Original Article

A systematic review and meta-analysis of treatment for hepatorenal syndrome with traditional Chinese medicine

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Background: Hepatorenal syndrome (HRS) is a life-threatening complication of end-stage liver diseases. It has been reported that traditional Chinese medicine (TCM) may improve liver function, delay disease progression, alleviate symptoms, and improve quality of life in HRS patients. The study aims to systematically review the efficacy of TCM for the treatment of HRS.

Methods: Publications were searched electronically from China National Knowledge Infrastructure (CNKI), Wanfang, VIP, PubMed, and EMBASE databases. Odds ratio (OR) and standardized mean difference (SMD) with 95% confidence interval (CI) were calculated. Heterogeneity was assessed. The Cochrane Collaboration's tool was used to assess the risk of bias.

Results: Fourteen randomized controlled trials involving 788 patients with HRS were included. Random generation sequence was reported in only two studies. Blinding was not used in any study. Compared to conventional treatment without TCM, TCM led to a significant survival benefit during hospitalization (OR: 0.18; 95% CI: 0.08–0.39; P<0.0001), a significantly higher complete response (OR: 3.20; 95% CI: 2.06–4.97; P<0.00001), and a significantly lower no response (OR: 0.20; 95% CI: 0.14–0.30; P<0.00001). Partial response was not significantly different between the two groups (OR: 1.39; 95% CI: 0.90–2.15; P=0.14). Regardless of TCM, blood urea nitrogen and abdominal circumference were significantly decreased, and urine volume was significantly increased after treatment. Compared to conventional treatment without TCM, TCM led to a significantly lower serum creatinine, blood urea nitrogen, bilirubin, plasma ammonia, and abdominal circumference and significantly higher urine volume after treatment. There was significant heterogeneity.

Conclusions: TCM might have a better survival and a higher complete response in patients with HRS. However, the quality of published studies was unsatisfactory.

Keywords: Traditional Chinese medicine (TCM); hepatorenal syndrome (HRS); response; liver function; renal function; terlipressin

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Introduction

Hepatorenal syndrome (HRS) is a lethal complication of end-stage liver diseases, which is a functional kidney injury developing as a consequence of the severe reduction in the renal perfusion secondary to splanchnic arterial vasodilation (1). HRS can occur spontaneously or is secondary to hypovolemia and bacterial infection (2,3). The prognosis of HRS remains dismal with a median survival time of approximately 3 months (4). Terlipressin, noradrenaline, midodrine, and octreotide have been used for the treatment of HRS (5-7), which can result in splanchnic vasoconstriction and then lead to an increase in effective circulating blood volume and renal blood flow (8,9).

According to the traditional Chinese medicine (TCM) theory, HRS, which is called as bulging, is caused by the "qi" stagnation, blood stasis, and phlegm-retained fluid. The current TCM expert consensus suggests that TCM may improve liver function, delay disease progression, alleviate symptoms, and improve quality of life in HRS patients (10).

A systematic review and meta-analysis aimed to evaluate the efficacy of TCM for the treatment of HRS.

Methods

Registration

The number of registration in PROSPERO was CRD42017076055.

Search strategy

Relevant publications were searched electronically from the China National Knowledge Infrastructure (CNKI), Wanfang, VIP, PubMed, and EMBASE databases. The search items were "hepatorenal syndrome", "traditional Chinese medicine", "herb", and "random". The date of last search was September 9, 2017.

Paper selection

The eligibility criteria included: (I) patients with HRS; (II) TCM with and without conventional therapy as the TCM group; (III) conventional therapy without TCM as the control group; (IV) randomized controlled trials (RCTs); and (V) studies reporting the efficacy of TCM.

Exclusion criteria were as follows: (I) duplicate publications; (II) reviews; (III) basic researches; (IV) systematic reviews and meta-analyses; (V) irrelevant topics; (VI) unable to extract the data regarding patients with HRS; and (VII) catalogues, indexes, and conference reports. No language and publication status were limited.

Data extraction

Primary data were extracted, including characteristics of studies, baseline characteristics of patients, response of HRS, and changes of biomedical variables after the treatment. The characteristics of studies were as follows: first author, study design, year of publication, region, enrollment period, number of patients in TCM/control group, methods of intervention, treatment period, and follow-up time. The characteristics of patients were as follows: age, gender, serum creatinine, blood urea nitrogen, bilirubin, urine volume, and abdominal circumference.

Risk of bias assessment

The Cochrane Collaboration's tool to assess the risk of bias was employed. It includes 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Endpoints

Outcomes of interest were: (I) the death of patients with HRS; (II) the response; and (III) the changes of biomedical variables. Response was divided into complete, partial, and no response according to the definitions established by original articles.

