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Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis (Review)

Best LMJ, Freeman SC, Sutton AJ, Cooper NJ, Tng EL, Csenar M, Hawkins N, Pavlov CS, Davidson BR, Thorburn D, Cowlin M, Milne EJ, Tsochatzis E, Gurusamy KS

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[Intervention Review]

Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis

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ABSTRACT

Background

Hepatorenal syndrome is defined as renal failure in people with cirrhosis in the absence of other causes. In addition to supportive treatment such as albumin to restore fluid balance, the other potential treatments include systemic vasoconstrictor drugs (such as vasopressin analogues or noradrenaline), renal vasodilator drugs (such as dopamine), transjugular intrahepatic portosystemic shunt (TIPS), and liver support with molecular adsorbent recirculating system (MARS). There is uncertainty over the best treatment regimen for hepatorenal syndrome.

Objectives

To compare the benefits and harms of different treatments for hepatorenal syndrome in people with decompensated liver cirrhosis.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trial registers until December 2018 to identify randomised clinical trials on hepatorenal syndrome in people with cirrhosis.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or publication status) in adults with cirrhosis and hepatorenal syndrome. We excluded randomised clinical trials in which participants had previously undergone liver transplantation.

Data collection and analysis

Two authors independently identified eligible trials and collected data. The outcomes for this review included mortality, serious adverse events, any adverse events, resolution of hepatorenal syndrome, liver transplantation, and other decompensation events. We performed

a network meta-analysis with OpenBUGS using Bayesian methods and calculated the odds ratio (OR), rate ratio, hazard ratio (HR), and mean difference (MD) with 95% credible intervals (CrI) based on an available-case analysis, according to National Institute of Health and Care Excellence Decision Support Unit guidance.

Main results

We included a total of 25 trials (1263 participants; 12 interventions) in the review. Twenty-three trials (1185 participants) were included in one or more outcomes. All the trials but two were at high risk of bias, and all the evidence was of low or very low certainty. The trials included participants with liver cirrhosis of varied aetiologies as well as a mixture of type I hepatorenal syndrome only, type II hepatorenal syndrome only, or people with both type I and type II hepatorenal syndrome. Participant age ranged from 42 to 60 years, and the proportion of females ranged from 5.8% to 61.5% in the trials that reported this information. The follow-up in the trials ranged from one week to six months. Overall, 59% of participants died during this period and about 35% of participants recovered from hepatorenal syndrome. The most common interventions compared were albumin plus terlipressin, albumin plus noradrenaline, and albumin alone.

There was no evidence of a difference in mortality (22 trials; 1153 participants) at maximal follow-up between the different interventions. None of the trials reported health-related quality of life. There was no evidence of differences in the proportion of people with serious adverse events (three trials; 428 participants), number of participants with serious adverse events per participant (two trials; 166 participants), proportion of participants with any adverse events (four trials; 402 participants), the proportion of people who underwent liver transplantation at maximal follow-up (four trials; 342 participants), or other features of decompensation at maximal follow-up (one trial; 466 participants). Five trials (293 participants) reported number of any adverse events, and five trials (219 participants) reported treatment costs. Albumin plus noradrenaline had fewer numbers of adverse events per participant (rate ratio 0.51, 95% CrI 0.28 to 0.87). Eighteen trials (1047 participants) reported recovery from hepatorenal syndrome (as per definition of hepatorenal syndrome). In terms of recovery from hepatorenal syndrome, in the direct comparisons, albumin plus midodrine plus octreotide and albumin plus octreotide had lower recovery from hepatorenal syndrome than albumin plus terlipressin (HR 0.04; 95% CrI 0.00 to 0.25 and HR 0.26, 95% CrI 0.07 to 0.80 respectively). There was no evidence of differences between the groups in any of the other direct comparisons. In the network meta-analysis, albumin and albumin plus midodrine plus octreotide had lower recovery from hepatorenal syndrome compared with albumin plus terlipressin.

Funding: two trials were funded by pharmaceutical companies; five trials were funded by parties who had no vested interest in the results of the trial; and 18 trials did not report the source of funding.

Authors' conclusions

Based on very low-certainty evidence, there is no evidence of benefit or harm of any of the interventions for hepatorenal syndrome with regards to the following outcomes: all-cause mortality, serious adverse events (proportion), number of serious adverse events per participant, any adverse events (proportion), liver transplantation, or other decompensation events. Low-certainty evidence suggests that albumin plus noradrenaline had fewer 'any adverse events per participant' than albumin plus terlipressin. Low- or very low-certainty evidence also found that albumin plus midodrine plus octreotide and albumin alone had lower recovery from hepatorenal syndrome compared with albumin plus terlipressin.

Future randomised clinical trials should be adequately powered; employ blinding, avoid post-randomisation dropouts or planned cross-overs (or perform an intention-to-treat analysis); and report clinically important outcomes such as mortality, health-related quality of life, adverse events, and recovery from hepatorenal syndrome. Albumin plus noradrenaline and albumin plus terlipressin appear to be the interventions that should be compared in future trials.

PLAIN LANGUAGE SUMMARY

Treatment of hepatorenal syndrome

What is the aim of this Cochrane review?

To find out the best treatment for decreased kidney function (hepatorenal syndrome) in people with liver cirrhosis (a form of advanced liver disease with scarring of the liver) with complications. The authors collected and analysed all relevant studies to answer this question and found 25 randomised controlled trials (participants receive the treatment based on method similar to coin toss or lottery; this is to ensure that the people who receive the different treatments are similar in all aspects except the treatment, so that any differences in the results between the treatments can be attributed to the treatment rather than differences in the type of people who received the treatment). During analysis of data, authors used standard Cochrane techniques, which allows comparison of two treatments at a time. Authors also used advanced techniques, that allow comparison of many treatments at the same time (usually referred as 'network meta-analysis' or 'multiple treatment comparisons'). The aim is to gather reliable evidence on the relative benefits and harms of the different treatments.

Date of literature search
December 2018

Key messages

Only two studies were conducted well. The remaining studies had one or more flaws. Therefore, there is high uncertainty in the results of the analysis. The authors could not recommend one treatment over another on the basis of risk of death, serious complications, percentage of people who developed any complication, percentage of participants who underwent liver transplantation (replacement of a diseased liver with a healthy one), or the number of other liver failure events. Health-related quality of life was not reported in any of the trials. The number of complications of any severity was lower with albumin plus noradrenaline than albumin plus terlipressin. Recovery from hepatorenal syndrome may be lower with albumin plus midodrine plus octreotide and albumin alone than albumin plus terlipressin and albumin plus noradrenaline.

Funding source was unclear in 18 studies. Industrial organisations funded two studies and the remaining five studies did not receive any funding from industrial organisations.

What was studied in the review?

This review studied people of any sex, age, and origin, having advanced liver disease due to various causes, and who had developed hepatorenal syndrome. People were administered different treatments. The review authors excluded studies with liver-transplanted participants. Participants age, when reported, ranged from 42 to 60 years. The number of females ranged from 6 to 62 out of 100 in the studies that reported this information. The main treatments compared were albumin alone, albumin plus terlipressin, and albumin plus noradrenaline. The authors gathered and analysed data on death, quality of life, serious and non-serious complications, time to liver transplantation, recovery from hepatorenal syndrome, and disappearance of symptoms.

What were the main results of the review?

The 25 studies included a small number of participants (1263 participants). Study data were sparse. Twenty-three studies with 1185 participants provided data for analyses. The follow-up in the trials ranged from one week to six months. The review shows that:

- About 60 out of every 100 people died within three months, and 35 out of every 100 people recovered from hepatorenal syndrome.

- The provided treatment may make no difference to the percentage of people who died or developed serious complications, number of serious complications per person, percentage of people who developed complications of any severity, or the percentage of people undergoing liver transplantation.

- None of the trials reported health-related quality of life.

- The number of complications of any severity was lower with albumin plus noradrenaline than albumin plus terlipressin.

- Recovery from hepatorenal syndrome may be lower with albumin plus midodrine plus octreotide and albumin alone than albumin plus terlipressin and albumin plus noradrenaline.

- We have very low confidence in the overall results.

- Future trials with proper design and quality are needed to clarify the best treatment for people with advanced liver disease having hepatorenal syndrome.

Summary of findings for the main comparison.

Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis

Patient or population: people with hepatorenal syndrome with decompensated liver cirrhosis

Intervention: various interventions

Comparison: albumin plus terlipressin

Setting: tertiary care

Follow-up period: 1 week to 6 months

Network geometry plots: Figure 1

Interventions	Relative effect (95% CrI)*	Anticipated absolute effect** (95% CrI)			Certainty of evidence	Ranking***
		Albumin plus terlipressin	Various interventions	Difference		
Mortality at maximal follow-up **Total studies: 19** **Total participants: 1089**						
Albumin plus noradrenaline (9 RCTs; 486 participants)	**HR 1.33** (0.87 to 2.00) **Network estimate**	**517 per 1000**	**687 per 1000** (449 to 1000)	**170 more per 1000** (68 fewer to 483 more)	**Very low**[1,2,3]	-
Albumin (6 RCTs; 480 participants)	**HR 1.06** (0.69 to 1.80) **Network estimate**	**517 per 1000**	**549 per 1000** (354 to 932)	**32 more per 1000** (163 fewer to 415 more)	**Very low**[1,2,3]	-
Albumin plus midodrine plus octreotide (1 RCT; 48 participants)	**HR 1.42** (0.52 to 3.79) **Network estimate**	**517 per 1000**	**734 per 1000** (267 to 1000)	**217 more per 1000** (250 fewer to 483 more)	**Very low**[1,2,3]	-
Albumin plus midodrine plus octreotide plus pentoxifylline	**HR 0.50** (0.06 to 4.07)	**517 per 1000**	**259 per 1000** (29 to 1000)	**258 fewer per 1000** (488 fewer to 483 more)	**Very low**[1,2,3]	-

(No RCTs)	**Network estimate**					
Albumin plus octreotide (1 RCT; 40 participants)	**HR 1.46** (0.35 to 6.49) **Network estimate**	**517 per 1000**	**752 per 1000** (180 to 1000)	**235 more per 1000** (337 fewer to 483 more)	**Very low**[1,2,3]	-
Health-related quality of life						
None of the trials reported this outcome						
Serious adverse events (proportion) **Total studies: 3** **Total participants: 428**						
Albumin plus noradrenaline (1 RCT; 120 participants)	**OR 0.82** (0.21 to 2.98) **Network estimate**	**608 per 1000**	**560 per 1000** (250 to 822)	**48 fewer per 1000** (358 fewer to 214 more)	**Very low**[1,2,4,5]	-
Albumin (2 RCTs; 308 participants)	**OR 0.80** (0.50 to 1.26) **Network estimate**	**608 per 1000**	**553 per 1000** (438 to 662)	**55 fewer per 1000** (170 fewer to 54 more)	**Very low**[1,2,4,5]	
Serious adverse events (number per participant) **Total studies: 2** **Total participants: 166**						
Albumin plus noradrenaline (1 RCT; 120 participants)	**Rate ratio 0.83** (0.23 to 2.83) **Network estimate**	**100 per 1000**	**83 per 1000** (23 to 283)	**17 fewer per 1000** (77 fewer to 183 more)	**Very low**[1,2,4,5]	-
Albumin (1 RCT; 46 participants)	**Rate ratio 0.91** (0.51 to 1.65) **Network estimate**	**100 per 1000**	**91 per 1000** (51 to 165)	**9 fewer per 1000** (49 fewer to 65 more)	**Very low**[1,2,4,5]	-
Any adverse events (proportion) **Total studies: 4**						

Total participants: 402						
Albumin plus noradrenaline (1 RCT; 46 participants)	**OR 0.16** (0.01 to 1.44) **Network estimate**	**928 per 1000**	**674 per 1000** (114 to 949)	**254 fewer per 1000** (814 fewer to 21 more)	**Very low**[1,2,4,5]	**1** (1 to 4)
Albumin (2 RCTs; 308 participants)	**OR 0.58** (0.25 to 1.25) **Network estimate**	**928 per 1000**	**882 per 1000** (765 to 941)	**46 fewer per 1000** (163 fewer to 13 more)	**Very low**[1,2,4,5]	**2** (1 to 4)
Albumin plus terlipressin	**Reference treatment**					**3** (2 to 4)
Albumin plus midodrine plus octreotide (1 RCT; 48 participants)	**OR 1.14** (0.30 to 4.30) **Network estimate**	**928 per 1000**	**936 per 1000** (795 to 982)	**8 more per 1000** (133 fewer to 54 more)	**Very low**[1,2,4,5]	**4** (1 to 4)
Any adverse events (number) **Total studies: 5** **Total participants: 293**						
Albumin plus noradrenaline (4 RCTs; 293 participants)	**Rate ratio 0.51** (0.28 to 0.87) **Direct estimate**	**317 per 1000**	**161 per 1000** (88 to 276)	**156 fewer per 1000** (229 fewer to 41 fewer)	**Low**[1,4]	**1** (1 to 2)
Albumin (1 RCT; 48 participants)	**Rate ratio 0.80** (0.52 to 1.22) **Network estimate**	**317 per 1000**	**252 per 1000** (166 to 386)	**65 fewer per 1000** (151 fewer to 69 more)	**Very low**[1,2,4,5]	**2** (1 to 3)
Albumin plus terlipressin	**Reference treatment**					**3** (2 to 3)
Liver transplantation at maximal follow-up **Total studies: 3** **Total participants: 330**						
Albumin plus noradrenaline	**HR 1.09**	**309 per 1000**	**336 per 1000**	**27 more per 1000**	**Very low**[1,2,4,5]	-

(1 RCT; 48 participants)	(0.36 to 3.31) **Network estimate**		(110 to 1000)	(199 fewer to 691 more)		
Albumin (2 RCTs; 308 participants)	**HR 1.01** (0.68 to 1.52) **Network estimate**	**309 per 1000**	**313 per 1000** (210 to 469)	**4 more per 1000** (99 fewer to 160 more)	**Very low**[1,2,4,5]	-
Recovery from hepatorenal syndrome at maximal follow-up **Total studies: 18** **Total participants: 1047**						
Albumin plus noradrenaline (10 RCTs; 518 participants)	**HR 0.85** (0.58 to 1.28) **Network estimate**	**400 per 1000**	**340 per 1000** (230 to 512)	**60 fewer per 1000** (170 fewer to 112 more)	**Very low**[1,2,3,4,5]	-
Albumin (4 RCTs; 406 participants)	**HR 0.28** (0.14 to 0.53) **Network estimate**	**400 per 1000**	**111 per 1000** (54 to 213)	**289 fewer per 1000** (346 fewer to 187 fewer)	**Very low**[1,3,4,5]	-
Albumin plus midodrine plus octreotide (1 RCT; 48 participants)	**HR 0.04** (0.00 to 0.25) **Direct estimate**	**400 per 1000**	**17 per 1000** (1 to 101)	**383 fewer per 1000** (399 fewer to 299 fewer)	**Very low**[1,3,4,5,6]	-
Albumin plus midodrine plus octreotide plus pentoxifylline (No RCTs)	**HR 0.25** (0.00 to 12.85) **Network estimate**	**400 per 1000**	**99 per 1000** (2 to 1000)	**301 fewer per 1000** (398 fewer to 600 more)	**Very low**[1,2,3,4,5]	-
Albumin plus octreotide (1 RCT; 40 participants)	**HR 0.26** (0.07 to 0.80) **Direct estimate**	**400 per 1000**	**105 per 1000** (28 to 321)	**295 fewer per 1000** (372 fewer to 79 more)	**Low**[1,4]	-
Other episodes of decompensation (per participant) **Total studies: 1** **Total participants: 46**						
Albumin plus terlipressin	**Reference treatment**					**1**

						(1 to 2)
Albumin (1 RCT; 46 participants)	**Rate ratio 1.10** (0.60 to 2.03) **Direct estimate**	**870 per 1000**	**959 per 1000** (518 to 1000)	**89 more per 1000** (352 fewer to 130 more)	**Very low**[1,2,4]	**2** (1 to 2)

*Direct estimates have been provided when there the quality of evidence is better for direct estimates than network estimates or when only the direct estimates were available.

**Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the weighted median risk of the control group.

***Ranking is provided only when the median rank was 1 for at least one of the ranking positions for each intervention for the outcome. When ranking is available, the treatments are ordered according to the ranks; otherwise, they are arranged according to the number of trials featuring the intervention.

CrI: credible intervals; **HR:** hazard ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1]Risk of bias: trial(s) were at high risk of bias (downgraded by one level).
[2]Imprecision: credible intervals overlapped a clinically significant benefits and harms (downgraded by one level).
[3]Heterogeneity: there were differences in the effect estimates obtained by fixed-effect model and random-effects models (downgraded by one level).
[4]Imprecision: small sample size (downgraded by one level)
[5]Indirectness: sparse network made up of trials at high risk of bias (downgraded by one level)
[6]Indirectness: incongruence (the inconsistency factor plot demonstrated inconsistency in the loop (downgraded by one level).

Figure 1. The network plots showing the outcomes for which network meta-analysis was performed. The size of the node (circle) provides a measure of the number of trials in which the particular Intervention was included as one of the intervention groups. The thickness of the line provides a

measure of the number of direct comparisons between two nodes (Interventions). Abbreviations: Pent = Pentoxyfylline The individual figures are available in the online supplement.

