally, the intestine loses its nutrition and the fu-viscera will be blocked, resulting in gastrointestinal dysfunction. The clinical manifestations of gastrointestinal dysfunction include abdominal distension, constipation, and little or no gas passing, which are quite similar to the distention, fullness, dryness, and excess of the syndrome of excess of Yangming fu-viscera in TCM (30). According to TCM, the six fu-viscera mainly function to transport and transform food and water, with urethral orifice and anus being the main channels for discharging turbid pathogen from human body. If the lung qi loses its function in purification and descending, it will be difficult to promote the discharge of turbid pathogen from the intestinal tract; accordingly, a large number of pathogenic toxin will gather in the intestinal tract, damage the intestinal tract, and make the latter become a new pathway for the invasion of pathogenic toxin. From the perspective of Western medicine, such a condition increases the abnormal reproduction of intestinal bacteria and the

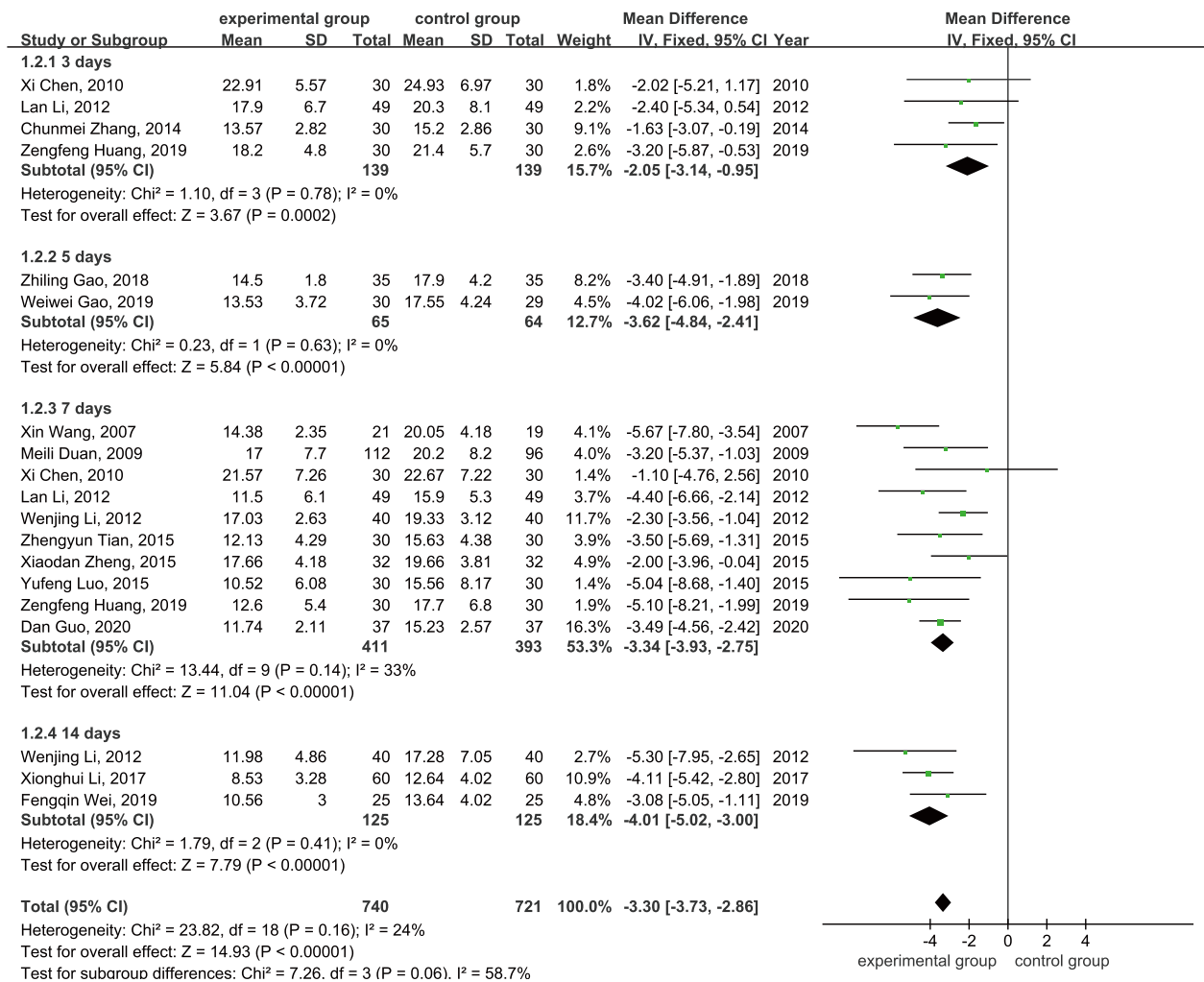


Figure 3 Influence of tongfu TCM preparation on APACHE II score of patients with septic gastrointestinal dysfunction. TCM, traditional Chinese medicine; CI, confidence interval; SD, standard deviation.

harmful effects of toxoids on the body, resulting in various complications or aggravating the primary disease (31). In TCM hospitals or clinics, Tongfu TCM preparations are often used after syndrome differentiation. Tongfu means dredging the qi in fu-viscera, regulating the visceral qi movement, and regulating the ascending and descending functions of the spleen and stomach, which corresponds to promoting gastrointestinal motor function, discharging toxic and harmful products, breaking the vicious cycle caused by toxin retention, improving intestinal microcirculation, reducing ischemia-reperfusion injury, regulating the internal environment of the human body, and thus preventing the worsening of the disease in modern medicine (32). Many studies (25,26,28) have demonstrated that Tongfu TCM

preparations, whenever administered orally, rectally, or by nasal feeding, can improve gastrointestinal dysfunction and reduce case-fatality rate in appropriately selected patients.

In our current Meta analysis, Tongfu TCM preparations were compared with conventional care in septic patients who have received routine treatment and nursing. The results showed that the gastrointestinal dysfunction score (MD = -0.50, 95% CI: -0.61 to -0.38), APACHE II score (MD = -3.30, 95% CI: -3.73 to -2.86), and mortality rate (MD = 0.34, 95% CI: 0.25-0.47) of the Tongfu TCM preparations group were significantly lower than those of the control group (all $P < 0.001$), suggesting that Tongfu TCM preparations can improve gastrointestinal function, prevent disease deterioration, and reduce mortality in