Statistical analysis

The meta-analyses were performed by the Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 12 (StataCorp, College Station, Texas, USA). Continuous data were expressed as mean ± standard deviation (SD). Random-effect model was employed. Odds ratio (OR) with 95% confidence interval (CI) was calculated for binary variables. Standardized mean difference (SMD) with 95%CI was calculated for continuous variables. $P<0.05$ was considered to indicate statistical significance. Heterogeneity was quantified using the Cochrane Q-test and the I^2 statistics. $P<0.1$ or $I^2>50\%$ was considered to indicate a statistically significant heterogeneity. Subgroup,

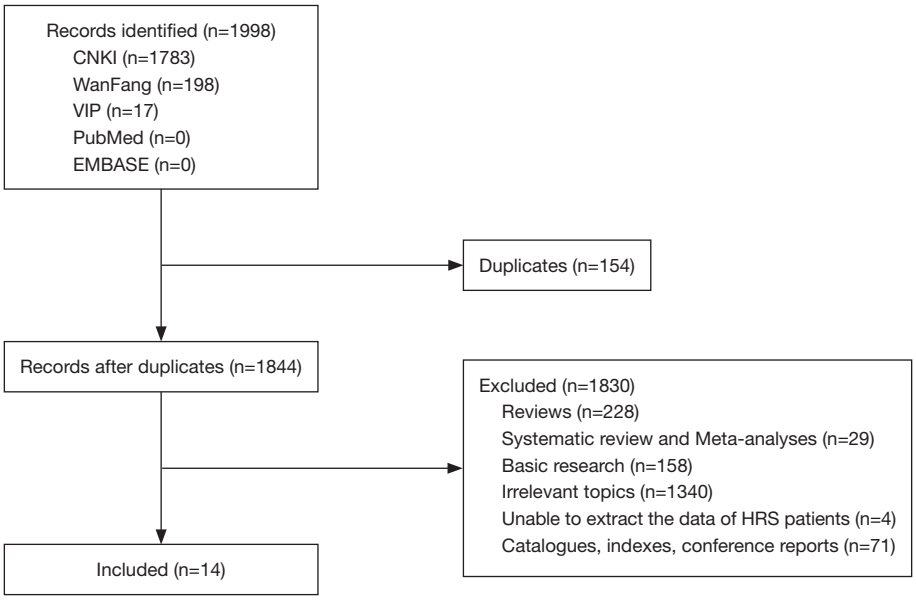

Figure 1 Flow chart of selection of publications.

sensitivity, and meta-regression analyses were used to analyze the source of heterogeneity. Subgroup analyses were performed according to the type of HRS and diagnostic criteria for HRS. As the number of included studies was ≥9, we conducted meta-regression analyses. In meta-regression analyses, the covariates included publication year, type of HRS, and diagnostic criteria for HRS.

Results

Characteristics of studies

A total of 1998 studies were identified. Fourteen studies were included (11-24) (*Figure 1*). The sample size ranged from 25 to 140. The publication year ranged from 2004 to 2017. The publication regions were all in China. Only two studies included patients with type 2 HRS alone, and others included patients with unclassified type of HRS. Characteristics of studies were summarized in *Table 1*. The diagnosis of HRS was based on the International Club of Ascites (ICA) in 7 studies or other diagnostic criteria in 5 studies and was unspecified in 2 studies.

Characteristics of patients

Age, gender, and urine volume were provided in 9 studies. Serum creatinine, blood urea nitrogen, and bilirubin were presented in 12, 11, and 5 studies, respectively. In 8 studies, the underlying liver disease was liver cirrhosis alone. In 3 studies, the underlying liver disease included liver cirrhosis, liver cancer, or severe hepatitis. In 3 other studies, the underlying liver disease remained unclear. Five studies provided information regarding etiology of liver disease. Viral hepatitis was the major etiology of liver disease followed by alcohol abuse. Characteristics of patients were summarized in *Table S1*.

Risk of bias

Only 2 studies reported the random sequence generation, of which one had a high risk and another had a low risk. All studies had low risks of attrition bias and reporting bias. Other risks of bias were unclear in most of studies (*Figure S1*).

Outcomes

Death

Six studies with 279 patients were included in the meta-analysis regarding in-hospital death (*Figure 2A*). TCM led to a significant survival benefit (OR: 0.18, 95% CI: 0.08–0.39, P<0.0001). There was no significant heterogeneity (P=0.18, I^2=32%).