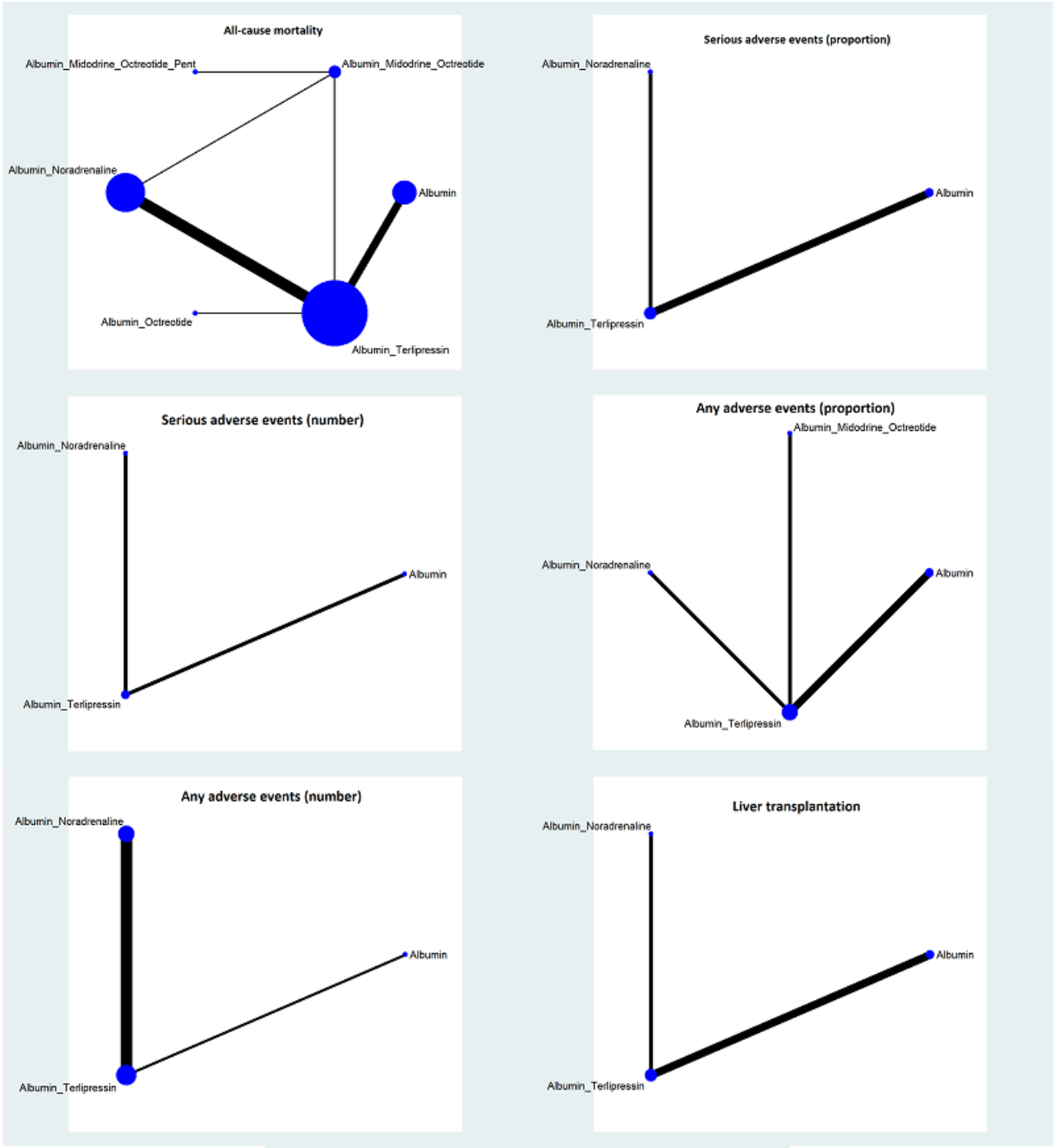
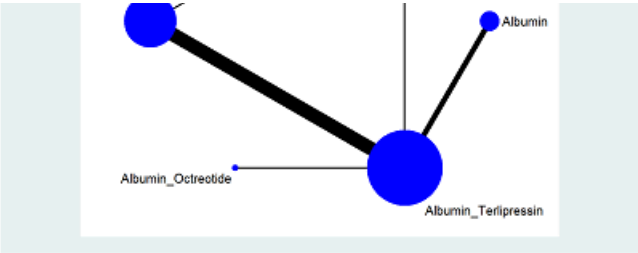


Figure 1. (Continued)



Summary of findings 2.

Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis (the two interventions with maximum number of trials)

Patient or population: people with hepatorenal syndrome with decompensated liver cirrhosis

Intervention: various interventions

Comparison: albumin and terlipressin

Setting: tertiary care

Follow-up period: 1 week to 6 months

Network geometry plots: Figure 1

Outcomes	Albumin		Albumin plus noradrenaline	
Mortality at maximal follow-up				
Albumin plus terlipressin comparator 517 per 1000 (51.7%)	**HR 1.06** (0.69 to 1.80) **Network estimate**	**32 more per 1000** (163 fewer to 415 more)	**HR 1.33** (0.87 to 2.00) **Network estimate**	**170 more per 1000** (68 fewer to 483 more)
	Very low[1,2,3] confidence in estimate		**Very low**[1,2,3] confidence in estimate	
Rank*: -	**Rank:** -		**Rank:** -	
	Based on 480 participants (6 RCTs)		Based on 486 participants (9 RCTs)	

Health-related quality of life				
None of the trials reported this outcome				
Serious adverse events (proportion of participants)				
Albumin plus terlipressin comparator 608 per 1000 (60.8%)	**OR 0.80** (0.50 to 1.26) **Network estimate**	**55 fewer per 1000** (170 fewer to 54 more)	**OR 0.82** (0.21 to 2.98) **Network estimate**	**48 fewer per 1000** (358 fewer to 214 more)
	Very low[1,2,4,5] confidence in estimate		**Very low**[1,2,4,5] confidence in estimate	
Rank: -	**Rank**: -		**Rank**: -	
	Based on 308 participants (2 RCTs)		Based on 120 participants (1 RCT)	
Serious adverse events (number per participant)				
Albumin plus terlipressin comparator 100 per 1000 (10.0 per 100 participants)	**Rate ratio 0.91** (0.51 to 1.65) **Network Estimate**	**9 fewer per 1000** (49 fewer to 65 more)	**Rate ratio 0.83** (0.23 to 2.83) **Network estimate**	**17 fewer per 1000** (77 fewer to 183 more)
	Very low[1,2,4,5] confidence in estimate		**Very low**[1,2,4,5] confidence in estimate	
Rank: -	**Rank**: -		**Rank**: -	
	Based on 46 participants (1 RCT)		Based on 120 participants (1 RCT)	
Any adverse events (proportion of participants)				
Albumin plus terlipressin comparator 928 per 1000 (92.8%)	**OR 0.58** (0.25 to 1.25) **Network estimate**	**46 fewer per 1000** (163 fewer to 13 more)	**OR 0.16** (0.01 to 1.44) **Network Estimate**	**254 fewer per 1000** (814 fewer to 21 more)
	Very low[1,2,4,5] confidence in estimate		**Very low**[1,2,4,5] confidence in estimate	

Rank: 3 (2 to 4)	**Rank: 2** (1 to 4)		**Rank: 1** (1 to 4)	
	Based on 308 participants (2 RCTs)		Based on 46 participants (1 RCT)	
Any adverse events (number per participant)				
Albumin plus terlipressin comparator 317 per 1000 (31.7 per 100 participants)	**Rate ratio 0.80** (0.52 to 1.22) **Network estimate**	**65 fewer per 1000** (151 fewer to 69 more)	**Rate ratio 0.51** (0.28 to 0.87) **Direct estimate****	**156 fewer per 1000** (229 fewer to 41 fewer)
	Very low[1,2,4,5] confidence in estimate		**Low**[1,2] confidence in estimate	
Rank: 3 (2 to 3)	**Rank: 2** (1 to 3)		**Rank: 1** (1 to 2)	
	Based on 48 participants (1 RCT)		Based on 293 participants (4 RCTs)	
Liver transplantation at maximal follow-up				
Albumin plus terlipressin comparator 309 per 1000 (30.9%)	**HR 1.01** (0.68 to 1.52) **Network estimate**	**4 more per 1000** (99 fewer to 160 more)	**HR 1.09** (0.36 to 3.31) **Network estimate**	**27 more per 1000** (199 fewer to 691 more)
	Very low[1,2,4,5] confidence in estimate		**Very low**[1,2,4,5] confidence in estimate	
Rank: -	**Rank:** -		**Rank:** -	
	Based on 308 participants (2 RCTs)		Based on 48 participants (1 RCT)	
Recovery from hepatorenal syndrome at maximal follow-up				
Albumin plus terlipressin comparator 400 per 1000 (40.0%)	**HR 0.28** (0.14 to 0.53) **Network estimate**	**289 fewer per 1000** (346 fewer to 187 fewer)	**HR 0.85** (0.58 to 1.28) **Network estimate**	**60 fewer per 1000** (170 fewer to 112 more)
	Very low[1,3,4,5]		**Very low**[1,2,3,4,5]	

	confidence in estimate		confidence in estimate
Rank: -	**Rank:** -		**Rank:** -
	Based on 406 participants (4 RCTs)		Based on 518 participants (10 RCTs)
Other episodes of decompensation (per participant)			
Albumin plus terlipressin **comparator** 870 per 1000 (87.0%)	**Rate ratio 1.10** (0.60 to 2.03) **Direct estimate****	**89 more per 1000** (352 fewer to 130 more)	Not reported
	Very low[1,2,4] confidence in estimate		
Rank: 1 (1 to 2)	**Rank: 2** (1 to 2)		
	Based on 46 participants (1 RCT)		

*Ranking is provided only when the median rank was 1 for at least one of the ranking positions for each intervention for the outcome. When ranking is available, the treatments are ordered according to the ranks; otherwise, they are arranged according to the number of trials featuring the intervention.

**Direct estimates have been provided when there the quality of evidence is better for direct estimates than network estimates or when only the direct estimates were available.

CrI: credible intervals; **HR:** hazard ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
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Very low certainty: We are very uncertain about the estimate.

[1]Risk of bias: trial(s) were at high risk of bias (downgraded by one level).
[2]Imprecision: credible intervals overlapped a clinically significant benefits and harms (downgraded by one level).
[3]Heterogeneity: there were differences in the effect estimates obtained by fixed-effect model and random-effects model (downgraded by one level).
[4]Imprecision: small sample size (downgraded by one level)
[5]Indirectness: sparse network made up of trials at high risk of bias (downgraded by one level)

BACKGROUND

Description of the condition

Liver cirrhosis

The liver is a complex organ with multiple functions including carbohydrate metabolism, fat metabolism, protein metabolism, drug metabolism, synthetic functions, storage functions, digestive functions, excretory functions, and immunological functions (Read 1972). Liver cirrhosis is a liver disease in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered with fibrous septa surrounding regenerated or regenerating parenchymal nodules (Tsochatzis 2014; NCBI 2018). The major causes of liver cirrhosis include excessive alcohol consumption, viral hepatitis, non-alcohol-related fatty liver disease, autoimmune liver disease, and metabolic liver disease (Williams 2014; Ratib 2015; Setiawan 2016). The global prevalence of liver cirrhosis is difficult to estimate as most estimates correspond to chronic liver disease (which includes liver fibrosis and liver cirrhosis). In studies from the USA, the prevalence of chronic liver disease varies between 0.3% to 2.1% (Scaglione 2015; Setiawan 2016); in the UK, the prevalence was 0.1% in one study (Fleming 2008). In 2010, liver cirrhosis was responsible for an estimated 2% of all global deaths, equivalent to one million deaths (Mokdad 2014). There is an increasing trend of cirrhosis-related deaths in some countries like the UK, while there is a decreasing trend in other countries like France (Mokdad 2014; Williams 2014). The major cause of complications and deaths in people with liver cirrhosis is due to the development of clinically significant portal hypertension (hepatic venous pressure gradient at least 10 mmHg) (De Franchis 2015). Some of the clinical features of decompensation include jaundice, coagulopathy, ascites, variceal bleeding, hepatic encephalopathy, and renal failure (De Franchis 2015; McPherson 2016; EASL 2018). Decompensated cirrhosis is the most common indication for liver transplantation (Merion 2010; Adam 2012).

Hepatorenal syndrome

Hepatorenal syndrome is renal failure in people with cirrhosis in the absence of other causes of renal failure such as nephrotoxic drugs and underlying renal pathology (Angeli 2015a). It is considered a functional disorder not associated with structural kidney damage and is potentially reversible. The current criteria for the diagnosis of hepatorenal syndrome are provided in Table 1 (Angeli 2015a). Hepatorenal syndrome can be classified into type I and type II hepatorenal syndrome. Type I hepatorenal syndrome has a rapidly progressive reduction in renal function, while type II hepatorenal syndrome does not follow a rapidly progressive course (Arroyo 1996). Type I hepatorenal syndrome is associated with acute kidney injury, while type II hepatorenal syndrome is associated with chronic kidney disease (Wong 2011). However, the most recent diagnostic criteria of hepatorenal syndrome include acute kidney injury (Angeli 2015a), that is, most individuals classified as having hepatorenal syndrome per the current definition will fall under the type I hepatorenal syndrome of past definitions. Approximately 10% of patients hospitalised for other complications of cirrhosis develop hepatorenal syndrome (Dong 2016). Approximately 30% to 60% of people hospitalised for hepatorenal syndrome die within a year (Israelsen 2017). The annual direct medical costs of treatment of hepatorenal syndrome range between approximately USD 3 billion (3000 million) and USD 3.8 billion (3800 million) (Rice 2017).

Pathophysiology of hepatorenal syndrome

Portal hypertension causes arterial vasodilatation of the splanchnic circulation (dilation of the blood vessels supplying the digestive organs in the abdomen such as liver, pancreas, and intestines) (Gines 2009). This decreases the intravascular volume. In the early stages of portal hypertension, the body maintains arterial blood pressure by increasing the cardiac output; however, in later stages of portal hypertension, the increase in cardiac output is not sufficient to ensure sufficient blood supply to vital organs, and the body maintains arterial blood pressure by the activation of vasoconstrictor mechanisms (Gines 2009). These vasoconstrictor mechanisms include the renin–angiotensin system, the sympathetic nervous system, and non-osmotic hypersecretion of antidiuretic hormone (Gines 2009), and lead to decreased blood flow to the kidneys by renal arterial vasoconstriction, and eventually to renal failure (Gines 2009).

Description of the intervention

Development of hepatorenal syndrome is considered one of the manifestations of end-stage liver disease, which is one of the indications for liver transplantation (EASL 2016). Liver transplantation is considered the definitive treatment for hepatorenal syndrome in people who can undergo liver transplantation (Gines 2009; Acevedo 2017; EASL 2018). Supportive measures like treatment of the precipitating cause of renal failure, such as infections or gastrointestinal bleeding and fluid overload, should be provided to people during waiting time for liver transplantation and to people who cannot undergo liver transplantation due to contraindications (e.g. metastatic liver disease) (Gines 2009; EASL 2016). In addition, treatment of hepatorenal syndrome in the form of systemic vasoconstrictor drugs such as vasopressin analogues or noradrenaline, as well as renal vasodilator drugs such as dopamine, albumin, transjugular intrahepatic portosystemic shunt (TIPS), liver support with molecular adsorbent recirculating system (MARS), and renal replacement therapy in the form of haemodialysis or haemofiltration have been used while waiting for liver transplantation or in people in whom transplantation cannot be performed (Gines 2009; Hinojosa-Azaola 2014; Acevedo 2017; Allegretti 2017; EASL 2018).

How the intervention might work

Systemic vasoconstrictor drugs decrease the systemic vasodilation, which is one of the mechanisms of developing hepatorenal syndrome. Renal vasodilator drugs decrease the renal vasoconstriction, which is one of the mechanisms of developing hepatorenal syndrome. Decreased intravascular volume is one of the mechanisms of developing hepatorenal syndrome; albumin may increase the intravascular oncotic pressure and prevent third-space loss, resulting in maintenance of the intravascular volume (Caironi 2009). Transjugular intrahepatic portosystemic shunt results in a reduction of portal hypertension, which is one of the mechanisms of developing hepatorenal syndrome. Liver support with MARS and renal replacement therapy can be considered as bridging measures to prevent further deterioration of patients until the time of liver transplantation, or recovery from the precipitating factors (e.g. infections or gastrointestinal bleeding).

Why it is important to do this review

It is important to provide optimal treatment to people with hepatorenal syndrome to improve their clinical outcomes while waiting for liver transplantation or potentially prevent the need for transplantation, or both. This is particularly important, given the shortage of donor organs. Several different treatments are available; however, their relative efficacy and optimal combination are not known. There have been two Cochrane Reviews on hepatorenal syndrome treatment (Allegretti 2017; Israelsen 2017); however, there has been no previous network meta-analysis on the topic. Network meta-analysis allows for a combination of direct and indirect evidence; and the ranking of different interventions for different outcomes (Salanti 2011; Salanti 2012). With this systematic review and network meta-analysis, we aim to provide the best level of evidence for the benefits and harms of different treatments for hepatorenal syndrome in people with decompensated liver cirrhosis. If it is not possible to perform this review with network meta-analysis methods, we will instead use standard Cochrane methods to perform head-to-head comparison meta-analysis, whenever possible. We will also present results from direct comparisons, whenever possible, even if we perform the network meta-analysis.