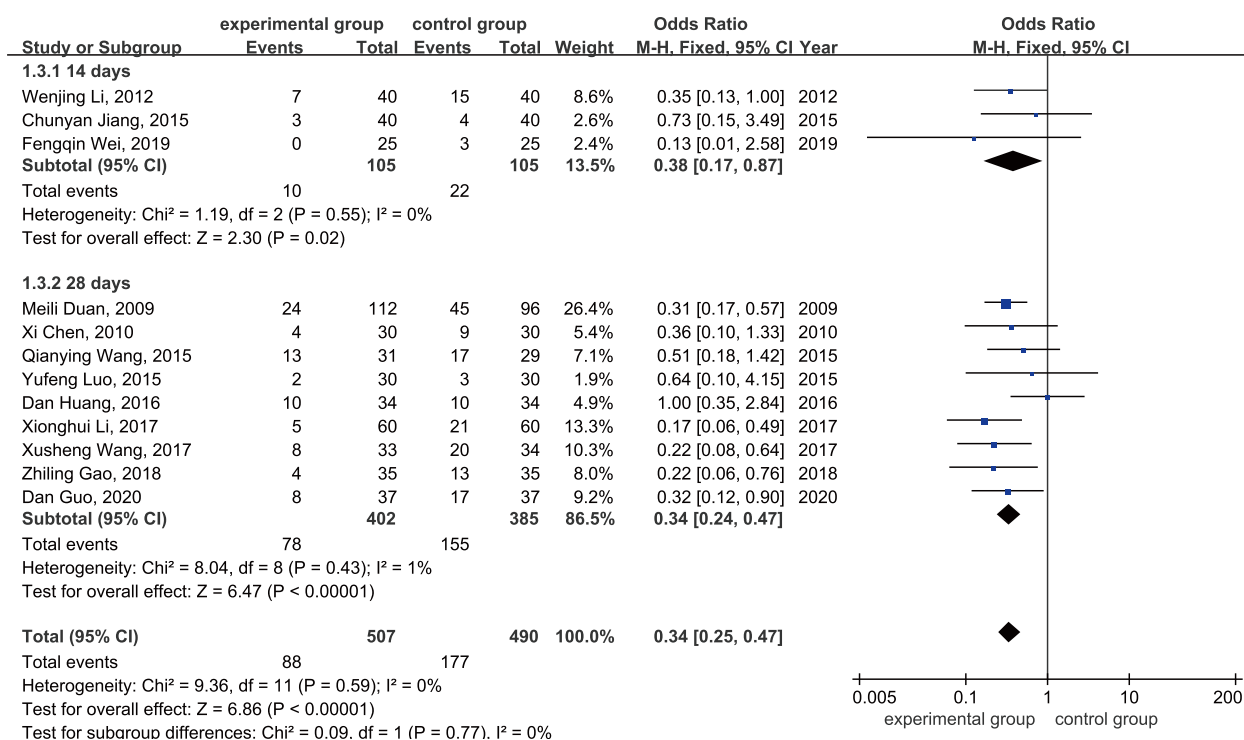


Figure 4 The effect of Tongfu TCM preparation on the mortality rate of patients with sepsis gastrointestinal dysfunction. TCM, traditional Chinese medicine; CI, confidence interval; SD, standard deviation.

Table 3 Sensitivity analysis of included references in the meta-analysis

Effect indicators	Statistical pattern		Effect model	
	Before the transformation	After the transformation	Before the transformation	After the transformation
Gastrointestinal dysfunction score	RE: MD (95% CI): -0.50 (-0.61 to -0.38)	RE: SMD (95% CI): -0.72 (-0.92 to -0.52)	RE: MD (95% CI): -0.50 (-0.61 to -0.38)	FE: MD (95% CI): -0.51 (-0.58 to -0.43)
APACHE II score	FE: MD (95% CI): -3.30 (-3.73 to -2.86)	FE: SMD (95% CI): -0.71 (-0.82 to -0.60)	RE: MD (95% CI): -3.33 (-3.86 to -2.81)	FE: MD (95% CI): -3.30 (-3.73 to -2.86)
Mortality	FE: OR (95% CI): 0.34 (0.25 to 0.47)	FE: RR (95% CI): 0.48 (0.38-0.59)	RE: OR (95% CI): 0.35 (0.25, 0.47)	FE: OR (95% CI): 0.34 (0.25 to 0.47)

SMD, standard mean difference; CI, confidence interval; SD, standard deviation; RR, relative risk; OR, odds ratio; RE, random effect; FE, fixed effect; APACHE II, Acute Physiology and Chronic Health Evaluation II.