Response

Ten studies with 685 patients were included in the meta-

Table 1 Characteristics of the included studies

Author [year]	Region	Study design	Enrollment period	Type of HRS	Number of patients included	Diagnostic criteria of HRS	Groups	Number of patients in control/ TCM (n)	Intervention method	Treatment time	Follow-up time
Chen LZ [2004]	Guangdong Province, Guangzhou	RCT	1998–2003	HRS	60	Diagnostic criteria revised by Shanghai National Viral Hepatitis Conference in 1990	Control [1]	23	Albumin intravenous injection; furosemide and dopamine intraperitoneal injection	7 days	2 months
							Control [2]	12	Albumin, furosemide and dopamine intravenous injection		
							TCM	25	Albumin and Danshen injection intravenous injection; furosemide and dopamine intraperitoneal injection		
Zou DG [2004]	Guangdong Province, Huizhou	RCT	1997–2003	HRS	62	Diagnosis of clinical disease basis and standards of cure and improvement	Control	30	Albumin; diuretic; antibiotics	28 days	NA
							TCM	32	Albumin; diuretic; antibiotics; phentolamine and ligustrazine injection intravenous injection; rhubarb hot water soak		
Wu GE [2007]	Shanxi Province, Luliang	RCT	2005–2007	HRS	38	NA	Control	18	Conventional treatment	28 days	NA
							TCM	20	Conventional treatment; colon dialysis machine; Changduqing granules retention enemas		
Gao H [2009]	Heilongjiang Province, Harbin	RCT	NA	HRS	38	International Ascites Club [1996]	Control	18	Antibiotics; furosemide and dopamine intravenous injection	14 days	NA
							TCM	20	Antibiotics; octreotide subcutaneous injection; Danhong injection and albumin (in need) intravenous injection		
Yan CW [2009]	Shanxi Province, Changzhi	RCT	2006–2008	HRS-2	25	International Ascites Club [1996]	Control	12	Albumin; diuretic	14 days	NA
							TCM	13	Albumin; diuretic; raw rhubarb, raw oyster shell, Daphne Genkwa retention enemas		
Tang RG [2011]	Jiangsu Province, Wuxi	RCT	NA	HRS	26	International Ascites Club [1996]	Control	12	Furosemide and dopamine intravenous injection	14 days	NA
							TCM	14	Prostaglandin E1 lipid microspheres agent intravenous injection; rhubarb hot water soak		

Table 1 (*continued*)

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Author [year]	Region	Study design	Enrollment period	Type of HRS	Number of patients included	Diagnostic criteria of HRS	Groups	Number of patients in control/ TCM (n)	Intervention method	Treatment time	Follow-up time
Xiao Q [2012]	Jiangsu Province, Nanjing	RCT	2007–2011	HRS	57	International Ascites Club [1996]	Control	28	Albumin; diuretic; antibiotics; vasodilators; alprostadil intravenous injection	21 days	NA
							TCM	29	In addition to the above interventions there was a TCM decoction including Radix Aconiti Carmichaeli, Cinnamon, Morinda Officinalis, Indian Buead, Concha Ostreae, Semen Cuscutae, Largehead Atractylodes Rhizome, Ligustrum lucidum Ait, the fruit of Chinese wolfberry, Oriental Waterplantain Rhizome and Plantain Seed		
Xing YM [2012]	Hebei Province, Xuchang	RCT	2008–2011	HRS	56	International Ascites Club	Control	28	Albumin, furosemide and dopamine intravenous injection	10 days	3 months
							TCM	28	In addition, TCM enema included: Raw Rhubarb, Radix Astragali, Salvia Miltiorrhiza Bunge, Safflower, Chuanxiong, Largehead Atractylodes Rhizome, Angelica sinensis and Indian Buead		
Zhu CQ [2012]	Jiangsu Province, Huaian	RCT	2007–2011	HRS	55	Diagnosis of clinical disease basis and standards of cure and improvement	Control	27	Diuretic; antibiotics; octreotide intravenous injection	7 days	NA
							TCM	28	In addition to the above interventions there was a TCM external application including Garlic and Mirabilite		
Tang G [2013]	Tianjin	RCT	2011–2012	HRS	50	International Ascites Club [2007]	Control	25	Albumin; diuretic	21 days	NA
							TCM	25	In addition to the above interventions there was a TCM decoction including Radix Astragali, Salvia Miltiorrhiza Bunge, Chinese Thorowax Root, Chinese Angelica, White Peony Root, Frucus Aurantii, Largehead Atractylodes Rhizome, Medicinal Indianmulberry Root, Fructus Amomi and Liquoric Root		

Table 1 (*continued*)

Table 1 (*continued*)

Author [year]	Region	Study design	Enrollment period	Type of HRS	Number of patients included	Diagnostic criteria of HRS	Groups	Number of patients in control/ TCM (n)	Intervention method	Treatment time	Follow-up time
Xia LM [2013]	Heilongjiang Province, Daqing	RCT	2008–2010	HRS-2	25	International Ascites Club [1996]	Control	12	Albumin; diuretic	14 days	NA
							TCM	13	Albumin; diuretic; alprostadil injection and Radix Astragali injection intravenous injection		
Qie LX [2014]	Hebei Province, Shijiazhuang	RCT	2011–2013	HRS	74	Internal medicine	Control	37	Diuretic; dopamine intravenous injection	30 days	NA
							TCM	37	In addition to the above interventions there was a TCM enema including Rhubarb, Salvia Miltiorrhiza Bunge, Cassia Twig, Calcined Oyster Shell, Snow of june herb, Safflower, Largehead Atractylodes Rhizome and Pinellia Tuber		
Luo B [2016]	Shanxi Province, Baoji	RCT	2015–2016	HRS	80	NA	Control	40	Albumin; diuretic; antibiotics; vasodilators; octreotide subcutaneous injection	14 days	NA
							TCM	40	In addition to the above interventions there was a Danhong injection		
Zou YZ [2017]	Heilongjiang Province, Heihe	RCT	2015–2016	HRS	140	Diagnosis of clinical disease basis and standards of cure and improvement	Control	68	Albumin; diuretic; antibiotics	28 days	NA
							TCM	72	In addition to the above interventions there was a TCM decoction including Rhubarb, Salvia Miltiorrhiza Bunge, Turmeric, Red Paeony Root, Largehead Atractylodes Rhizome, Cogongrass Rhizome, Oriental Waterplantain Rhizome, Panax Notoginseng, Indian Buead Peel, Radix Aconiti Carmichaeli and Coix Seed		