A glossary of terms is provided in Appendix 1.

OBJECTIVES

To compare the benefits and harms of different treatments for hepatorenal syndrome in people with decompensated liver cirrhosis.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised clinical trials for this network meta-analysis irrespective of language, publication status, or date of publication. We excluded studies of other designs due to the risk of bias in such studies. Inclusion of indirect observational evidence could weaken our network meta-analysis, but this could also be viewed as a strength for assessing rare adverse events. It is well established that exclusion of non-randomised studies increases the focus on potential benefits and reduces the focus on the risks of serious adverse events and those of any adverse events. However, due to the exponentially increased amount of work required for non-randomised studies, we planned to register and perform a new systematic review and meta-analysis of non-randomised studies for adverse events, if there was uncertainty in the balance of benefits and harms of effective treatment(s). We did not perform this because of the findings of the review.

Types of participants

We included randomised clinical trials with adult trial participants undergoing treatment for hepatorenal syndrome with decompensated liver cirrhosis. We excluded randomised clinical trials in which participants had previously undergone liver transplantation.

Types of interventions

We included any of the following interventions for comparison with one another; either alone, or in combination.

- Noradrenaline (systemic vasoconstrictor)
- Terlipressin (systemic vasoconstrictor)
- Midodrine (systemic vasoconstrictor)
- Dopamine (renal vasodilator)
- Prostaglandins (renal vasodilator)
- Albumin (maintain intravascular volume)
- TIPS procedure (decrease portal hypertension)
- Other forms of portosystemic shunt (decrease portal hypertension)
- Haemodialysis (renal replacement therapy)
- Haemofiltration (renal replacement therapy)
- MARS (liver support)
- No active intervention (no intervention or placebo)

We evaluated the plausibility of transitivity assumption by looking at the inclusion and exclusion criteria in the studies. The transitivity assumption is the assumption that participants included in the different trials with different treatments for hepatorenal syndrome can be considered to be a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the interventions (Salanti 2012). In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. This necessitates that information on potential effect-modifiers such as type of hepatorenal syndrome (type I or type II) and the co-interventions (use of prophylactic antibiotics) are the same across trials. Since, there was no concern about the transitivity assumption, we did not perform a separate meta-analysis on people with cirrhosis and hepatorenal syndrome with and without other features of decompensation.

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up (time to death).
- Health-related quality of life using a validated scale such as the EQ-5D or 36-Item Short Form Health Survey (SF-36) at maximal follow-up (EuroQol 2018; Optum 2018).
- Serious adverse events (during or within six months after cessation of intervention). We defined a serious adverse event as any event that would increase mortality; is life-threatening; requires hospitalisation; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it (ICH-GCP 1997). However, none of the authors defined serious adverse events. Therefore, we used the definitions provided by trial authors for serious adverse events (as indicated in our protocol).
  - Proportion of people with one or more serious adverse events.
  - Number of serious adverse events per participant.

Secondary outcomes

- Any adverse events (during or within six months after cessation of intervention). We defined an adverse event as any untoward

medical occurrence not necessarily having a causal relationship with the intervention but resulting in a dose reduction or discontinuation of intervention (any time after commencement of intervention) (ICH-GCP 1997). However, none of the authors defined 'adverse event'. Therefore, we used the lists provided by trial authors for adverse events (as indicated in our protocol).
    - Proportion of people with one or more adverse events.
    - Number of any adverse events per participant.
- Time to liver transplantation (maximal follow-up).
- Time to recovery from hepatorenal syndrome (maximal follow-up).
    - Symptomatic recovery.
    - Recovery as per definitions used for hepatorenal syndrome.
- Time to other features of decompensation (maximal follow-up).

Exploratory outcomes

- Length of hospital stay (all hospital admissions until maximal follow-up).
- Number of days of lost work (in people who work) (maximal follow-up).
- Treatment costs (including the cost of the treatment and any resulting complications).

We chose outcomes based on their importance to patients in a survey related to research priorities for people with liver diseases (Gurusamy 2019); on feedback of the patient and public representative of this project; and on an online survey about the outcomes promoted through Cochrane Consumer Network.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, and Science Citation Index Expanded (Web of Science) from inception to December 2018 for randomised clinical trials comparing two or more of the above interventions, applying no language restrictions (Royle 2003). We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/), which searches various trial registers, including ISRCTN and ClinicalTrials.gov. We also searched the European Medicines Agency (EMA) (www.ema.europa.eu/ema/) and US Food and Drug Administration (FDA) (www.fda.gov) registries for randomised clinical trials. The provisional search strategies are provided in Appendix 2.

Searching other resources

We searched the references of the identified trials and the existing Cochrane Reviews on hepatorenal syndrome to identify additional trials for inclusion.

Data collection and analysis

Selection of studies

Two review authors (KG and LB) independently screened the titles and abstracts of studies identified by the search for potential inclusion in the review, seeking full-text articles for any references identified by at least one of the review authors as potentially relevant. We selected trials for inclusion based on the full-text articles. The excluded full-text references with reasons for their exclusion are provided in the 'Characteristics of excluded studies' table. We have also listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up in the 'Characteristics of ongoing studies' table. We resolved any discrepancies through discussion.

Data extraction and management

Three review authors (LB, ELT, and MC) independently extracted the data below in a pre-piloted Microsoft Excel-based data extraction form (after translation of non-English articles), ensuring that two independent data extractions were performed for each trial. KG also extracted data related to risk of bias and outcome data.

- Outcome data (for each outcome and for each intervention group, whenever applicable):
    - number of participants randomised;
    - number of participants included for the analysis;
    - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes, and number of participants with events and the mean follow-up period for time-to-event outcomes;
    - natural logarithm of hazard ratio and its standard error if this was reported rather than the number of participants with events and the mean follow-up period for time-to-event outcomes;
    - definition of outcomes or scale used, if appropriate.
- Data on potential effect modifiers:
    - participant characteristics such as age, sex, definition and type of hepatorenal syndrome (type I or type II), the aetiology for cirrhosis, and the interval between diagnosis of hepatorenal syndrome and treatment;
    - details of the intervention and control (including dose, frequency, and duration);
    - length of follow-up;
    - information related to 'Risk of bias' assessment (see Assessment of risk of bias in included studies).
- Other data:
    - year and language of publication;
    - country in which the participants were recruited;
    - year(s) in which the trial was conducted;
    - inclusion and exclusion criteria.

We collected outcomes at maximum follow-up, but also at short-term follow-up (up to three months) and medium-term follow-up (from three months to five years) if applicable.

We attempted to contact the trial authors in the case of unclear or missing information. If there was any doubt as to whether trials shared the same participants, completely or partially (by identifying common authors and centres), we attempted to contact the trial authors to clarify whether the trial report was duplicated. Any differences in opinion between the review authors were resolved through discussion.

Assessment of risk of bias in included studies

We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* and that were described in the Cochrane Hepato-Biliary Group Module to assess the risk of bias in included trials (Higgins 2011; Gluud 2018). Specifically, we assessed sources of bias as defined below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent person not otherwise involved in the study. In general, we classified the risk of bias as low if the method used for allocation concealment suggested that it was extremely likely that the sequence was generated randomly (e.g. the use of an interactive voice response system).
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so that the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We excluded such quasi-randomised studies.

Blinding of participants and personnel

- Low risk of bias: any of the following: blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken; or, rarely, no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: any of the following: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or, rarely, no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias in the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported the following predefined outcomes related to the main reason for treatment of people with hepatorenal syndrome, namely, mortality, resolution of hepatorenal syndrome, and adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered reliable.
- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, despite the fact that data on these outcomes should have been available and even recorded.

Other bias

- Low risk of bias: the trial appeared to be free of other components that could put it at risk of bias (e.g. inappropriate control or dose or administration of control, baseline differences, early stopping).
- Unclear risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias (e.g. baseline differences, early stopping).

We considered a trial to be at low risk of bias if we assessed the trial to be at low risk of bias across all listed 'Risk of bias' domains. Otherwise, we considered the trial to be at high risk of bias. At the outcome level, we classified an outcome to be at low risk of bias if the allocation sequence generation; allocation concealment; blinding of participants, healthcare professionals, and outcome assessors; incomplete outcome data; and selective outcome reporting (at the outcome level) were at low risk of bias for objective and subjective outcomes (Savović 2018).

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. the proportion of participants with serious adverse events or any adverse event), we calculated the odds ratio (OR) with 95% credible interval (CrI) (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. length of hospital stay), we calculated the mean difference (MD) with 95% CrI. We planned to use standardised mean difference (SMD) values with 95% CrI for health-related quality of life if the included trials used different scales. We planned to obtain the final scores, whenever possible. For count outcomes (e.g. number of serious adverse events or number of any adverse event), we calculated the rate ratio (RaR) with 95% CrI. This assumes that the events are independent of each other, i.e. if a person has had an event, they are not at an increased risk of further outcomes, which is the assumption in Poisson likelihood. For time-to-event data (e.g. all-cause mortality at maximal follow-up), we calculated the hazard ratio (HR) with 95% CrI.

Relative ranking

We estimated the ranking probabilities with 95% CrI for all interventions of being at each possible rank for each intervention. We obtained the surface under the cumulative ranking curve (SUCRA) (cumulative probability), rankogram, and relative ranking table with CrI for the ranking probabilities (Salanti 2011; Chaimani 2013).

Unit of analysis issues

The unit of analysis was the participant undergoing treatment for hepatorenal syndrome according to the intervention group to which the participant was randomly assigned.

Cluster-randomised clinical trials

In case of cluster-randomised clinical trials, we planned to include cluster-randomised clinical trials, provided that the effect estimate adjusted for cluster correlation was available, or if there was sufficient information available to calculate the design effect (which would allow us to take clustering into account). We also planned to assess additional domains of risk of bias for cluster-randomised trials according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Cross-over randomised clinical trials

In the case of cross-over randomised clinical trials, we planned to include only the outcomes after the period of first intervention because the included treatments could have residual effects.

Trials with multiple intervention groups

We collected data for all trial intervention groups that met the inclusion criteria. The codes for analysis that we used accounted for the correlation between the effect sizes from studies with more than two groups.

Dealing with missing data

We performed an intention-to-treat analysis, whenever possible (Newell 1992); otherwise, we used the data available to us. When intention-to-treat analysis is not used and the data are not missing at random (for example, treatment was withdrawn due to adverse events or duration of treatment was shortened because of lack of response and such participants were excluded from analysis), this can lead to biased results; therefore, we conducted best-worst case scenario analysis (assuming a good outcome in intervention group and bad outcome in control group) and worst-best case scenario analysis (assuming a bad outcome in intervention group and good outcome in control group) as sensitivity analyses, whenever possible, for binary and time-to-event outcomes, where binomial likelihood was used.

For continuous outcomes, we imputed the standard deviation from P values, according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we planned to use the median for meta-analysis when the mean was not available; otherwise, we planned to simply provide a median and interquartile range of the difference in medians. If the data were likely to be normally distributed and it was not possible to calculate the standard deviation from the P value or the confidence intervals, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation can decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We planned to assess the presence of clinical heterogeneity by comparing effect estimates (see Subgroup analysis and investigation of heterogeneity) in trial reports of different drug dosages, different types of hepatorenal syndrome (type I and type II), different aetiologies for cirrhosis (e.g. alcohol-related liver disease, viral liver diseases, autoimmune liver disease), and based on the co-interventions (e.g. both groups receive prophylactic antibiotics to decrease the risk of subacute bacterial peritonitis). Different study designs and risk of bias can contribute to methodological heterogeneity.

We assessed statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study variance (tau^2 and comparing this with values reported in the study of the distribution of between-study heterogeneity) (Turner 2012), and by calculating I^2 (Jackson 2014) using Stata/SE 15.1. If we identified substantial clinical, methodological, or statistical heterogeneity, we planned to explore the heterogeneity and address it in subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We assessed the transitivity assumption by comparing the distribution of the potential effect modifiers (clinical: type of hepatorenal syndrome (type I versus type II); methodological: risk of bias, year of randomisation, duration of follow-up) across the different pairwise comparisons.

Assessment of reporting biases

For the network meta-analysis, we planned to perform a comparison-adjusted funnel plot. However, to interpret a comparison-adjusted funnel plot, it is necessary to rank the studies in a meaningful way, as asymmetry may be due to small sample sizes in newer studies (comparing newer treatments with older

treatments) or higher risk of bias in older studies (comparing older treatments with placebo) (Chaimani 2012). As there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we judged the reporting bias by the completeness of the search (Chaimani 2012).

Data synthesis

Methods for indirect and mixed comparisons

We conducted network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We obtained a network plot to ensure that the trials were connected by interventions using Stata/SE 15.1 (Chaimani 2013). We excluded any trials that were not connected to the network from the network meta-analysis and reported only the direct pairwise meta-analysis for such comparisons. We summarised the population and methodological characteristics of the trials included in the network meta-analysis in a table based on pairwise comparisons. We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3 as per guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2016). We modelled the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and the reference group ('basic parameters') using appropriate likelihood functions and links (Lu 2006). We used binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link for time-to-event outcomes (a semiparametric model which excludes censored individuals from the denominator of ‘at risk’ individuals at the point when they are censored), and normal likelihood and identity link for continuous outcomes. We used albumin plus terlipressin as the reference group as this was the commonest intervention across the trials. We performed a fixed-effect model and random-effects model for the network meta-analysis. We have reported both models for comparison with the reference group in a forest plot. For each pairwise comparison in a table, we reported the fixed-effect model if the two models reported similar results; otherwise, we reported the most conservative model.

We used a hierarchical Bayesian model using three different sets of initial values to start the simulation-based parameter estimation, employing codes provided by NICE DSU (Dias 2016). We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors) centred at no effect. For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for the between-trial standard deviation and assumed this variability would be the same across treatment comparisons (Dias 2016). We used a 'burn-in' of 30,000 iterations, checked for convergence (of effect estimates and between-study heterogeneity) visually (i.e. whether the values in different chains mix very well by visualisation), and ran the models for another 30,000 simulations to obtain effect estimates. If we did not obtain convergence, we increased the number of simulations for the 'burn-in' and use the 'thin' and 'over relax' functions to decrease the autocorrelation. If we still did not obtain convergence, we used alternate initial values and priors employing methods suggested by Van Valkenhoef 2012. We also estimated the probability that each intervention ranks at each of the possible positions using the NICE DSU codes (Dias 2016).

Assessment of inconsistency

We assessed inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We used the inconsistency models employed in the NICE DSU manual, as we used a common between-study standard deviation (Dias 2014). In addition, we used a design-by-treatment full interaction model and planned to create inconsistency factor (IF) plots to assess inconsistency (Higgins 2012; Chaimani 2013). Where possible, we created inconsistency factor plots using Stata/SE 15.1. In the presence of inconsistency, we planned to assess whether the inconsistency was due to clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the Subgroup analysis and investigation of heterogeneity section.

If there was evidence of inconsistency, we planned to identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit network meta-analysis to a more compatible subset of trials.

Direct comparison

We performed the direct comparisons using the same codes and the same technical details.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups and investigate heterogeneity and inconsistency using meta-regression with the help of the codes provided in NICE DSU guidance (Dias 2012a), if we included a sufficient number of trials (when there were at least two trials in at least two of the subgroups) and when the interaction term could be calculated. We planned to use the following trial-level covariates for meta-regression.

- Trials at low risk of bias compared to trials at high risk of bias.
- Based on the type of hepatorenal syndrome (type I versus type II).
- Based on the aetiology for cirrhosis (e.g. alcohol-related liver disease, viral liver diseases, autoimmune liver disease).
- Based on the interval between the diagnosis of hepatorenal syndrome and the start of treatment (less than or equal to one-week interval between diagnosis and start of treatment versus more than one week between diagnosis and start of treatment).
- Based on the co-interventions (e.g. both groups received prophylactic antibiotics to decrease the risk of subacute bacterial peritonitis).
- Based on the period of follow-up (short-term: up to three months; medium-term: more than three months to five years; long-term: more than five years).
- Based on the definition used by authors for serious adverse events and any adverse events (ICH-GCP 1997 compared to other definitions).

We calculated a single common interaction term (which assumes each relative treatment effect versus a common comparator treatment is impacted in the same way by the covariate in question), when applicable (Dias 2012a). If the 95% CrIs of the interaction term did not overlap zero, we considered this statistically significant heterogeneity or inconsistency (depending upon the factor being used as a covariate).

Sensitivity analysis

If there were post-randomisation dropouts, we reanalysed the results using the best-worst case scenario and worst-best case scenario as sensitivity analyses, whenever possible. We also performed a sensitivity analysis excluding the trials in which mean or standard deviation, or both were imputed, and use of the median standard deviation in the trials to impute missing standard deviations.