patients with sepsis. This is consistent with the results of Zhang's research (14). It is possible that traditional Chinese medicine preparations for intestinal tract can help increase gastrointestinal motility, protect the intestinal mucosal barrier, prevent the retention and reproduction of bacteria or reduce the secretion of endotoxins, inhibit the occurrence of sepsis, and prevent gastrointestinal dysfunction from further developing into MODS, thereby reducing the fatality rate of patients with sepsis. It can

be seen that protecting the intestines is very important for improving the prognosis of patients with sepsis and increasing the success rate of treatment. This discovery is of great significance to the prevention and treatment of sepsis.

In the 22 articles included in this analysis, the Tongfu TCM preparations mentioned were mainly: (I) Tongfu and Fuzheng (i.e., strengthening vital qi) prescriptions; (II) preparations for supplementing qi and warming yang; (III) preparations for regulating qi and relieving heat;

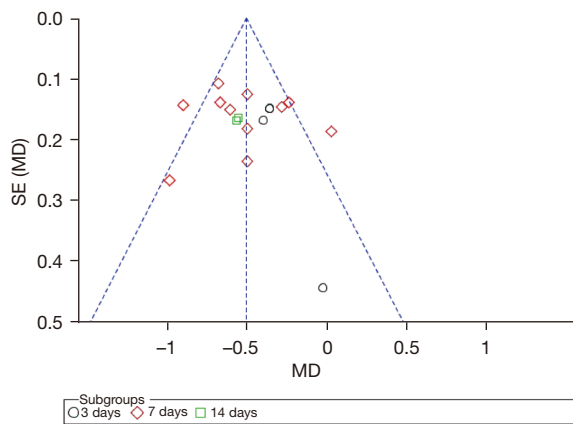


Figure 5 Funnel plot of gastrointestinal dysfunction score.