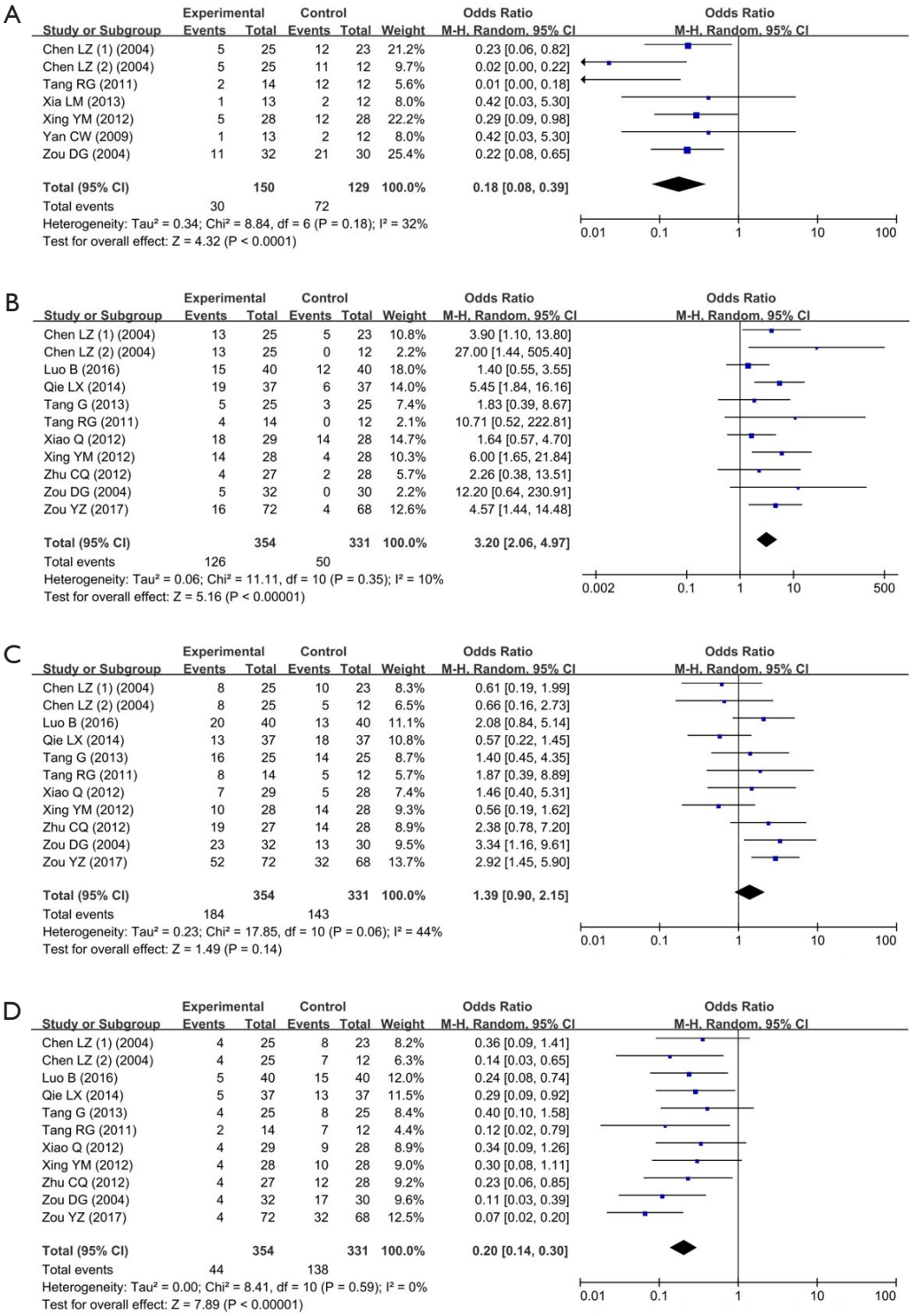

Figure 2 Summary of pooled results regarding death and response. (A) meta-analysis regarding in-hospital death; (B) meta-analysis regarding complete response; (C) meta-analysis regarding partial response; (D) meta-analysis regarding no response.