Presentation of results

We followed the PRISMA-NMA statement while reporting our results (Hutton 2015). We presented the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and network meta-analysis. We originally planned to present the cumulative probability of the treatment ranks (i.e. the probability that the intervention is within the top two, the probability that the intervention is within the top three, etc.) in graphs (SUCRA) (Salanti 2011). We plotted the probability that each intervention was best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b) and ranking probability tables with CrI, but we did not present these because of the sparse data which can lead to misinterpretation of results due to large uncertainty in the rankings (the CrI was 0 to 1 for all the ranks). We uploaded all the raw data and the codes used for analysis in The European Organization for Nuclear Research open source database (Zenodo): the link is: https://doi.org/10.5281/zenodo.3256099.

Grading of evidence

We presented 'Summary of findings' tables for all the primary and secondary outcomes (see Primary outcomes; Secondary outcomes) (Summary of findings for the main comparison; Summary of findings 2). We followed the approach suggested by Yepes-Nunez and colleagues (Yepes-Nunez 2019). First, we calculated the direct and indirect effect estimates (when possible) and 95% CrI using the node-splitting approach (Dias 2010), that is, calculating the direct estimate for each comparison by including only trials in which there was direct comparison of interventions and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of interventions (and ensuring a connected network). Next, we rated the quality of direct and indirect effect estimates using GRADE methodology which takes into account the risk of bias, inconsistency (heterogeneity), directness of evidence (including incoherence, the term used in GRADE methodology for inconsistency in network meta-analysis), imprecision, and publication bias (Guyatt 2011). We then presented the relative and absolute estimates of the meta-analysis with the best certainty of evidence (Yepes-Nunez 2019). We also presented the 'Summary of findings' tables in a second format presenting all the outcomes for selected interventions (Yepes-Nunez 2019): we selected the three interventions (albumin plus terlipressin, albumin plus noradrenaline, and albumin alone) which were compared in the most trials (Table 1; Table 2; Table 3; Table 4; Table 5).

Recommendations for future research

We provided recommendations for future research in the population, intervention, control, outcomes, period of follow-up, and study design based on the uncertainties that we identified in the existing research.

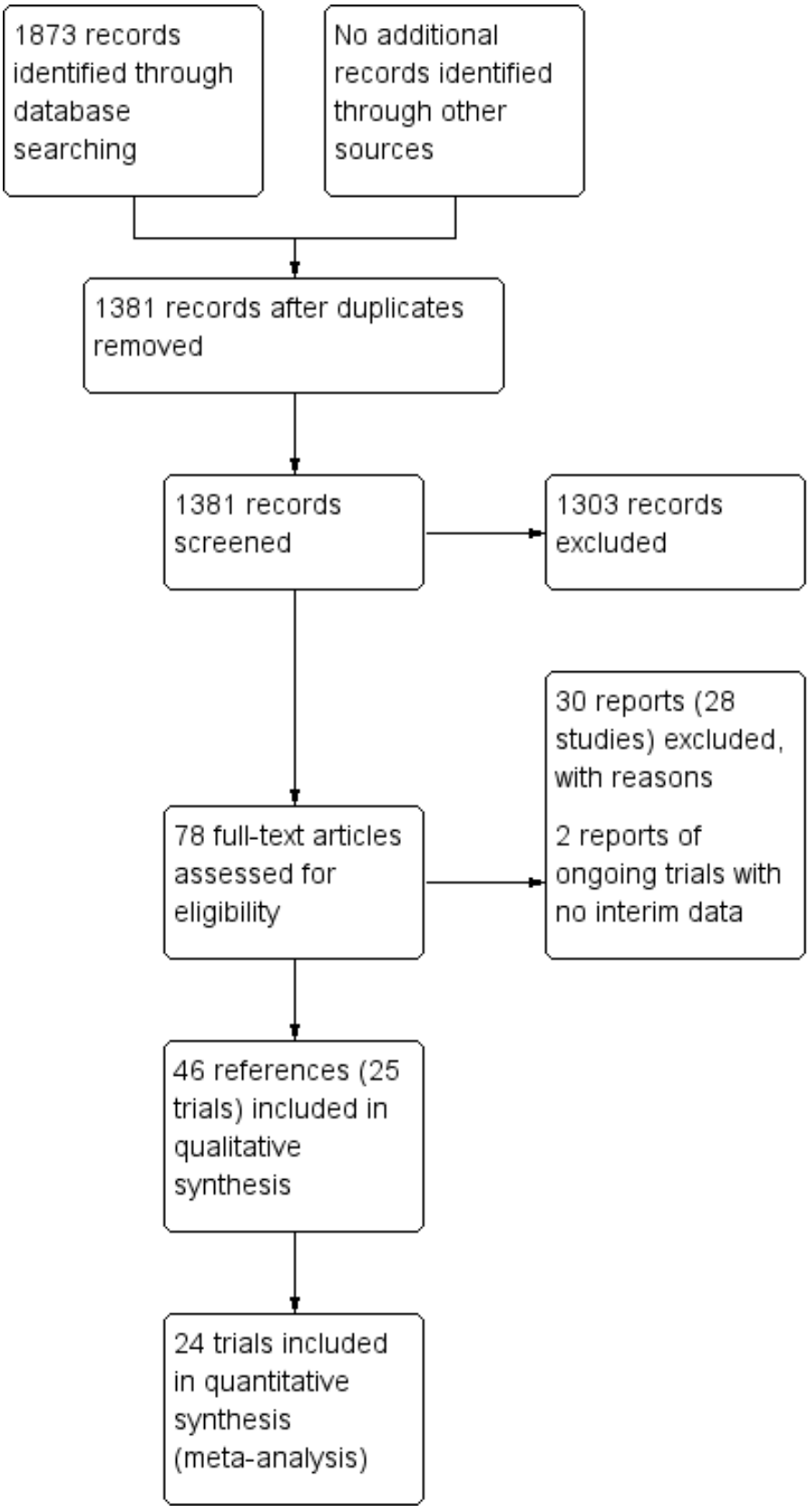
RESULTS

Description of studies

Results of the search

We identified 1873 references through electronic searches of CENTRAL (n = 291), MEDLINE (n = 654), Embase (n = 343), Science Citation Index Expanded (n = 531), World Health Organization International Clinical Trials Registry Platform (n = 33), and ClinicalTrials.gov (n = 21). We did not identify any new eligible study from EMA or FDA searches. After removing 492 duplicates, we obtained 1381 references. We then excluded 1303 clearly irrelevant references through screening titles and reading abstracts and retrieved 78 references for further assessment. We identified no references through scanning reference lists of the identified randomised trials. We excluded 30 references (28 studies) for the reasons stated in the Characteristics of excluded studies table. Two ongoing trials identified through ClinicalTrials.gov did not report interim data (NCT02770716; NCT03455322). A total of 46 references (describing 25 trials) met the inclusion criteria. The reference flow is summarised in the study flow diagram (Figure 2).

Figure 2. Study flow diagram.



Included studies

A total of 25 trials met the inclusion criteria for and were included in this review. A total of 1263 participants from these trials were randomised to different interventions. The number of participants ranged from 12 to 196. A total of 1185 participants from 23 trials provided data for one of more outcomes (Daskalopoulos 1985; Mitzner 2000; Chelarescu 2003; Solanki 2003; Alessandria 2007; Goyal 2008; Martin-Llahi 2008; Neri 2008; Sanyal 2008; Sharma 2008; Singh 2012; Tavakkoli 2012; Zafar 2012; Badawy 2013; Copaci 2013; Ghosh 2013; Indrabi 2013; Cavallin 2015; Boyer 2016; Goyal 2016; Arora 2018; Saif 2018; Stine 2018). Participant age ranged from 42 to 60 years and the proportion of females ranged from 5.8% to 61.5% in the trials that reported this information. Seven trials included both participants with hepatorenal syndrome type I and hepatorenal syndrome type II (Alessandria 2007; Goyal 2008; Martin-Llahi 2008; Tavakkoli 2012; Zafar 2012; Copaci 2013; Cavallin 2015), one trial included participants with only hepatorenal syndrome type II (Ghosh 2013), 13 included participants with only hepatorenal syndrome type I (Mitzner 2000; Solanki 2003; Neri 2008; Sanyal 2008; Sharma 2008; Singh 2012; Badawy 2013; Indrabi 2013; Boyer 2016; Goyal 2016; Arora 2018; Saif 2018; Stine 2018), and four trials did not state the type of hepatorenal syndrome (Daskalopoulos 1985; Yang 2001; Chelarescu 2003; Koch 2016). No study explicitly stated only including participants with a single cause of cirrhosis from alcohol, viral, or autoimmune-related cirrhosis. All trials had two intervention groups. We identified no cluster-randomised trials.

The follow-up in the trials ranged from one week to six months (Table 2). The interventions, controls, number of included participants, potential effect modifiers, and reported follow-up period for the different trials are provided in Table 2.

Overall, no systematic clinical or methodological differences between any of the comparisons seemed to exist. None of the trials used 'no treatment' as a control group.

Funding: Two trials were funded by pharmaceutical companies (Boyer 2016; Sanyal 2008); five trials did not receive funding from pharmaceutical companies (Alessandria 2007; Arora 2018; Martin-Llahi 2008; Stine 2018; Tavakkoli 2012), and the remaining 18 trials did not report the source of funding.

Any available further details of each study can be found in the Characteristics of included studies section.

Excluded studies

The reasons for exclusion are provided in the Characteristics of excluded studies table. Two trials had cross-over design, but had very short duration of the intervention and short or no wash-out periods; these were excluded because no meaningful data can be obtained from these studies (Hadengue 1998; Pomier-Layrargues 2003). None of the remaining trials were randomised clinical trials.

Risk of bias in included studies

The risk of bias is summarised in Figure 3, Figure 4, and Table 3. Only two trials were considered to be at low risk of bias in all the domains (Sanyal 2008; Boyer 2016). The remaining trials were at unclear or high risk of bias in one or more domains and were considered to be at high risk of bias.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

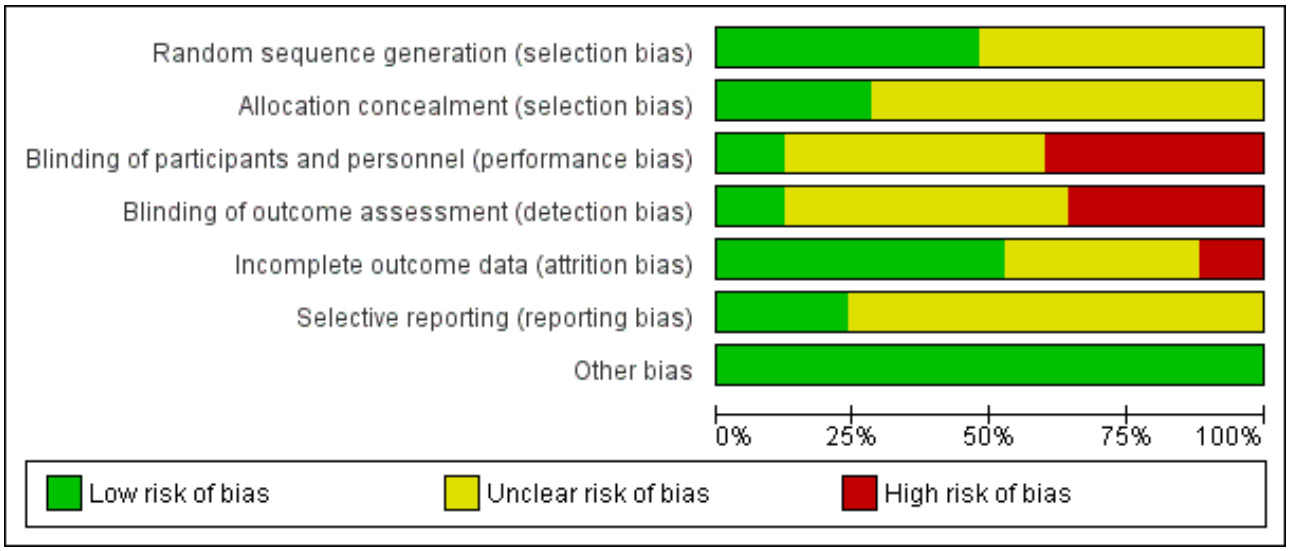


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

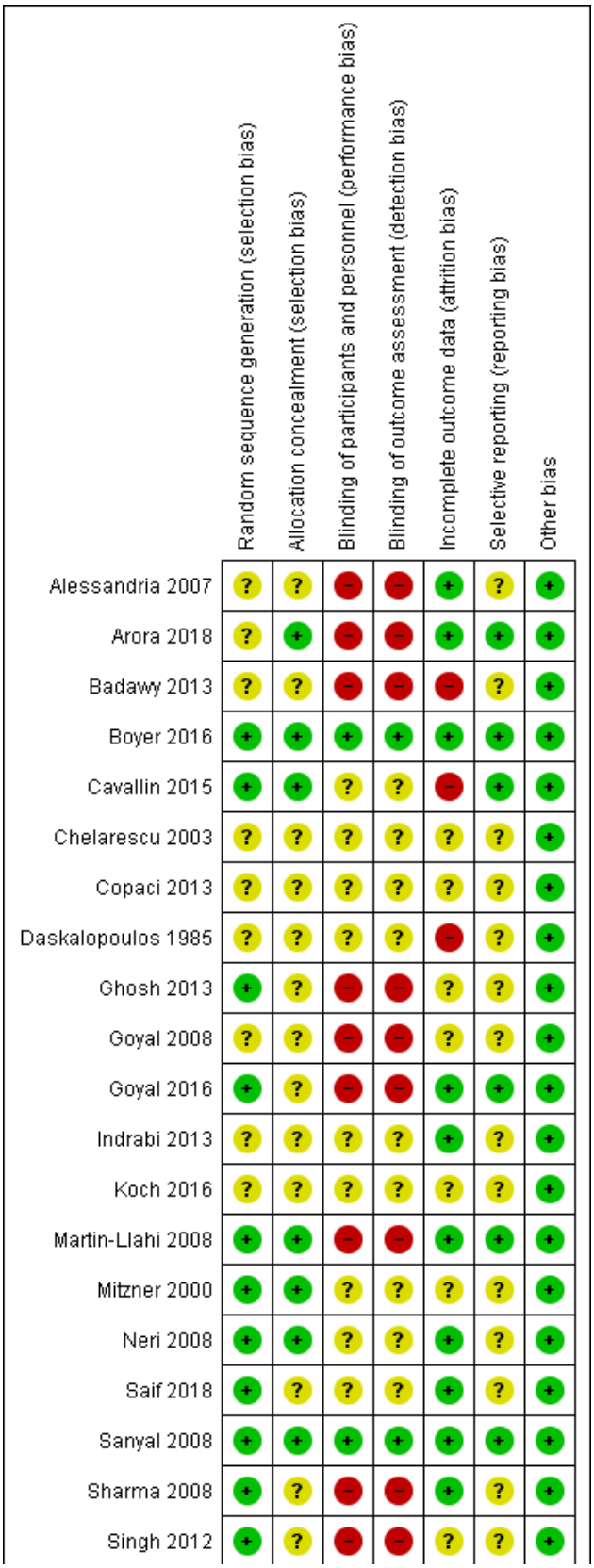


Figure 4. (Continued)

Allocation

Twelve trials were at low risk of bias due to random sequence generation (Boyer 2016; Cavallin 2015; Ghosh 2013; Goyal 2016; Martin-Llahi 2008; Mitzner 2000; Neri 2008; Saif 2018; Sanyal 2008; Sharma 2008; Singh 2012; Solanki 2003); the remaining trials were at unclear risk of bias due to random sequence generation (Alessandria 2007; Arora 2018; Badawy 2013; Chelarescu 2003; Copaci 2013; Daskalopoulos 1985; Goyal 2008; Indrabi 2013; Koch 2016; Stine 2018; Tavakkoli 2012; Yang 2001; Zafar 2012). Seven trials were at low risk of bias due to allocation concealment (Arora 2018; Boyer 2016; Cavallin 2015; Martin-Llahi 2008; Mitzner 2000; Neri 2008; Sanyal 2008); the remaining trials were at unclear risk of bias due to allocation concealment (Alessandria 2007; Badawy 2013; Chelarescu 2003; Copaci 2013; Daskalopoulos 1985; Ghosh 2013; Goyal 2008; Goyal 2016; Indrabi 2013; Koch 2016; Saif 2018; Sharma 2008; Singh 2012; Solanki 2003; Stine 2018; Tavakkoli 2012; Yang 2001; Zafar 2012). Overall, six trials were at low risk of selection bias (Boyer 2016; Martin-Llahi 2008; Mitzner 2000; Neri 2008; Sanyal 2008).

Blinding

Three trials were at low risk of bias of performance bias and detection bias (Boyer 2016; Sanyal 2008; Stine 2018); nine trials were at high risk of bias due to lack of blinding of participants and health professionals and bias due to lack of blinding of outcome assessors (Alessandria 2007; Arora 2018; Badawy 2013; Ghosh 2013; Goyal 2008; Goyal 2016; Martin-Llahi 2008; Sharma 2008; Singh 2012); one trial was at high risk of bias due to blinding of participants and health professionals, but unclear risk of bias due to lack of blinding of outcome assessors (Solanki 2003); the remaining trials were at unclear risk of bias due to lack of blinding of participants and health professionals and bias due to lack of blinding of outcome assessors (Cavallin 2015; Chelarescu 2003; Copaci 2013; Daskalopoulos 1985; Indrabi 2013; Koch 2016; Mitzner 2000; Neri 2008; Saif 2018; Tavakkoli 2012; Yang 2001; Zafar 2012).