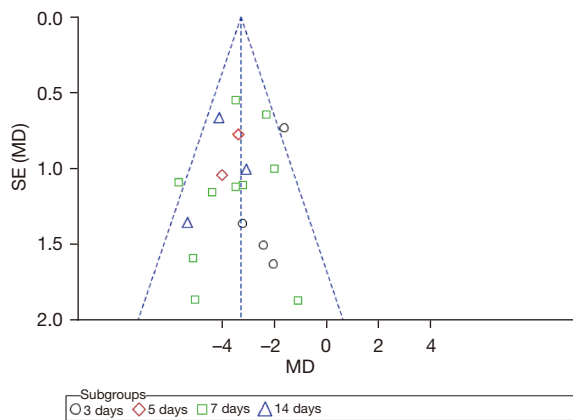


Figure 6 Funnel plot of APACHE II score.

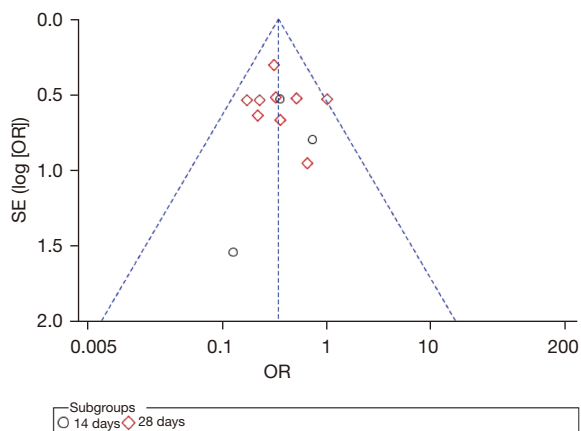


Figure 7 Funnel plot of mortality.

or (IV) preparations for promoting blood circulation, removing blood stasis, and detoxification. Rhubarb root and rhizome was the most commonly used medicine in these preparations (in up to 21 articles). Literature (33) has shown that rhubarb root and rhizome can protect the barrier function of intestinal mucosa and has a definite efficacy in treating gastrointestinal dysfunction in patients with sepsis. Therefore, rhubarb root and rhizome is widely used in clinical settings. However, rhubarb root and rhizome is a purgative and has certain toxicity, and it should be used with caution in patients with chronic diseases. Unfortunately, few articles included in our current analysis described the adverse reactions and drug safety, which should be addressed in future research.

Limitations of the study

There were still some limitations in this paper: (I) the high literature bias may have affected the evidence quality of the systematic evaluation. (II) All the included studies were published in Chinese, and the study sites were all in China. The lack of relevant data from international studies limits the generalizability of the results. (III) Most of the included studies had small sample sizes and low methodological quality, and there was a possibility of selective bias and measurement bias. In addition, only 1 study reported the concealment of random allocation scheme, so it was impossible to judge whether it had genuinely followed the RCT research method. (IV) In the literature collected in this article, there are some differences in the traditional Chinese medicine preparations for intestinal tract formulas, and their components are quite different, but the theory of traditional Chinese medicine is the same. We have not considered thoroughly in the research process, and will pay attention to and perfect the research in future.

In conclusion, Tongfu TCM preparations can effectively improve the gastrointestinal function of patients with septic gastrointestinal dysfunction, prevent the deterioration of the disease, and reduce the mortality, but there was not enough evidence to strongly support these findings. It was suggested that future clinical trials should be carried out according to the standard of RCTs and reported according to the Consolidated Standards of Reporting Trials (CONSORT) declaration, especially the generation of random sequences and the implementation of the allocation concealment

scheme. At the same time, it was recommended to use objective evaluation indicators as far as possible, to avoid the use of comprehensive indicators. We anticipate to more local and regional studies with large sample sizes to effectively control possible bias and improve the quality of evidence in related studies to better guide clinical decision-making.

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Footnote

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