Table 2 Summary of pooled results regarding biochemical and clinical variables

Variable	Studies included (n)	Patients included (n)	SMD	95% CI	Significance, P	Heterogeneity	
						P	I^2
Serum creatinine							
After treatment, TCM *vs.* control	10	462	–1.78	–2.78, –0.78	0.0005	<0.00001	95%
TCM, before *vs.* after	10	474	–2.56	–3.60, –1.52	<0.00001	<0.00001	95%
Control, before *vs.* after	10	456	–0.77	–1.49, –0.05	0.04	<0.00001	92%
Blood urea nitrogen							
After treatment, TCM *vs.* control	9	407	–1.79	–2.87, –0.70	0.001	<0.00001	95%
TCM, before *vs.* after	9	420	–2.26	–3.24, –1.27	<0.00001	<0.00001	93%
Control, before *vs.* after	9	400	–0.77	–1.53, 0.00	0.005	<0.00001	92%
Bilirubin							
After treatment, TCM *vs.* control	6	257	–1.77	–2.86, –0.67	0.002	<0.00001	92%
TCM, before *vs.* after	6	266	–3.66	–5.89, –1.42	0.001	<0.00001	97%
Control, before *vs.* after	6	254	–1.4	–2.99, 0.18	0.08	<0.00001	96%
Urine volume							
After treatment, TCM *vs.* control	9	400	2.95	1.07, 4.83	0.002	<0.00001	97%
TCM, before *vs.* after	9	410	4.72	3.12, 6.33	<0.00001	<0.00001	95%
Control, before *vs.* after	9	396	3.51	1.81, 5.22	<0.0001	<0.00001	97%
Plasma ammonia							
After treatment, TCM *vs.* control	2	64	–4.83	–7.72, –1.95	0.001	0.005	87%
TCM, before *vs.* after	2	68	–5.02	–8.32, –1.71	0.003	0.001	90%
Control, before *vs.* after	2	60	–0.22	–0.73, 0.29	0.39	0.34	0%
Abdominal circumference							
After treatment, TCM *vs.* control	3	180	–0.57	–1.54, 0.40	0.25	<0.0001	90%
TCM, before *vs.* after	3	180	–1.79	–2.87, –0.72	0.001	0.0001	89%
Control, before *vs.* after	3	180	–1.04	–1.35, –0.73	<0.00001	0.83	0%

SMD, standardized mean difference; CI, confidence interval; TCM, traditional Chinese medicine.

analyses regarding response.

TCM led to a significantly higher complete response (OR: 3.20, 95% CI: 2.06–4.97, P<0.00001). There was no significant heterogeneity (P=0.35, I^2=10%) (*Figure 2B*).

The rate of partial response was not significantly different between TCM and control groups (OR: 1.39, 95% CI: 0.90–2.15, P=0.14). There was a mild heterogeneity (P=0.06, I^2=44%) (*Figure 2C*).

TCM led to a significantly lower no response (OR: 0.20, 95% CI: 0.14–0.30, P<0.00001). There was no significant heterogeneity (P=0.59, I^2=0%) (*Figure 2D*).

Biomedical and clinical variables

The results of meta-analyses regarding biomedical and clinical variables were summarized in *Table 2*.

Serum creatinine, blood urea nitrogen, bilirubin, urine volume, plasma ammonia, and abdominal circumference were significantly improved in TCM group. Serum creatinine, blood urea nitrogen, urine volume, and abdominal circumference were also significantly improved in control group. TCM led to a significantly better improvement in terms of serum creatinine, blood urea nitrogen, bilirubin, urine volume, plasma ammonia, and

abdominal circumference. In most meta-analyses regarding biomedical and clinical variables, there was significant heterogeneity.

Subgroup analyses

The results of subgroup analyses were summarized in *Table S2*.

The subgroup analyses of HRS-1 patients were unavailable due to the absence of relevant data.

The subgroup analyses of HRS-2 patients demonstrated that TCM led to a significantly better improvement in terms of serum creatinine, blood urea nitrogen, and urine volume, and there was statistical significance. There was no significant heterogeneity.

The subgroup analyses of HRS patients diagnosed based on ICA criteria demonstrated that TCM led to a significantly better improvement in terms of serum creatinine, blood urea nitrogen, bilirubin, and urine volume. Heterogeneity remained significant.

Sensitivity analyses

The results of sensitivity analyses were summarized in *Table S3*. Heterogeneity remained significant.

Meta-regression

The results of meta-regression analyses were summarized in *Table S4*.

Heterogeneity in the meta-analysis regarding serum creatinine in the control group was related to the publication year (P=0.022). Heterogeneity in the meta-analysis regarding serum creatinine in the TCM group was not related to the publication year, type of HRS, or diagnostic criteria for HRS. Heterogeneity in the meta-analyses regarding blood urea nitrogen and urine volume was not related to the publication year, type of HRS, or diagnostic criteria for HRS.

Discussion

The present analysis shows that TCM treatment significantly improved the survival and response of patients with HRS compared with conventional treatment. In addition, serum creatinine, blood urea nitrogen, urine volume, and abdominal circumference were improved irrespective of TCM. Finally, the improvement of serum creatinine, blood urea nitrogen, bilirubin, urine volume, serum ammonia, and abdominal circumference was significantly better in TCM group.

China has a long history of TCM application. The theory of TCM is primarily based on the ancient Chinese philosophy. TCM can cure diseases by correcting the maladjustments and restoring self-regulation ability (25). Among the included studies, 7 applied rhubarb (12,13,15,16,18,22,24), 7 applied Salvia Miltiorrhiza Bunge (11,14,18,20,22-24), and 2 applied Ligusticum Wallichii (12,18) in TCM group.