Incomplete outcome data

Thirteen trials were at low risk of incomplete outcome data (attrition bias) (Alessandria 2007; Arora 2018; Boyer 2016; Goyal 2016; Indrabi 2013; Martin-Llahi 2008; Neri 2008; Saif 2018; Sanyal 2008; Sharma 2008; Solanki 2003; Stine 2018; Tavakkoli 2012); three trials were at high risk of incomplete outcome data (attrition bias) (Badawy 2013; Cavallin 2015; Daskalopoulos 1985); the remaining trials were at unclear risk of incomplete outcome data (attrition bias) (Chelarescu 2003; Copaci 2013; Ghosh 2013; Goyal 2008; Koch 2016; Mitzner 2000; Singh 2012; Yang 2001; Zafar 2012).

Selective reporting

We did not find a published protocol for any of the trials. Seven trials were at low risk of selective reporting (reporting bias) as they reported all-cause mortality, adverse events, and recovery from hepatorenal syndrome (Arora 2018; Boyer 2016; Cavallin 2015; Ghosh 2013; Goyal 2016; Martin-Llahi 2008; Sanyal 2008); the remaining trials were at unclear risk of selective reporting (reporting bias) (Alessandria 2007; Badawy 2013; Chelarescu 2003; Copaci 2013; Daskalopoulos 1985; Goyal 2008; Indrabi 2013; Koch 2016; Mitzner 2000; Neri 2008; Saif 2018; Sharma 2008; Singh 2012; Solanki 2003; Stine 2018; Tavakkoli 2012; Yang 2001; Zafar 2012).

Other potential sources of bias

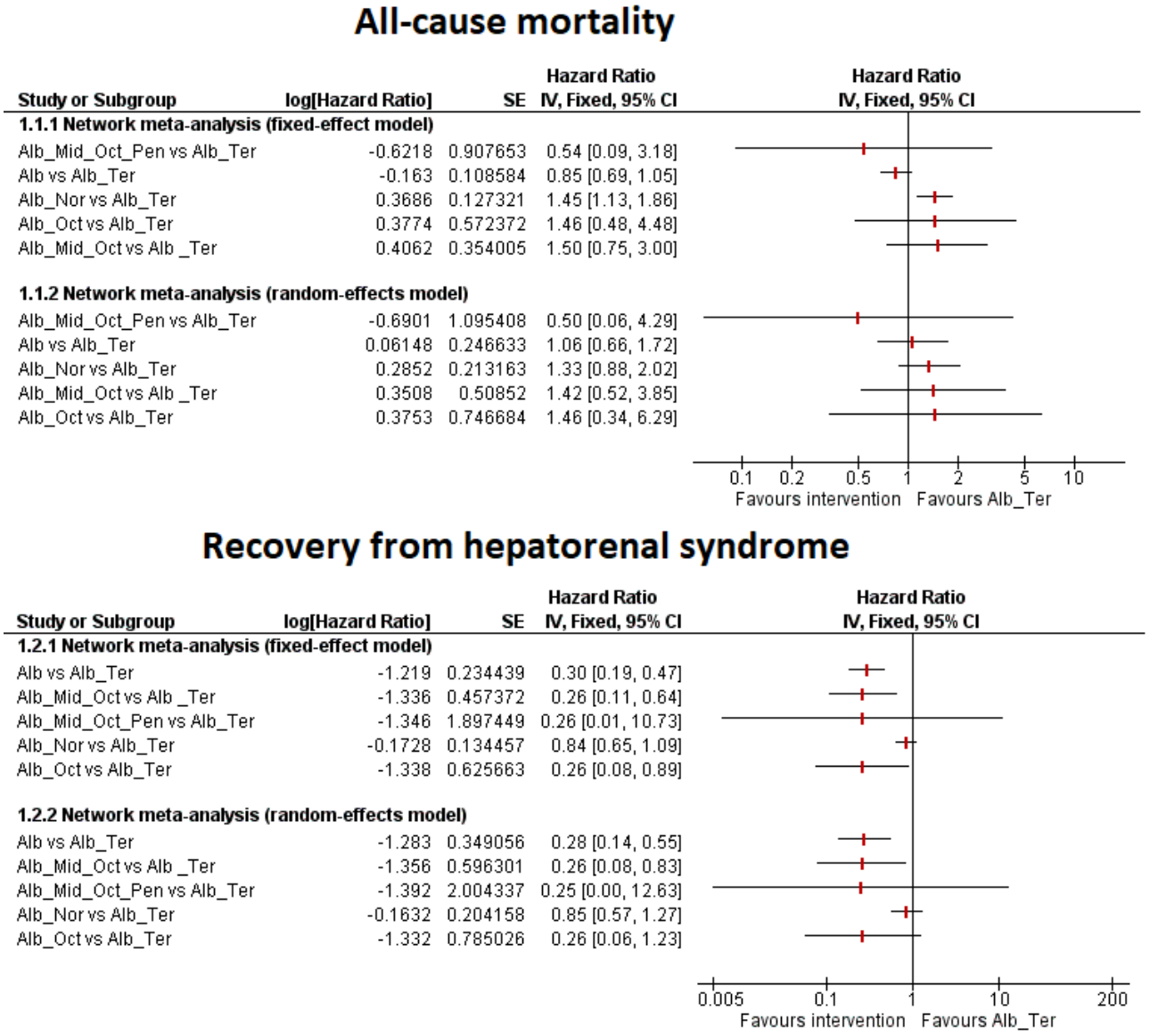
All trials were at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

The network plot for all outcomes for which network meta-analysis was performed is shown in Figure 1. If NMA was not performed, the reason for not performing the NMA is reported under the outcome. The model fit is available in Table 4. When we have reported the fixed-effect model, the use of the random-effects model did not alter the interpretation of results. The forest plots for the two outcomes (all-cause mortality and recovery from hepatorenal syndrome) where the fixed-effect model and random-effects model resulted in different interpretations are shown in Figure 5.

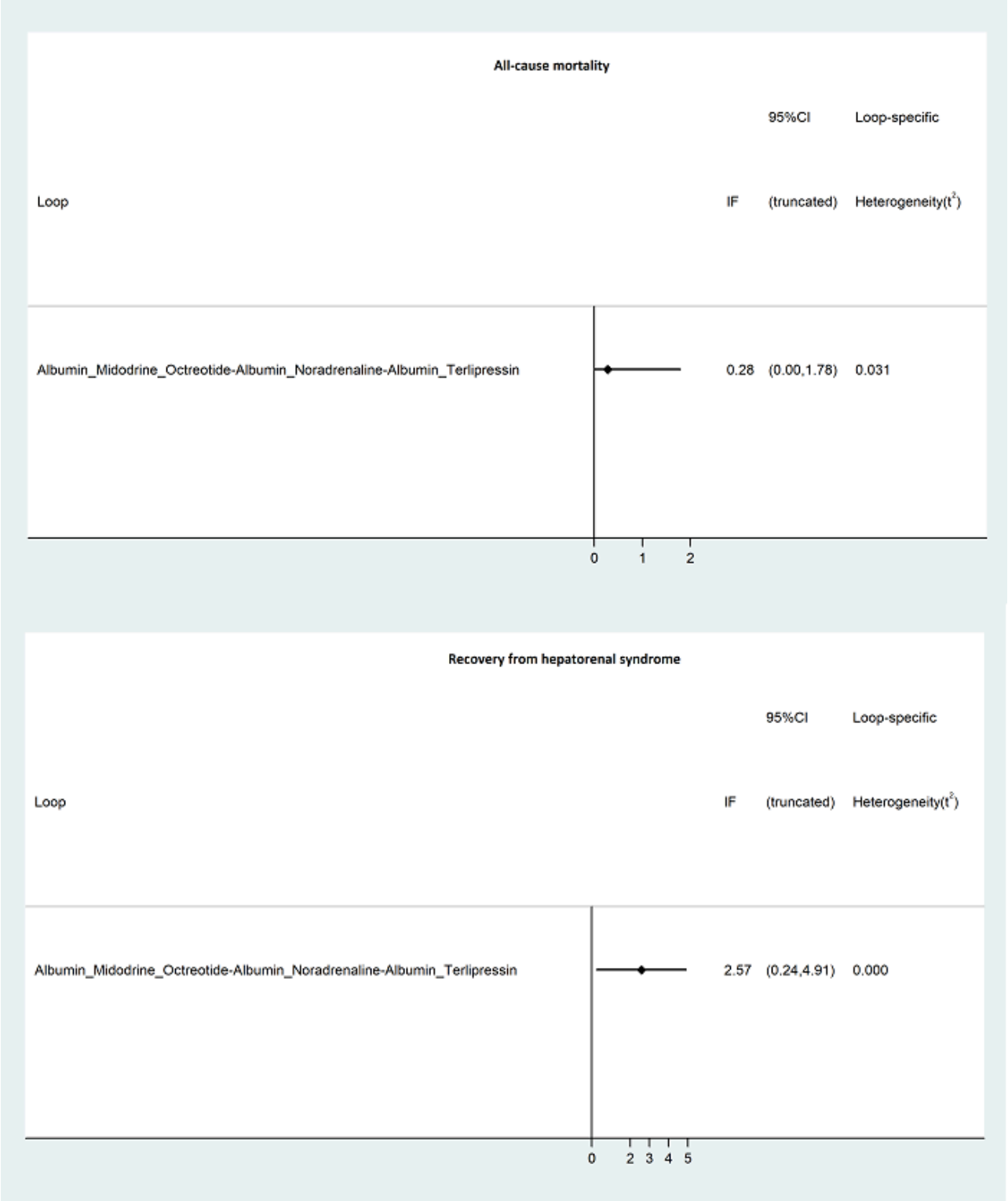
Figure 5. The forest plots for all-cause mortality and recovery from hepatorenal syndrome for which fixed-effect model and random-effects model showed different results. The more conservative random-effects model was used for interpretation. Abbreviations: Alb = albumin
Mid = midodrine
Nor = noradrenaline
Oct = Octreotide
Pen = Pentoxyfylline
Ter = Terlipressin



Inconsistency

Only two outcomes (all-cause mortality at maximal follow-up and resolution of hepatorenal syndrome at maximal follow-up) had triangular or quadrangular closed loops to allow assessment of inconsistency. There was no evidence of inconsistency as indicated by deviance information criterion (DIC) for these two outcomes, as indicated in Table 4. However, the Inconsistency Factor plot showed that there was inconsistency in the recovery from hepatorenal syndrome (Inconsistency Factor: 2.57; 95% CrI 0.24 to 4.91), although there was no evidence of inconsistency in mortality at maximal follow-up (Figure 6). We were unable to obtain convergence for design-by-treatment results for either of the outcomes, despite the different measures such as altering the initial values and giving different prior distributions as described above; probably because of the complex model with sparse data.

Figure 6. Inconsistency Factor (IF) plot showing that there was no evidence of inconsistency for all-cause mortality, but there was inconsistency for recovery from hepatorenal syndrome, the two outcomes for which inconsistency could be assessed. All-cause mortality: direct estimate The X-axis shows the difference in the direct and indirect effect estimates.



Probability ranks

The 95% CrI of the probability ranks were wide and included 0 and 1 in all the comparisons for all the outcomes. This was probably because of the sparse data from small trials. Therefore, we did not present the ranking probabilities (in a table), rankograms, and SUCRA plots: we considered that presenting this information would be unhelpful and potentially misleading and would ignore the systematic errors in the trials. However, we have presented the median probability ranks, when possible, in the Summary of findings for the main comparison and Summary of findings 2.

Certainty of evidence

The overall certainty of the evidence was low or very low for all outcomes. The main reasons for this were the trials at high risk of bias, in particular, lack of blinding; small sample size; and imprecision. There was also heterogeneity as the fixed-effect and random-effects models gave different interpretations for all-cause mortality and recovery from hepatorenal syndrome. For network meta-analysis, there was no evidence of inconsistency in terms of model fit for the two outcomes (all-cause mortality and recovery from hepatorenal syndrome), where it was possible to compare the direct and indirect evidence. There was no evidence of inconsistency by inconsistency factor plot for all-cause mortality. However, the inconsistency factor plot indicated inconsistency (Inconsistency Factor: 2.57; 95% CrI 0.24 to 4.91) and point effect estimates were in different directions for direct comparison and indirect comparison for recovery from hepatorenal syndrome; therefore, the results of network meta-analysis may indicate inconsistency and should be interpreted with caution. The summary of findings and certainty of evidence is available in Summary of findings for the main comparison.

Mortality at maximal follow-up

Twenty-two trials (1153 participants) reported mortality at maximal follow-up (Daskalopoulos 1985; Mitzner 2000; Chelarescu 2003; Solanki 2003; Alessandria 2007; Martin-Llahi 2008; Neri 2008; Sanyal 2008; Sharma 2008; Singh 2012; Tavakkoli 2012; Zafar 2012; Badawy 2013; Copaci 2013; Ghosh 2013; Indrabi 2013; Cavallin 2015; Boyer 2016; Goyal 2016; Arora 2018; Saif 2018; Stine 2018). A total of 12 treatments were compared in these 22 trials. A total of 19 trials (six treatments) could be included in the network meta-analysis. Three trials could not be included because they were not connected to the network (Daskalopoulos 1985; Mitzner 2000; Chelarescu 2003). The random-effects model was used as it had better model fit (Table 4) and was more conservative. The between-study variance was 0.19 (95% CrI 0.05 to 0.70). There was no evidence of differences (equivalent to statistically significant difference in frequentist analysis) in any of the comparisons included in the network meta-analysis or direct comparisons.

The comparisons in the three trials unconnected to the network were as follows (Daskalopoulos 1985; Mitzner 2000; Chelarescu 2003).

- Octreotide versus captopril plus octreotide (Chelarescu 2003): HR 2.73 (95% CrI 0.21 to 83.01).
- MARS (Molecular Adsorbent Recirculating System) versus haemofiltration (Mitzner 2000): no convergence in the Bayesian direct comparison analysis; all five participants who received haemofiltration and 6/8 (75%) people who received MARS died during the follow-up period.
- Surgical (peritoneovenous shunt) versus medical (no further details) (Daskalopoulos 1985): HR 0.63 (95% CrI 0.23 to 1.66).

Health-related quality of life

None of the trials reported health-related quality of life.

Serious adverse events

Three trials (428 participants) reported the proportion of people with serious adverse events (Sanyal 2008; Boyer 2016; Arora 2018); all were included in the network meta-analysis. Three treatments were compared in these trials. The fixed-effect model was used. There was no evidence of a difference in the network meta-analysis or in the direct comparisons (Table 5).

Two trials (166 participants) reported number of serious adverse events (Martin-Llahi 2008; Arora 2018); both were included in the network meta-analysis. Three treatments were compared. Overall, 57 serious adverse events were reported in 166 participants (0.3 serious adverse events per participant). The fixed-effect model was used. There was no evidence of a difference in the network meta-analysis or in the direct comparisons (Table 5).

Adverse events

Four trials (402 participants) reported the proportion of people with any adverse events (Sanyal 2008; Ghosh 2013; Cavallin 2015; Boyer 2016); all were included in the network meta-analysis. Four treatments were compared. The fixed-effect model was used. There was no evidence of a difference in the network meta-analysis or in the direct comparisons (Table 5).

Five trials (293 participants) reported number of (any) adverse events (Martin-Llahi 2008; Sharma 2008; Singh 2012; Goyal 2016; Arora 2018); all were included in the network meta-analysis. Three treatments were compared. The fixed-effect model was used. The number of any adverse events were lower in albumin plus noradrenaline versus albumin plus terlipressin (rate ratio 0.51 (95% CrI 0.28 to 0.87) by direct comparison and rate ratio 0.50 (95% CrI 0.28 to 0.88) by network meta-analysis). There was no evidence of a difference in the remaining network meta-analysis or in the direct comparisons (Table 5).

Liver transplantation

Four trials (342 participants) reported liver transplantation at maximal follow-up (Alessandria 2007; Sanyal 2008; Boyer 2016; Stine 2018). A total of five treatments were compared in these four trials. Three trials (three treatments) could be included in the network meta-analysis. The fixed-effect model was used. There was no evidence of differences in any of the comparisons included in the network meta-analysis or in the direct comparisons (Table 5).

One trial was not included in the network meta-analysis because it was not connected to the network (Stine 2018). In this trial, there was no evidence of a difference in the proportion of people who underwent liver transplantation between albumin plus midodrine plus octreotide plus pentoxifylline versus albumin plus midodrine plus octreotide: HR 0.99 (95% CrI 0.02 to 38.59).

Recovery from hepatorenal syndrome

None of the trials reported symptomatic recovery from hepatorenal syndrome (for example, recovery from oliguria or anuria or recovery from hepatorenal syndrome that required renal replacement

therapy). Eighteen trials (1047 participants) reported recovery from hepatorenal syndrome (as per definition) at maximal follow-up (Alessandria 2007; Goyal 2008; Martin-Llahi 2008; Neri 2008; Sanyal 2008; Sharma 2008; Singh 2012; Tavakkoli 2012; Badawy 2013; Copaci 2013; Ghosh 2013; Indrabi 2013; Cavallin 2015; Boyer 2016; Goyal 2016; Arora 2018; Saif 2018; Stine 2018); all were included in the network meta-analysis. Six treatments were compared. The random-effects model was used as it had better model fit (Table 4) and was more conservative. The between-study variance was 0.16 (95% CrI 0% to 0.86). In the direct comparisons, albumin plus midodrine plus octreotide and albumin plus octreotide had lower recovery from hepatorenal syndrome than albumin plus terlipressin (HR 0.04; 95% CrI 0.00 to 0.25 and HR 0.26, 95% CrI 0.07 to 0.80 respectively). There was no evidence of differences between the groups in any of the other direct comparisons. However, in the network meta-analysis, albumin and albumin plus midodrine plus octreotide had lower recovery from hepatorenal syndrome than albumin plus terlipressin and albumin plus noradrenaline.