Rhubarb has defecation-accelerating, heat-clearing, blood-cooling, toxin-relieving, blood stasis-dredging, dampness-dredging, jaundice-resolving effects according to the Chinese Pharmacopoeia. Rhubarb in the colon can regulate intestinal flora and reduce intestine-derived uremic toxins produced by gut bacteria (26). Rhubarb has a cathartic effect on accelerating the excretion of intestinal toxins, reducing the absorption of toxins, and preventing from liver and kidney damage (27).

Salvia Miltiorrhiza Bunge has a role in blood circulation-promoting, blood stasis-dredging, blood-nourishing, and mind-tranquilizing according to the Chinese Pharmacopoeia. Salvia Miltiorrhiza Bunge has a protective effect on the liver and kidney. Animal study showed that the anti-inflammatory properties of Salvia Miltiorrhiza Bunge extracts might prevent hepatocyte injury possibly by the inhibition of p38 and nuclear factor ĸB signaling in Kupffer cells (28). Salvia Miltiorrhiza Bunge extracts can significantly improve blood urea nitrogen levels associated with impaired renal function and improve renal structural changes (29).

Ligusticum Wallichii has a role in blood circulation-promoting, blood stasis-dredging, "qi" stagnation-regulating, pain-alleviating, and dampness-dredging. The mechanism of blood-activating and stasis-resolving medicine on renal hemodynamics is mainly manifested on the levels of vasomotor factors and the action of renin-angiotensin, prostaglandins, endothelin, and nitric oxide (30).

Tetramethylpyrazine is an alkaloid found in the roots of Ligusticum Wallichii, which includes the function of anti-inflammation, anti-oxidation, anti-atherosclerosis, and anti-fibrosis. Tetramethylpyrazine plays a protective role in hepatic and renal injury caused by ischemia-reperfusion by inhibiting the adhesion and activation of neutrophils mediated by P-selection and the interaction of neutrophils and endothelium (31).

Except for intravenous injection, oral, and external application, enema is also a major route of TCM among the included studies, which can improve the intestinal environment and reduce the production and absorption of

enterotoxin (10).

There were some limitations in our study. First, although the studies included in the meta-analysis were reported as RCTs, the study quality was poor. The same situation was reported by Teschke *et al.* (32). Second, the sample size of each included study was relatively small. Third, the diagnostic criteria of HRS were inconsistent among the included studies. Fourth, the type of HRS was unspecified in some studies. Fifth, all the publication regions were in China. Sixth, the heterogeneity was mostly significant in the meta-analyses regarding biochemical and clinical variables. Despite subgroup analysis, sensitivity analysis, and meta-regression analysis were performed, the source of heterogeneity was not well explained. Seventh, only two included studies provided the follow-up time. One study reported that the follow-up time was 2 months. Another study reported that the follow-up time was 3 months. Therefore, it was impossible to explore the effects of follow-up times on the outcomes.

In conclusions, TCM may be effective for the treatment of HRS. However, our conclusions are hardly generalizable until more well-designed RCTs are performed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

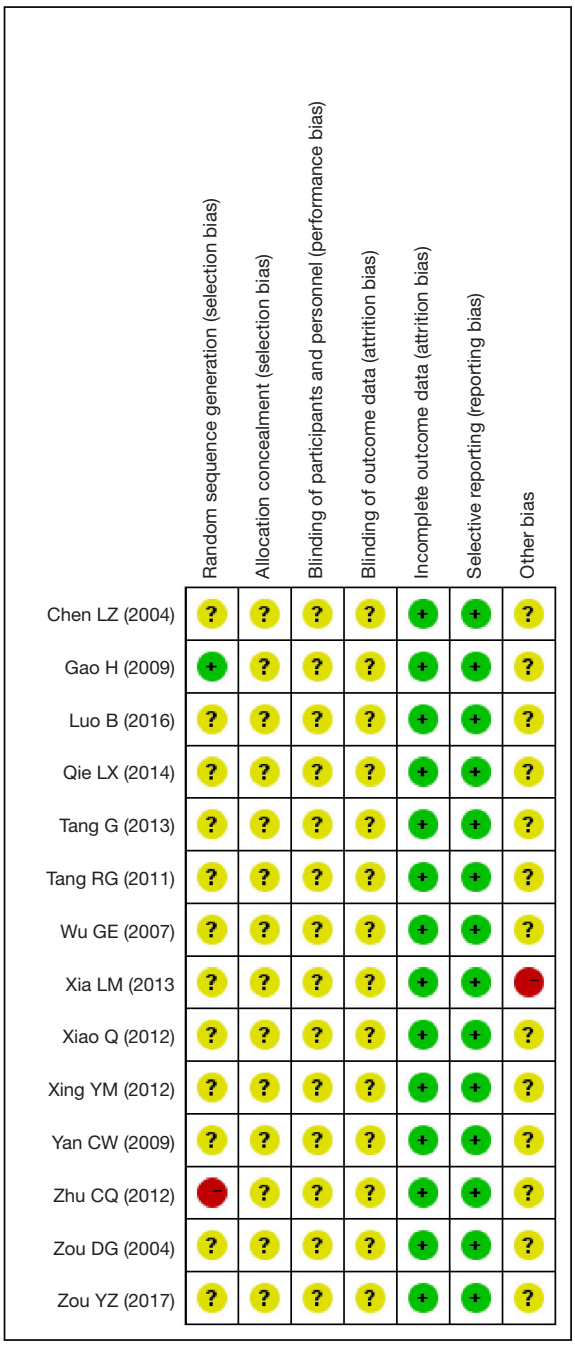

Figure S1 Risk of bias assessment.

Table S1 Characteristic of the included patients

Author [year]	Groups	Age	Gender (man/female)	Serum creatinine (μmol/L)	Blood urea nitrogen (mmol/L)	Bilirubin (μmol/L)	Urine volume (mL/24 h)
Chen LZ [2004]	Control [1]	Mean ± SD: 45±2.2	18/5	Mean: 176	Mean: 29.1	NA	NA
	Control [2]	Mean ± SD: 46±1.1	9/3	Mean: 205	Mean: 27.3	NA	NA
	TCM	Mean ± SD: 43±1.5	16/9	Mean: 196	Mean: 26.8	NA	NA
Zou DG [2004]	Control	Range: 31–71	26/4	NA	NA	NA	NA
	TCM	Range: 28–69	28/4	289.09±15.02	25.23±4.26	NA	NA
Wu GE [2007]	Control	NA	NA	818.3±108.5	796.7±106.1	NA	NA
	TCM	NA	NA	825.2±104.5	38.4±6.7	NA	NA
Gao H [2009]	Control	NA	NA	174.15±15.38	15.93±2.59	NA	484.31±132.69
	TCM	NA	NA	182.07±37.12	15.51±3.12	NA	512.43±144.22
Yan CW [2009]	Control	NA	NA	147.06±54.31	17.05±3.21	103.25±92.23	583.21±189.25
	TCM	NA	NA	154.08±47.70	16.30±4.08	108.83±90.79	652.21±135.37
Tang RG [2011]	Control	Mean: 51; range: 30–70	9/3	463.56±106.31	21.69±4.31	59.61±29.12	583.63±133.21
	TCM	Mean: 48.5; range: 28–69	10/4	416.23±53.18	20.93±4.13	93.84±30.14	586.34±130.12
Xiao Q [2012]	Control	Mean: 44.7	18/10	235.7±63.2	20.9±5.3	96.3±4.7	492.5±142.6
	TCM	Mean: 42.1	20/9	236.8±67.5	21.4±5.8	97.6±5. 6	488.6±135.7
Xing YM [2012]	Control	Mean ± SD: 46±1.1	16/12	NA	NA	NA	440.31±40.51
	TCM	Mean ± SD: 43±1.5	18/10	NA	NA	NA	450.50±30.57
Zhu CQ [2012]	Control	NA	NA	189.40±72.25	NA	NA	484±162
	TCM	NA	NA	198.39±57.43	NA	NA	451±170
Tang G [2013]	Control	Mean: 53.7	20/5	226±43	21.6±5.2	71.1±7.9	483±19
	TCM	Mean: 54.2	18/7	218±54.2	22.7±4.9	75.9±8.7	471±18
Xia LM [2013]	Control	NA	NA	146±53.98	16.15±3.32	NA	579±188.95
	TCM	NA	NA	153.9±47.9	16.29±4.18	NA	652±135.41
Qie LX [2014]	Control	Mean ± SD: 54.4±3.8	22/15	154.01±50.45	17.08±3.24	NA	451.11±32.45
	TCM	Mean ± SD: 52.8±3.2	20/17	147.11±54.23	17.10±3.33	NA	440.51±40.48
Luo B [2016]	Control	Mean ± SD: 56.22±6.02	21/19	111.89±4.54	11.03±0.82	145.72±23.98	NA
	TCM	Mean ± SD: 55.92±5.83	24/26	113.22±4.82	10.32±0.73	142.39±22.47	NA
Zou YZ [2017]	Control	Mean:36.5; range:27–71	44/24	NA	NA	NA	NA
	TCM	Mean:38.5; range:23–74	40/32	NA	NA	NA	NA

TCM, traditional Chinese medicine; SD, standard deviation; NA, not available.