- Albumin versus albumin plus terlipressin: HR 0.28 (95% CrI 0.14 to 0.53)
- Albumin plus midodrine plus octreotide versus albumin plus terlipressin: HR 0.26 (95% CrI 0.08 to 0.79)
- Albumin versus albumin plus noradrenaline: HR 0.33 (95% CrI 0.14 to 0.69)
- Albumin plus midodrine plus octreotide versus albumin plus noradrenaline: HR 0.30 (95% CrI 0.09 to 0.92)

There was no evidence of differences in any of the other comparisons in the network meta-analysis.

Other features of decompensation

None of the trials reported the proportion of people with one or more features of decompensation. One trial (46 participants) reported other features of decompensation at maximal follow-up (Martin-Llahi 2008). A total of 42 decompensation events occurred in these 46 participants (0.91 events per participant). There was no evidence of a difference between albumin versus albumin plus terlipressin: rate ratio 1.10 (95% CrI 0.60 to 2.03).

Length of hospital stay

None of the trials reported this outcome.

Number of days of lost work

None of the trials reported this outcome.

Treatment costs

Five trials (219 participants) reported costs (maximal follow-up) (Alessandria 2007; Sharma 2008; Singh 2012; Badawy 2013; Saif 2018). All five trials compared albumin + terlipressin versus albumin + noradrenaline. We used an international exchange rate based on purchasing power parities (PPP) to convert cost estimates to US dollars (USD), and we used the gross domestic product (GDP) deflators (or implicit price deflators for GDP) to convert cost estimates to 2017 USD using PPP conversion rates and GDP deflator values available from the International Monetary Fund in the World Economic Outlook Database (www.imf.org/external/data.htm). The fixed-effect model was used. The cost of albumin plus noradrenaline was lower (i.e. cheaper) than albumin plus terlipressin (USD -1066.00; 95% CrI -1093.00 to -1039.00).

Subgroup analyses

Because of the nature of the data (most trials included participants with varied aetiology without separate outcome data based on aetiology; and the presence of two trials at low risk of bias), the only subgroup analysis performed was based on the type of hepatorenal syndrome. Even for type of hepatorenal syndrome, subgroup analysis was possible only for mortality at maximal follow-up and recovery from hepatorenal syndrome because of sparse data for the remaining outcomes.

Although the interaction term did not overlap 0 for all-cause mortality at maximal follow-up (interaction term -0.30 (95% CrI -0.57 to -0.01), there was no evidence of differences in all-cause mortality for any of the subgroups, i.e. hepatorenal syndrome type 1, hepatorenal syndrome type 2, or when this information was not available. However, the differences between the interventions versus albumin plus terlipressin were generally larger in type II hepatorenal syndrome than in other categories. The interaction term did overlap 0 for recovery of hepatorenal syndrome (interaction term 0.05 (95% CrI -0.45 to 0.61)).

Sensitivity analysis

The scenario analysis that we performed for post-randomisation dropouts for binary and time-to-event outcomes (where binomial likelihood was used) did not reveal any alterations in the results. Excluding three trials in which the standard deviation was initially imputed (Sharma 2008; Singh 2012; Saif 2018) for treatment costs, did not alter our conclusions.

Assessment of reporting biases

Since there was no meaningful way in which to rank these studies (i.e. there was no specific change in the risk of bias in the studies, sample size, or the control group used over time), we did not perform the comparison-adjusted funnel plot.

DISCUSSION

Summary of main results

We included a total of 25 trials (1263 participants) in this review. A total of 1185 participants from 23 trials were included in one or more outcomes. Overall, 58.6% of participants died and about 35.3% of participants recovered from hepatorenal syndrome within three months. There was no evidence of inconsistency based on model fit in the two networks (mortality at maximal follow-up and recovery from hepatorenal syndrome at maximal follow-up) in which we could assess this. However, the Inconsistency Factor indicated inconsistency, and the effect estimates from direct comparisons and indirect comparisons were not similar for recovery from hepatorenal syndrome. Generally, the networks were sparse, and they involved mostly comparisons between albumin plus terlipressin, albumin plus noradrenaline, and albumin alone. Therefore, the results from network meta-analysis should be interpreted with caution. None of the trials included 'no treatment' as the control group. Therefore, the effects of these treatments against no treatment is not known. However, it is unlikely that patients with hepatorenal syndrome are not treated in any fashion.

There was no evidence of a difference for any of the treatments regarding the following outcomes: mortality at maximal follow-up, serious adverse events (proportion), serious adverse events (number), any adverse events (proportion), liver transplantation

at maximal follow-up, or other decompensation events. The number of adverse events and costs were lower with albumin plus noradrenaline than with albumin plus terlipressin. The implications of an increased number of adverse events is unclear, as the impact of these adverse events on the participant's health-related quality of life was not reported by any of the trials. Albumin alone and albumin plus midodrine plus octreotide had lower recovery from hepatorenal syndrome than both albumin plus terlipressin and albumin plus noradrenaline. However, these were hepatorenal syndrome as per definitions and the impact of recovery from hepatorenal syndrome on clinical outcomes is not known.

Future trials can and should be powered on short-term all-cause mortality. Albumin plus terlipressin and albumin plus noradrenaline were the commonest interventions used in the trials and had higher recovery from hepatorenal syndrome than albumin alone and albumin plus midodrine plus octreotide. Thus, these two interventions seem to be the two interventions that should be compared in future trials. The sample size required in such trials based on a control group proportion of 52% (the weighted median mortality proportion in albumin plus terlipressin), a relative risk reduction of 20% in the experimental group, type I error of 5%, and type II error of 20% is 720 participants. It is important that health-related quality of life and adverse events (due to any cause: disease-related, treatment-related, or co-morbidity-related) should be measured as outcomes in such a trial. A short period of follow-up of 90 days may be sufficient to determine the effectiveness of an intervention.

Overall completeness and applicability of evidence

The trials included people who had developed various aetiologies of liver cirrhosis and included people with both type I and II hepatorenal syndrome. The findings of this review are, therefore, applicable to people undergoing treatment for either type I or II hepatorenal syndrome with any underlying liver cirrhosis aetiology. However, we did not include trials in people who had previously undergone liver transplantation. Therefore, the findings of this review are applicable only to people who had not previously undergone liver transplantation.

Quality of the evidence

The overall quality (certainty) of the evidence was low or very low for all outcomes. The main reasons for this were the trials at high risk of bias, in particular, lack of blinding or inadequate blinding; small sample size; and imprecision. There was also heterogeneity as the fixed-effect and random-effects model gave different interpretations for all-cause mortality and recovery from hepatorenal syndrome. For network meta-analysis, there was no evidence of inconsistency in terms of model fit for the two outcomes (all-cause mortality and recovery from hepatorenal syndrome), where it was possible to compare the direct and indirect evidence. However, the Inconsistency Factor Plot indicated inconsistency and the point effect estimates were in different directions for direct comparison and indirect comparison for recovery from hepatorenal syndrome; therefore, the results of network meta-analysis may indicate inconsistency and should be interpreted with caution.

Potential biases in the review process

We selected a range of databases to search without using any language restrictions and conducted the network meta-analysis according to NICE DSU guidance (Dias 2016). In addition, we have presented the results from the fixed-effect model and random-effects model and used the more conservative model. These are the strengths of the review process.

We have excluded studies that compared variations in duration or dose in the different interventions. Hence, this review does not provide information on whether one dose or duration of treatment is better than another. Another major limitation of this review was the paucity of data. Few trials were included for each comparison; in many comparisons, only one trial was included. This makes it difficult to assess whether the effect estimates are reproducible. This paucity of data decreases the confidence in the results.

All of the network meta-analyses included only sparse data from trials at high risk of bias. We were able to compare the direct and indirect estimates for very few comparisons. This means that the tests for inconsistency are underpowered. One of the underpinning assumptions of a network meta-analysis is that the participants in the different comparisons are similar. There was no evidence of systematic differences across comparisons from clinical or methodological points of view. However, one cannot rule out violation of the transitivity assumption because of the sparse data; potential differences in the co-interventions, and potential differences in the definitions used by trial authors for adverse events and serious adverse events.

We only included randomised clinical trials, which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. According to our choice of studies (i.e. only randomised clinical trials), it is possible that we have missed a large number of studies addressing reporting of harms. Accordingly, this review is biased towards benefits ignoring harms. We may have, therefore, overlooked evidence of harm from non-randomised studies. On the other hand, inclusion of non-randomised studies in the network meta-analysis can increase the differences in potential modifiers and decrease the reliability of the findings of the network meta-analysis.

Agreements and disagreements with other studies or reviews

We agree with the findings of one Cochrane review and another systematic review which found no evidence of benefit for albumin plus terlipressin and very low-certainty evidence of increased adverse events with albumin plus terlipressin versus albumin plus noradrenaline (Israelsen 2017; Nassar Junior 2014). We also agree with another Cochrane review that stated that albumin alone has lower recovery from hepatorenal syndrome than albumin plus terlipressin (Allegretti 2017). However, we do not agree that albumin plus terlipressin decreases mortality: the probable reason for the different interpretation is the trials included in the analysis. We excluded one trial (Hadengue 1998) as this was a cross-over randomised clinical trial with 48 hours of treatment and only 24 hours of wash-out period because of concerns for residual effect; we also considered two likely publications of the same trial, based on the common authors included, the intervention, control, and partial overlapping of recruitment period (Neri 2008). We were unable to confirm whether these were one and the same trial or two different trials. Israelsen 2017 treated them as two different trials, while we treated these as two different reports of the same trial (Neri 2008). Other reasons could be different analyses methods used (for example, no zero error correction in the Bayesian methods

used in our review versus frequentist method with zero correction with the default 0.5 added in Review Manager).

In another systematic review, Nanda and colleagues concluded that intravenous infusion of terlipressin (in combination with albumin) is the most effective medical therapy for reversing hepatorenal syndrome (Nanda 2018). The possible reasons for disagreement is that Nanda and colleagues did not take into account the risk of bias in the trials and the information on adverse events was not taken into account while arriving at those conclusions (Nanda 2018). While we found that albumin plus terlipressin was better than albumin alone in terms of recovery from hepatorenal syndrome (based on very low-certainty evidence), we did not find any evidence to suggest that albumin plus terlipressin was better than albumin plus noradrenaline in terms of recovery from hepatorenal syndrome.

AUTHORS' CONCLUSIONS

Implications for practice

Based on very low-certainty evidence, there is no evidence of benefit or harm of any of the interventions for hepatorenal syndrome with regards to the following outcomes: all-cause mortality, serious adverse events (proportion), number of serious adverse events per participant, any adverse events (proportion), liver transplantation, or other decompensation events. Low-certainty evidence suggests that albumin plus noradrenaline had fewer 'any adverse events per participant' and costs than albumin plus terlipressin. Low- or very low-certainty evidence also found that albumin plus midodrine plus octreotide and albumin alone had lower recovery from hepatorenal syndrome compared with albumin plus terlipressin and albumin plus noradrenaline.

Implications for research

Further well-designed randomised clinical trials are necessary. Some aspects of the design of the randomised clinical trials are as follows.

Study design: placebo-controlled, parallel, randomised clinical trial
Participants: people with cirrhosis in whom hepatorenal syndrome has developed
Intervention: albumin plus noradrenaline
Control: albumin plus terlipressin
Outcomes:
Primary outcome: short-term mortality (90-day all-cause mortality)
Secondary outcomes: health-related quality of life, adverse events, recovery from hepatorenal syndrome, and resource utilisation measures including length of hospital stay
Minimum length of follow-up: 90 days
Sample size: Please see discussion
Trials need to be designed and conducted according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013) and reported according to the CONSORT statement (Schulz 2010).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alessandria 2007

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 22 Post-randomisation dropouts: 0 (0%) Revised sample size: 22 Average age: 55 years Females: 6 (27.3%) Hepatorenal syndrome type 1: 9 (40.9%) Hepatorenal syndrome type 2: 13 (59.1%) Alcoholic cirrhosis: 6 (27.3%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: yes Alcoholic cirrhosis: yes Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • Heart failure • Respiratory failure

Alessandria 2007 *(Continued)*

- Coronary disease
- Peripheral artery disease
- Patients not considered eligible for improvement in renal function after blood volume expansion

Interventions	Patients were randomly assigned to two groups. Group 1: noradrenaline plus albumin (n = 10) Further details: noradrenaline: continuous infusion at 0.1 µg/kg/min increased every 4 hours based on arterial blood pressure in steps of 0.05 µg/kg/min up to a maximum dose of 0.7 µg/kg/min. Albumin: given to maintain central venous pressure between 10 and 15 cm H_2O Group 2: terlipressin plus albumin (n = 12) Futher details: terlipressin: intravenous bolus 1 mg every 4 hours, increased to 2 mg every 4 hours after 3 days of treatment if reduction of at least 25% serum creatinine not observed. Albumin: given to maintain central venous pressure between 10 and 15 cm H_2O.
Outcomes	The outcomes reported were: • mortality • liver transplantation • recovery from HRS • costs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was made by using the sealed opaque envelopes method"
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was made by using the sealed opaque envelopes method". Comment: Further details were not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Prospective, randomized, unblinded, pilot study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Prospective, randomized, unblinded, pilot study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Arora 2018

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 120 Post-randomisation dropouts: 0 (0%) Revised sample size: 120 Average age: 40 years Females: 7 (5.8%) Patients with HRS type I: 120 (100%) Patients with HRS type II: 0 (0%) Alcoholic cirrhosis: 87 (72.5%) Viral-related cirrhosis: 18 (15%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 5 (4.2%) Other causes for cirrhosis: 10 (8.3%) Follow-up in months: 1 Years of recruitment: 2015-2016 Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: yes Other causes for cirrhosis: yes Other important exclusion criteria • Age < 18 years • Decompensated cirrhosis • Patients on renal replacement therapy • Renal transplantation • Liver transplantation • History of coronary disease • Ischaemic cardiomyopathy • Ventricular arrhythmia • Peripheral vascular disease • Chronic kidney disease • Obstructive uropathy
Interventions	Patients were randomly assigned to two groups. Group 1: noradrenaline plus albumin (n = 60)

Arora 2018 *(Continued)*

	Further details: noradrenaline: continuous intravenous infusion starting at 0.5 mg/h with doubling of dose up to 3 mg/h after every 4 hours designed to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in 4 h urine output > 200 mL. Albumin 20-40 g/day given until the end of reversal of hepatorenal syndrome acute kidney injury or evidence of volume overload (central venous pressure > 18cm H_2O or inferior vena cava > 22 mm) or requirement of renal replacement therapy. Group 2: terlipressin plus albumin (n = 60) Futher details: terlipressin: continuous infusion started at the dosage of 2 mg/24h. The dosage of terlipressin was doubled every 48 hours in case of non-response (< 25% of pretreatment value) to the maximum dosage of 12 mg/24h. Albumin 20-40 g/day given until the end of reversal of hepatorenal syndrome acute kidney injury or evidence of volume overload (central venous pressure > 18cm H_2O or inferior vena cava > 22 mm) or requirement of renal replacement therapy.
Outcomes	The outcomes reported were: • mortality • serious adverse events • adverse events • recovery from HRS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was done by sequentially numbered opaque sealed envelopes (SNOSE) technique".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was conducted as a randomized open label trial".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The study was conducted as a randomized open label trial".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: No protocol was available, but the authors reported expected clinical outcomes adequately.
Other bias	Low risk	Comment: No other bias noted

Badawy 2013

Methods	Randomised clinical trial
Participants	Country: Egypt

Badawy 2013 *(Continued)*

Number randomised: 60

Post-randomisation dropouts: 9 (15%)

Revised sample size: 51

Average age: 45 years

Females: 16 (31.4%)

Patients with HRS type I: 51 (100%)

Patients with HRS type II: 0 (0%)

Alcoholic cirrhosis: 5 (9.8%)

Viral-related cirrhosis: 47 (92.2%)

Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 7 (13.7%)

Other causes for cirrhosis: 11 (21.6%)

Follow-up in months: 0.5
Years of recruitment: 2009-2012
Prophylactic antibiotics for subacute bacterial peritonitis: not stated
Additional treatment for ascites: not stated

Important inclusion and exclusion criteria

Patients with hepatorenal syndrome type I: yes

Patients with hepatorenal syndrome type II: no

Alcoholic cirrhosis: yes

Viral-related cirrhosis: yes

Autoimmune disease-related cirrhosis: yes

Other causes for cirrhosis: yes

Other important exclusion criteria

- Multinodular hepatocellular carcinoma
- Septic shock
- Parenchymal kidney disease
- Peripheral vascular disease
- Coronary artery disease
- Heart failure
- Respiratory failure
- Previous myocardial infarction
- Hypersensitivity to any of the study medications
- Any contraindication for central venous line insertion
- Patients on nephrotoxic medications
- Pateints enrolled in another trial
- Pregnant women
- Lactating women

Interventions	Patients were randomly assigned to two groups. Group 1: noradrenaline plus albumin (n = 26)

Badawy 2013 *(Continued)*

	Further details: noradrenaline initial dose of 0.5 mg/hr by intravenous continuous infusion to revert type 1 hepatorenal syndrome. If the target was not achieved, the norepinephrine dose was increased stepwise by 0.5 mg/hr every 4 h until the maximum dose (3 mg/h) was reached. Norepinephrine infusion was titrated guided by the mean arterial blood pressure. Mean arterial pressure was kept at a level of 85-90 mmHg or less. Albumin 20% 200-400 g/day. Group 2: terlipressin plus albumin (n = 25) Futher details: terlipressin initial dose of 3 mg/24hr by intravenous continuous infusion. If during the following 48 hr the hepatorenal syndrome did not revert, the dose was increased to 6 mg/24 hr. If the hepatorenal syndrome reversal was not achieved within 48 hr, the dose of terlipressin was increased to the maximal dose of 12 mg/24hr. Albumin 20% 200-400 g/day.
Outcomes	The outcomes reported were: • Mortality • Recovery from HRS • Costs
Notes	Reasons for post-randomisation dropouts: Died within 72 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was done by sealed envelopes".
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was done by sealed envelopes". Comment: Further details were not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The treatment was not blinded".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The treatment was not blinded".
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Patients who were dead within 72 hours were excluded: this was highly likely to be related to the outcomes.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Boyer 2016

Methods	Randomised clinical trial
Participants	Country: United States & Canada Number randomised: 196 Post-randomisation dropouts: 0 (0%) Revised sample size: 196

Boyer 2016 *(Continued)*

	Average age: 55 years Females: 77 (39.3%) Hepatorenal syndrome type 1: 196 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: 103 (52.6%) Viral-related cirrhosis: 85 (43.4%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 9 (4.6%) Other causes for cirrhosis: 55 (28.1%) Follow-up in months: 3 Years of recruitment: 2010-2013 Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: yes Other causes for cirrhosis: yes Other important exclusion criteria • Serum creatinine level greater than 7 mg/dL • Hypotension (MAP < 70 mmHg) with evidence of hypoperfusion • Sepsis • Untreated infection • Evidence of other intrinsic renal disease • Recent exposure (≥ 48 hours) to octreotide, midodrine, vasopressin, dopamine, or other vasopressors
Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 97) Further details: terlipressin 1 mg slow intravenous bolus injections over 2 minutes every 6 hours (total amount of terlipressin, 4 mg/day). If serum creatinine had decreased but not by more than 30% from the baseline value on day 4 of treatment after a minimum of 10 doses, the dose was increased to 2 mg every 6 hours (total amount of terlipressin, 8 mg/day). Albumin 20-40 g/day as clinically indicated. Treatment was continued until at least 2 serum creatinine values of 1.5 mg/dL or less were obtained at least 40 hours apart (minimum of 22 hours apart in the event of transplant or hospital discharge)18 and no more than 24 hours after the last dose, or up to 14 days (maximum of 15–16 days if serum creatinine first reached 1.5 mg/dL on days 13–14, respectively). If serum creatinine was at or above the baseline value on day 4 after a minimum of 10 doses, the study medication was discontinued. Treatment also was discontinued for patients who had to undergo renal replacement therapy or liver transplantation. Dosing was discontinued permanently if an ischaemic event occurred. If investigators judged it to be potentially beneficial, patients with at least a 30% reduction in serum creatinine during initial treatment and who developed recurrence of hepatorenal syndrome type I could be re-treated once with the initially assigned study medication. Group 2: albumin (n = 99) Further details: placebo was administered via a slow intravenous bolus injection over 2 minutes every 6 hours (total amount of terlipressin, 4 mg/day). Detailed criteria for dose increases, re-treatment, and discontinuation have been described in group 1.
Outcomes	The outcomes reported were: • Mortality • Serious adverse events

Boyer 2016 *(Continued)*

- Adverse events
- Liver transplantation
- Recovery from hepatorenal syndrome

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "by using a central interactive voice response system"
Allocation concealment (selection bias)	Low risk	Quote: "by using a central interactive voice response system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo-controlled, double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "placebo-controlled, double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: study protocol was available, and the authors have reported the expected clinical outcomes adequately.
Other bias	Low risk	Comment: No other bias noted

Cavallin 2015

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 49 Post-randomisation dropouts: 1 (2%) Revised sample size: 48 Average age: 62 years Females: 16 (33.3%) Hepatorenal syndrome type 1: 44 (91.7%) Hepatorenal syndrome type 2: 4 (8.3%) Alcohol-related cirrhosis: 0 (0%) Viral-related cirrhosis: 18 (37.5%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 3 Years of recruitment: 2008-2012 Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria**

Cavallin 2015 *(Continued)*

	Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: yes Alcoholic cirrhosis: no Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: yes Other important exclusion criteria • Hepatocellular carcinoma outside Milan criteria • Septic shock • Cardiac failure • Respiratory failure • Stroke • Coronary artery disease
Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 27) Further details: terlipressin (Glypressin; Ferring AB, Malmo, Sweden) was administered initially at a dose of 3 mg/24 hours by continuous intravenous infusion. Response to treatment was evaluated every 48 hours. If serum creatinine decreased by < 25% of the pretreatment value, the dose of terlipressin was progressively increased to 12 mg/24 hours. Albumin (Albumina 20%; Kedrion S.p.A., Barga, Italy) was administered intravenously, 1 g/kg at day 1 and 20-40 g/day subsequently for the duration of the study. Group 2: midodrine, octreotide and albumin (n = 21) Further details: midodrine (Gutron; Lusofarmaco, Peschiera Borromeo, Italy) was administered orally at a starting dose of 7.5 mg every 8 hours along with octreotide (Longastatina; Italfarmaco S.p.A., Milan, Italy) administered subcutaneously at a starting dose of 100 µg every 8 hours. If serum creatinine decreased by < 25% of the pretreatment value, the dose of midodrine was progressively increased to a maximum of 12.5 mg every 8 hours and octreotide to 200 µg every 8 hours. Albumin (Albumina 20%; Kedrion S.p.A., Barga, Italy) was administered intravenously, 1 g/kg at day 1 and 20-40 g/day subsequently for the duration of the study.
Outcomes	The outcomes reported were: • Mortality • Adverse events • Recovery from hepatorenal syndrome
Notes	Reasons for post-randomisation dropouts: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized at each hospital using sealed opaque envelopes containing the treatment assignments based on random numbers generated by the Stata statistical package".
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized at each hospital using sealed opaque envelopes containing the treatment assignments based on random numbers generated by the Stata statistical package".

Cavallin 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: One patient was excluded on the basis of undergoing liver transplantation on day 2: this was highly likely to be related to the outcomes.
Selective reporting (reporting bias)	Low risk	Comment: Study protocol was not available, but the authors have reported the expected clinical outcomes adequately.
Other bias	Low risk	Comment: No other bias noted

Chelarescu 2003

Methods	Randomised clinical trial
Participants	Country: Romania Number randomised: 25 Post-randomisation dropouts: not stated Revised sample size: 25 Average age: not stated Females: not stated Hepatorenal syndrome type 1: not stated Hepatorenal syndrome type 2: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 0.23 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: not stated Patients with hepatorenal syndrome type II: not stated Alcoholic cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • None stated
Interventions	Participants were randomly assigned to two groups. Group 1: Captopril and octreotide (n = 13)

Chelarescu 2003 *(Continued)*

	Further details: Octreotide 100 µg intravenously at '8h/d, 7d'. Group 2: Octreotide (n = 12) Further details: Octreotide same dose and captopril 6.25 mg twice daily for 7 days
Outcomes	The outcomes reported were: • Mortality
Notes	Reasons for post-randomisation dropouts: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind manner" Comment: Also stated double-blind; there was no mention of a placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind manner" Comment: Also stated double-blind; there was no mention of a placebo.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: This information was not available.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Copaci 2013

Methods	Randomised clinical trial
Participants	Country: Romania Number randomised: 40 Post-randomisation dropouts: not stated Revised sample size: 40 Average age: not stated Females: not stated Hepatorenal syndrome type 1: 36 (90%) Hepatorenal syndrome type 2: 4 (10%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 1 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated

Copaci 2013 *(Continued)*

	Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: yes Alcoholic cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • None stated
Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 20) Further details: patients received terlipressin by continuous intravenous infusion at initial dose of 4 mg/24 hrs, which in case of non-response was progressively increased to 12 mg/24hrs. Patients in both groups received albumin 1 g/kg body weight on first day, followed by 20–40 g/day. Group 2: octreotide and albumin (n = 20) Further details: patients received octreotide at initial dose of 100 µg subcutaneously three times daily, which in case of non-response was increased to 200 µg three times daily. Patients in both groups received albumin 1 g/kg body weight on first day, followed by 20–40 g/day.
Outcomes	The outcomes reported were: • Mortality • Recovery from hepatorenal syndrome
Notes	Reasons for post-randomisation dropouts: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: This information was not available.

Copaci 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Daskalopoulos 1985

Methods	Randomised clinical trial
Participants	Country: United States Number randomised: 28 Post-randomisation dropouts: 2 Revised sample size: 26 Average age: not stated Females: 5 randomised, unclear after dropouts Hepatorenal syndrome type 1: not stated Hepatorenal syndrome type 2: not stated Alcohol-related cirrhosis: 28 Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 0.5 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: not stated Patients with hepatorenal syndrome type II: not stated Alcoholic cirrhosis: yes Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • Other cause of acute renal failure
Interventions	Participants were randomly assigned to two groups. Group 1: surgical (n = 11) Further details: peritoneovenous shunt within 2 days of randomisation Group 2: medical (n = 15) Further details: control, unclear what standard treatment involved, trial from 1978-1983
Outcomes	The outcomes reported were: • Mortality
Notes	Reasons for post-randomisation dropouts: refused treatment, developed variceal bleed
Risk of bias	

Daskalopoulos 1985 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: One patient was excluded on the basis of variceal bleeding on the day of planned surgery: this was highly likely to be related to the treatment and outcomes.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Ghosh 2013

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 58 Post-randomisation dropouts: 12 (20.7%) Revised sample size: 46 Average age: 47 years Females: 10 (21.7%) Hepatorenal syndrome type 1: 0 (0%) Hepatorenal syndrome type 2: 46 (100%) Alcohol-related cirrhosis: 31 (67.4%) Viral-related cirrhosis: 8 (17.4%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 2 (4.3%) Other causes for cirrhosis: 5 (10.9%) Follow-up in months: 3 Years of recruitment: 2009-2011 Prophylactic antibiotics for subacute bacterial peritonitis: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: no Patients with hepatorenal syndrome type II: yes Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: yes

Ghosh 2013 *(Continued)*

	Other causes for cirrhosis: yes Other important exclusion criteria • Shock • Fluid losses • Treatment with nephrotoxic drugs • Improvement in renal function following diuretic withdrawal and plasma volume expansion • Ultrasound evidence of renal parenchymal disease • Obstructive uropathy and absence of proteinuria more than 500 mg/24 hours • History of coronary artery disease • History of cardiomyopathy • History of ventricular arrhythmia • History of obstructive arterial disease of the limbs
Interventions	Participants were randomly assigned to two groups. Group 1: noradrenaline and albumin (n = 23) Further details: continuous infusion of noradrenaline at an initial dose of 0.5 mg/h, designed to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in 4 h urine output to more than 200 mL. When one of these goals was not achieved, the noradrenaline dose increased every 4 h in steps of 0.5 mg/h, up to the maximum dose of 3 mg/h. 20 g albumin/day administered. Albumin was withheld if central venous pressure was more than 18 cm of saline. Group 2: terlipressin and albumin (n = 23) Further details: terlipressin as an intravenous bolus of 0.5 mg every 6 h. If a significant reduction in serum creatinine level was not observed during the 3-day period, the dose of terlipressin was increased in a stepwise fashion every 3 days to a maximum of 2 mg every 6 h. 20 g albumin/day administered, albumin was withheld if central venous pressure was more than 18 cm of saline. Unclear which group post-randomisation dropouts were in
Outcomes	The outcomes reported were: • Mortality • Adverse events • Recovery from hepatorenal syndrome
Notes	Reasons for post-randomisation dropouts: severe coronary artery disease in 1, sepsis in 7, hepatocellular carcinoma in 1, diabetic nephropathy in 1 and refusal to participate in 2 patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computer made the randomization code…".
Allocation concealment (selection bias)	Unclear risk	Quote: "with 46 envelopes with half of..". Comment: Further details of how the allocation was concealed were not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and investigators were not blinded to the treatment assignments".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Patients and investigators were not blinded to the treatment assignments".

Ghosh 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: abstracts presented information on 60 patients while full article presented data only on 46. It was not clear from the full text whether the exclusions were after randomisation. If they were, the outcomes were related to the dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: study protocol was not available, but the authors have reported the expected clinical outcomes adequately.
Other bias	Low risk	Comment: No other bias noted

Goyal 2008

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 32 Post-randomisation dropouts: not stated Revised sample size: 32 Average age: 54 years Females: 2 (6.3%) Hepatorenal syndrome type 1: 10 (31.3%) Hepatorenal syndrome type 2: 22 (68.8%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 0.5 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: yes Alcoholic cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • None stated
Interventions	Participants were randomly assigned to two groups. Group 1: noradrenaline and albumin (n = 16) Further details: noradrenaline (0.5-3 mg/h) plus furosemide, along with intravenous albumin Group 2: terlipressin and albumin (n = 16) Further details: terlipressin (1-2 mg/4h) along with intravenous albumin
Outcomes	The outcomes reported were: • Recovery from hepatorenal syndrome

Goyal 2008 *(Continued)*

Notes	Reasons for post-randomisation dropouts: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "unblinded study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "unblinded study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: This information was not available.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Goyal 2016

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 41 Post-randomisation dropouts: 0 (0%) Revised sample size: 41 Average age: 56 years Females: 4 (9.8%) Hepatorenal syndrome type 1: 41 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: 28 (68.3%) Viral-related cirrhosis: 7 (17.1%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: 7 (17.1%) Follow-up in months: 0.5 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no

Goyal 2016 *(Continued)*

Alcoholic cirrhosis: yes

Viral-related cirrhosis: yes

Autoimmune disease-related cirrhosis: not stated

Other causes for cirrhosis: yes

Other important exclusion criteria

- Improvement in renal function after central blood volume expansion
- Presence of severe sepsis
- Presence of pancreatitis
- Presence of shock
- Use of nephrotoxic drugs
- History of coronary artery disease
- History of obstructive cardiomyopathy
- History of ventricular arrhythmia
- History of obliterative arterial disease of the limbs

Interventions	Participants were randomly assigned to two groups. Group 1: noradrenaline and albumin (n = 21) Further details: continuous infusion of noradrenaline (Adrenor, Samarth Life Sciences, Mumbai, India) at an initial dose of 0.5 mg/h administered by an automatic syringe pump, aimed to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in 1 h urine output to > 40 mL. If either of these goals was not achieved, the noradrenaline dose was stepped up by 0.5 mg/h every 4 h, up to the maximum dose of 3 mg/h. Furosemide was added as intravenous infusion at a dose of 0.001 mg/kg/min if adequate urine output was not achieved despite an increase in mean arterial pressure. Furosemide dose was adjusted to maintain a urine output of at least 40 mL/1hr. Patients received daily IV albumin (Buminate, Baxter private limited, Gurgaon, India) 20 g/day until the end of the study period. Albumin administration was stopped temporarily if central venous pressure increased above 12 cm of saline or if serum albumin was > 4 g/L. All patients received intravenous third-generation cephalosporins prophylactically during the study period. All patients had an indwelling urinary catheter for accurate measurement of urine output, which was removed when the patient recovered. Group 2: terlipressin and albumin (n = 20) Further details: terlipressin (Remestyp, Ferring Pharmaceuticals , Saint Prex, Switzerland) at an initial dose of 0.5 mg every 6 hour IV. If a significant (> 25%) reduction in serum creatinine level was not observed at 3 days, the dose of terlipressin was stepped up to 1 mg every 6 hours, up to a maximum of 2 mg every 6 hours. Patients received daily IV albumin (Buminate, Baxter private limited, Gurgaon, India) 20 g/day until the end of the study period. Albumin administration was stopped temporarily if central venous pressure increased above 12 cm of saline or if serum albumin was > 4 g/L. All patients received intravenous third-generation cephalosporins prophylactically during the study period. All patients had an indwelling urinary catheter for accurate measurement of urine output, which was removed when the patient recovered.
Outcomes	The outcomes reported were: • Mortality • Adverse events • Recovery from hepatorenal syndrome
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized into two groups (A and B) using a computer-generated randomization table to receive treatment for 2 weeks".