Table S2 Subgroup analyses regarding biomedical variables

Variable	Studies included (n)	Patients included (n)	SMD	95% CI	Significance, P	Heterogeneity	
						P	I^2
Subgroup analyses of HRS-2 patients							
Serum creatinine							
After treatment, TCM *vs.* control	2	50	–0.416	–1.016, 0.184	0.174	0.981	0.0%
TCM, before *vs.* after	2	50	–0.946	–1.534, –0.359	0.002	0.983	0.0%
Control, before *vs.* after	2	50	–0.199	–0.794, 0.396	0.512	0.999	0.0%
Blood urea nitrogen							
After treatment, TCM *vs.* control	2	50	–0.669	–1.280, –0.058	0.032	0.997	0.0%
TCM, before *vs.* after	2	50	–0.951	–1.539, –0.364	0.002	0.993	0.0%
Control, before *vs.* after	2	50	–0.343	–0.941, 0.256	0.262	0.727	0.0%
Bilirubin							
After treatment, TCM *vs.* control	2	50	–0.404	–1.004, 0.196	0.187	0.989	0.0%
TCM, before *vs.* after	2	50	–0.520	–1.085, 0.045	0.071	0.879	0.0%
Control, before *vs.* after	2	50	–0.228	–0.824, 0.367	0.453	0.982	0.0%
Urine volume							
After treatment, TCM *vs.* control	2	50	2.488	1.682, 3.294	0.001	0.963	0.0%
TCM, before *vs.* after	2	50	2.505	1.750, 3.260	0.001	0.967	0.0%
Control, before *vs.* after	2	50	–0.003	–0.596, 0.590	0.992	0.992	0.0%
Subgroup analyses of diagnosis criteria based on ICA							
Serum creatinine							
After treatment, TCM *vs.* control	6	215	–1.591	–2.435, –0.747	0.001	0.001	85.1%
TCM, before *vs.* after	6	154	–2.029	–2.875, –1.183	0.001	0.001	84.2%
Control, before *vs.* after	6	107	–0.295	–0.836, 0.247	0.287	0.003	72.2%
Blood urea nitrogen							
After treatment, TCM *vs.* control	6	215	–1.792	–2.546, –1.039	0.001	0.001	80.2%
TCM, before *vs.* after	6	114	–1.931	–2.548, –1.314	0.001	0.004	71.4%
Control, before *vs.* after	6	95	–0.225	–0.498, 0.048	0.106	0.561	0.0%
Bilirubin							
After treatment, TCM *vs.* control	5	177	–1.843	–3.346, –0.341	0.016	0.001	93.4%
TCM, before *vs.* after	5	94	–3.258	–5.543, –0.972	0.005	0.001	96.4%
Control, before *vs.* after	5	89	–0.801	–2.103, 0.501	0.228	0.001	93.0%
Urine volume							
After treatment, TCM *vs.* control	7	271	4.037	2.524, 5.550	0.001	0.001	93.2%
TCM, before *vs.* after	7	142	5.096	3.098, 7.093	0.001	0.001	95.3%
Control, before *vs.* after	7	135	2.191	0.663, 3.718	0.005	0.001	95.7%

SMD, standardized mean difference; CI, confidence interval; HRS, hepatorenal syndrome; TCM, traditional Chinese medicine; ICA, International Club of Ascites.

Table S3 Sensitivity analyses regarding biomedical variables

Variable	Studies included (n)	Patients included (n)	SMD	95% CI	Significance, P	Heterogeneity	
						P	I^2
Serum creatinine							
After treatment, TCM *vs.* control	9	382	–1.30	–2.07, –0.53	0.0009	<0.00001	91%
TCM, before *vs.* after	9	394	–1.78	–2.48, –1.07	<0.00001	<0.00001	88%
Control, before *vs.* after	9	376	–0.39	–0.74, –0.04	0.03	0.005	63%
Blood urea nitrogen							
After treatment, TCM *vs.* control	8	333	–2.11	–2.91, –1.30	<0.00001	<0.00001	87%
TCM, before *vs.* after	8	340	–1.74	–2.41, –1.06	<0.00001	<0.00001	85%
Control, before *vs.* after	8	320	–0.37	–0.73, –0.02	0.04	0.02	57%
Bilirubin							
After treatment, TCM *vs.* control	5	207	–1.34	–2.34, –0.35	0.008	<0.00001	89%
TCM, before *vs.* after	5	208	–2.51	–4.49, –0.53	0.01	<0.00001	96%
Control, before *vs.* after	5	174	–0.79	–2.07, 0.49	0.23	<0.00001	93%
Urine volume							
After treatment, TCM *vs.* control	8	350	1.54	–0.15, 3.24	0.07	<0.00001	97%
TCM, before *vs.* after	8	360	3.64	2.47, 4.81	<0.00001	<0.00001	91%
Control, before *vs.* after	8	346	2.21	0.71, 3.71	0.004	<0.00001	96%

SMD, standardized mean difference; CI, confidence interval; TCM, traditional Chinese medicine.

Table S4 Summary results regarding meta-regression

Variable	P		
	Publication year	Type of HRS	Diagnostic criteria
Serum creatinine			
After treatment, TCM *vs.* control	0.622	0.277	0.747
TCM, before *vs.* after	0.400	0.358	0.575
Control, before *vs.* after	0.022	0.567	0.196
Blood urea nitrogen			
After treatment, TCM *vs.* control	0.990	0.260	0.983
TCM, before *vs.* after	0.352	0.249	0.438
Control, before *vs.* after	0.051	0.655	0.067
Urine volume			
After treatment, TCM *vs.* control	0.883	0.814	0.209
TCM, before *vs.* after	0.363	0.542	0.715
Control, before *vs.* after	0.127	0.394	0.707

HRS, hepatorenal syndrome; TCM, traditional Chinese medicine.