Goyal 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but the authors have reported the expected clinical outcomes adequately.
Other bias	Low risk	Comment: No other bias noted

Indrabi 2013

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 60 Post-randomisation dropouts: 0 (0%) Revised sample size: 60 Average age: not stated Females: not stated Hepatorenal syndrome type 1: 60 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 3 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no Alcoholic cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria

Indrabi 2013 *(Continued)*

	• None stated
Interventions	Participants were randomly assigned to two groups. Group 1: noradrenaline and albumin (n = 30) Further details: none reported Group 2: terlipressin and albumin (n = 30) Further details: none reported
Outcomes	The outcomes reported were: • Mortality • Recovery from hepatorenal syndrome
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Koch 2016

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 25 Post-randomisation dropouts: not stated Revised sample size: 25 Average age: not stated Females: 9 (36%) Hepatorenal syndrome type 1: not stated Hepatorenal syndrome type 2: not stated Alcohol-related cirrhosis: 22 (88%)

Koch 2016 *(Continued)*

	Viral-related cirrhosis: 2 (8%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 1 (4%) Other causes for cirrhosis: 0 (0%) Follow-up in months: 1 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: not stated Patients with hepatorenal syndrome type II: not stated Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: yes Other causes for cirrhosis: no Other important exclusion criteria • None stated
Interventions	Participants were randomly assigned to two groups. Group 1: goal directed therapy (n = 16) Further details: This protocol was based on three sequential algorithms including global end-diastolic volume index (GEDVI), extravascular lung water index (EVLWI), cell count in the ascitic fluid and pO2/FiO2. In summary these algorithms aimed at GEDVI-guided volume expansion within the first 48 h, followed by a transpulmonary thermodilation-guided strategy for fluid support using the PiCCO-2-device (Pulsion Medical Systems SE, Feldkirchen, Germany). Group 2: no goal directed therapy (n = 9) Further details: standard care
Outcomes	No outcomes of interest for this review were reported.
Notes	Reasons for post-randomisation dropouts: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias)	Unclear risk	Comment: This information was not available.

Koch 2016 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Martin-Llahi 2008

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 46 Post-randomisation dropouts: 0 (0%) Revised sample size: 46 Average age: 57 years Females: 17 (37%) Hepatorenal syndrome type 1: 35 (76.1%) Hepatorenal syndrome type 2: 11 (23.9%) Alcohol-related cirrhosis: 33 (71.7%) Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 3 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: yes Alcoholic cirrhosis: yes Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • Bacterial infection diagnosed by body temperature below 36°C or above 38°C, heart rate above 90 beats/min, respiratory rate above 20 breaths/min and white cell count below 4 or above 12 x 10^6/L of above 6% of band forms. N.B. patients could be included if renal failure persisted after infection resolution. • Cardiovascular diseases • Any extrahepatic disease that could affect the short-term prognosis • Organic nephropathy • Advanced hepatocellular carcinoma
Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 23) Further details: terlipressin (Glypressin, Ferring AB, Sweden) was administered initially at a dose of 1 mg/4 hour as intravenous (IV) bolus for 3 days. If after the first 3 days serum creatinine had decreased at least 25% of the pretreatment values, the dose was not modified. In patients in whom serum creatinine had not decreased at least 25% of the pretreatment values within the first 3 days, the dose was in-

Martin-Llahi 2008 *(Continued)*

	creased to a maximum of 2 mg/4 hour. Terlipressin was given until serum creatinine had decreased below 133 µmol/L or for a maximum of 15 days. Terlipressin administration was withheld if patients developed signs or symptoms compatible with ischaemic complications. An amendment was made during the study to allow treatment with terlipressin in patients assigned to albumin therapy who were potential candidates for liver transplantation if there was no improvement in renal function after 7 days. Albumin (Albumin 20 percent; Instituto Grífols, Barcelona, Spain) was given at a dose of 1 g/kg during the first 24 hours, followed by 40 g/day, targeted to obtain a central venous pressure (CVP) between 10 and 15 cm of water. CVP was measured at least once a day throughout the study period. When CVP increased over 15 cm of water, the albumin dose was reduced to 20 g/day and was withheld when CVP increased above 18 cm of water or there were clinical or radiologic signs of pulmonary oedema. In addition, these patients received IV boluses of furosemide. Group 2: albumin (n = 23) Further details: albumin (Albumin 20 percent; Instituto Grífols, Barcelona, Spain) was given at a dose of 1 g/kg during the first 24 hours, followed by 40 g/day, targeted to obtain a central venous pressure (CVP) between 10 and 15 cm of water. CVP was measured at least once a day throughout the study period. When CVP increased over 15 cm of water, the albumin dose was reduced to 20 g/day and was withheld when CVP increased above 18 cm of water or there were clinical or radiologic signs of pulmonary oedema. In addition, these patients received IV boluses of furosemide.
Outcomes	The outcomes reported were: • Mortality • Serious adverse events • Adverse events • Recovery from hepatorenal syndrome • Other features of decompensation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was centralized in the Hospital Clínic of Barcelona and was done with the use of sealed opaque envelopes containing the treatment assignments, which were based on random numbers generated by the STATA statistical package".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centralized in the Hospital Clínic of Barcelona and was done with the use of sealed opaque envelopes containing the treatment assignments, which were based on random numbers generated by the STATA statistical package".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Second, ideally, the study should have been performed using a double-blind design. However, this was not possible because our study was not…".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Second, ideally, the study should have been performed using a double-blind design. However, this was not possible because our study was not…".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: study protocol was not available, but authors have reported the expected clinical outcomes adequately.

Martin-Llahi 2008 *(Continued)*

Other bias	Low risk	Comment: No other bias noted

Mitzner 2000

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 13 Post-randomisation dropouts: not stated Revised sample size: 13 Average age: 47 years Females: 8 (61.5%) Hepatorenal syndrome type 1: 13 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: 7 (53.8%) Viral-related cirrhosis: 4 (30.8%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 1 (7.7%) Other causes for cirrhosis: 1 (7.7%) Follow-up in months: 1 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: yes Other causes for cirrhosis: yes Other important exclusion criteria • Fulminant hepatic failure • Sepsis unresponsive to antibiotic treatment • Severe acute haemorrhages • Malignancies • Obstructive/chronic renal failure • Pregnancy • Severe cardiopulmonary disease
Interventions	Participants were randomly assigned to two groups. Group 1: MARS (n = 8) Further details: patients underwent MARS treatment for 6 to 8 hours per treatment day in addition to standard medical treatment, including haemodiafiltration (HDF), when indicated (need for water removal, severe azotaemia, clinical signs of uremia). The maximum number of MARS treatments allowed per patient was 10. It was performed daily. A maximum of 2 treatment pauses of 1 d/wk was allowed to perform HDF or other diagnostic or therapeutic measures. No MARS treatment was performed when no spontaneous increase in total bilirubin level was observed between the value at the end of 1 single treatment and the next morning value or if the haemodynamic situation of the patient did not permit the initiation or maintenance of extracorporeal circulation. Group 2: haemofiltration (n = 5)

Mitzner 2000 *(Continued)*

	Further details: The patients underwent standard treatment plus HDF using bicarbonate-buffered dialysate, performed intermittently for 6 to 8 hours per session. The same type and size dialysis membrane as in the MARS treatment was used for HDF (P5S; Gambro, Hechingen, Germany). Heparin was administered as the anticoagulant. The indication for HDF was the need for water removal, severe azotaemia, and/or presence of uraemic symptoms.
Outcomes	The outcomes reported were: • Mortality
Notes	Reasons for post-randomisation dropouts: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computerized random-number generating program".
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes….randomization was performed by pulling the envelope with lowest number in the sequence..".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: This information was not available.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Neri 2008

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 52 Post-randomisation dropouts: 0 (0%) Revised sample size: 52 Average age: 60 years Females: 31 (59.6%) Hepatorenal syndrome type 1: 52 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: 7 (13.5%) Viral-related cirrhosis: 45 (86.5%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 0 (0%) Other causes for cirrhosis: 0 (0%) Follow-up in months: 3

Neri 2008 *(Continued)*

Years of recruitment: 2002-2005
Prophylactic antibiotics for subacute bacterial peritonitis: not stated
Additional treatment for ascites: not stated

Important inclusion and exclusion criteria

Patients with hepatorenal syndrome type I: yes

Patients with hepatorenal syndrome type II: no

Alcoholic cirrhosis: yes

Viral-related cirrhosis: yes

Autoimmune disease-related cirrhosis: no

Other causes for cirrhosis: no

Other important exclusion criteria

- Heart failure
- Respiratory failure
- Arterial hypertension
- Coronary artery disease
- Peripheral artery disease
- Age > 75 years
- Hepatocellular carcinoma

Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 26) Further details: intravenous boluses of terlipressin (Glipressin 0.5 mg; Laboratoires Ferring SpA, Milano, Italy) at the dose of 1 mg/8h/5days followed by 0.5 mg/8h for two weeks plus albumin (described in albumin group). In patients developing recurrence of hepatorenal syndrome, terlipressin and albumin were administered again following the same schedule of the initial treatment. Group 2: albumin (n = 26) Further details: intravenous boluses of albumin alone (Albumina Grifols 20%, 20 g of Albumin/100 mL; Barcelona, Spain). Albumin was given at a weight-based dosage (1 g/kg body weight during the first day and 20–40 g/day thereafter).
Outcomes	The outcomes reported were: • Mortality • Recovery from hepatorenal syndrome
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "For inclusion, randomization divided eligible subjects at study start into group A and B individually and sequentially, in a 1:1 ratio from a computer generated list ".
Allocation concealment (selection bias)	Low risk	Quote: "For inclusion, randomization divided eligible subjects at study start into group A and B individually and sequentially, in a 1:1 ratio from a computer generated list ".
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: This information was not available.

Neri 2008 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Saif 2018

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 60 Post-randomisation dropouts: 0 (0%) Revised sample size: 60 Average age: 53 years Females: not stated Hepatorenal syndrome type 1: 60 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 3 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no Alcoholic cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • Improvement in renal function after plasma volume expansion • Evidence of sepsis excluding spontaneous bacterial peritonitis • Coronary artery disease • Obstructive cardiomyopathy • Ventricular arrhythmia • Obliterative arterial disease

Saif 2018 *(Continued)*

Interventions	Participants were randomly assigned to two groups. Group 1: noradrenaline and albumin (n = 30) Further details: either continuous infusion of noradrenaline at an initial dose of 0.5 mg/h, designed to achieve an increase in mean arterial pressure of at least 10 mmHg, or an increase in 4-h urine output to more than 200 mL. When one of these goals was not achieved, the noradrenaline dose was increased every 4 h in steps of 0.5 mg/h, up to the maximum dose of 3 mg/h. Group 2: terlipressin and albumin (n = 30) Further details: terlipressin as an IV bolus of 0.5 mg every 6 h; if a significant reduction in serum creatinine level (≥ 1 mg/dL) was not observed during each 3-day period, the dose of terlipressin was increased in a stepwise fashion every 3 days to a maximum of 2 mg every 6 h to maximum of 8 mg per day.
Outcomes	The outcomes reported were: • Mortality • Recovery from hepatorenal syndrome • Costs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated randomization ".
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Sanyal 2008

Methods	Randomised clinical trial
Participants	Country: multicentre - 30 US, 2 Germany, 3 Russia Number randomised: 112 Post-randomisation dropouts: 0 (0%) Revised sample size: 112

Sanyal 2008 *(Continued)*

Average age: 52 years
Females: 32 (28.6%)
Hepatorenal syndrome type 1: 112 (100%)
Hepatorenal syndrome type 2: 0 (0%)
Alcohol-related cirrhosis: 40 (35.7%)
Viral-related cirrhosis: 46 (41.1%)
Autoimmune disease-related cirrhosis (example, PSC, PBC, AIH): 3 (2.7%)
Other causes for cirrhosis: 17 (15.2%)
Follow-up in months: 6
Years of recruitment: not stated
Prophylactic antibiotics for subacute bacterial peritonitis: not stated
Additional treatment for ascites: not stated

Important inclusion and exclusion criteria

Patients with hepatorenal syndrome type I: yes

Patients with hepatorenal syndrome type II: no

Alcoholic cirrhosis: yes

Viral-related cirrhosis: yes

Autoimmune disease-related cirrhosis: yes

Other causes for cirrhosis: yes

Other important exclusion criteria

- Evidence of obstructive or parenchymal renal disease (e.g. acute tubular necrosis, glomerular diseases, interstitial nephritis, and urinary obstruction)
- Use of nephrotoxic drugs
- Shock
- Uncontrolled bacterial infection
- Uncorrected fluid losses
- Acute liver disease because of factors known to also be nephrotoxic
- Severe cardiovascular disease as determined by the clinical judgement of individual investigators

Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 56) Further details: terlipressin at a dose of 1 mg administered by slow intravenous (IV) push every 6 hours, patients receive concomitant IV albumin (100 g on day 1 and 25 g daily until end of treatment) as per standard medical practice. If after 3 days of therapy, serum creatinine level had not decreased by at least 30% from the baseline value, the dose of terlipressin was increased to 2 mg every 6 hours. Patients could receive study drug for a maximum of 14 days but were to be discontinued from the study earlier for treatment failure or liver transplantation. Patients could also be withdrawn for an adverse event, withdrawal of consent, or physician decision/administrative reason. Patients who achieved treatment success could be discontinued or continue on therapy at the investigator's discretion until the maximum of 14 days. If judged by the investigator to be potentially beneficial, patients who demonstrated at least a partial response during the initial 14-day treatment course and then developed recurrence of hepatorenal syndrome type 1 during the follow-up period were eligible to be retreated with the initially assigned study drug for up to an additional 14 days. Group 2: albumin (n = 56) Further details: patients receive concomitant IV albumin (100 g on day 1 and 25 g daily until end of treatment) as per standard medical practice. If after 3 days of therapy, serum creatinine level had not decreased by at least 30% from the baseline value, the dose of the placebo was increased to 2 mg every 6 hours. Patients could receive placebo for a maximum of 14 days but were to be discontinued from the study earlier for treatment failure or liver transplantation. Patients could also be withdrawn for an adverse event, withdrawal of consent, or physician decision/administrative reason. Patients who achieved treatment success could be discontinued or continue on therapy at the investigator's discretion until the maximum of 14 days. If judged by the investigator to be potentially beneficial, patients

Sanyal 2008 *(Continued)*

	who demonstrated at least a partial response during the initial 14-day treatment course and then developed recurrence of hepatorenal syndrome type 1 during the follow-up period were eligible to be retreated with the initially assigned study drug for up to an additional 14 days..
Outcomes	The outcomes reported were: • Mortality • Serious adverse events • Adverse events • Liver transplantation • Recovery from hepatorenal syndrome
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomized through an interactive voice response system and computer-generated randomization scheme".
Allocation concealment (selection bias)	Low risk	Quote: "subjects were randomized through an interactive voice response system and computer-generated randomization scheme".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-Blind, Placebo-Controlled"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-Blind, Placebo-Controlled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: Study protocol was not available, but authors have reported the expected clinical outcomes adequately.
Other bias	Low risk	Comment: No other bias noted

Sharma 2008

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 40 Post-randomisation dropouts: 0 (0%) Revised sample size: 40 Average age: 48 years Females: 6 (15%) Hepatorenal syndrome type 1: 40 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: 26 (65%) Viral-related cirrhosis: 9 (22.5%)

Sharma 2008 *(Continued)*

	Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 1 (2.5%) Other causes for cirrhosis: 4 (10%) Follow-up in months: 0.5 Years of recruitment: 2005-2006 Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: yes Other causes for cirrhosis: yes Other important exclusion criteria • Improvement in renal function after central blood volume expansion • History of infection within the past week, excluding spontaneous bacterial peritonitis • History of coronary artery disease • History of obstructive cardiomyopathy • History of ventricular arrhythmia • History of obliterative arterial disease of the limbs
Interventions	Participants were randomly assigned to two groups. Group 1: noradrenaline and albumin (n = 20) Further details: patients received a continuous infusion of noradrenaline at an initial dose of 0.5 mg/h, designed to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in 4 h urine output to more than 200 mL. When one of these goals was not achieved, the noradrenaline dose was increased every 4 h in steps of 0.5 mg/h, up to the maximum dose of 3 mg/h. The patients from both groups received daily IV albumin 20–40 g/day until the end of the study period. Albumin administration was transiently stopped if central venous pressure increased above 18 cm of saline. Diuretics were not given during the treatment period. All patients received third-generation cephalosporins prophylactically during the study period. All patients had an indwelling urinary catheter until recovery from the hepatorenal syndrome for better measurement of urine output. It was removed when the patient recovered. Group 2: terlipressin and albumin (n = 20) Further details: patients received terlipressin as an IV bolus of 0.5 mg every 6 h. If a significant reduction in serum creatinine level (≥ 1 mg/dL) was not observed during each 3-day period, the dose of terlipressin was increased in a stepwise fashion every 3 days to a maximum of 2 mg every 6 h. The patients from both groups received daily IV albumin 20–40 g/day until the end of the study period. Albumin administration was transiently stopped if central venous pressure increased above 18 cm of saline. Diuretics were not given during the treatment period. All patients received third-generation cephalosporins prophylactically during the study period. All patients had an indwelling urinary catheter until recovery from the hepatorenal syndrome for better measurement of urine output. It was removed when the patient recovered.
Outcomes	The outcomes reported were: • Mortality • Adverse events • Recovery from hepatorenal syndrome • Costs

Sharma 2008 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized into two groups by a computer-generated randomization chart".
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Singh 2012

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 60 Post-randomisation dropouts: 14 (23.3%) Revised sample size: 46 Average age: 49 years Females: 8 (17.4%) Hepatorenal syndrome type 1: 46 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: 22 (47.8%) Viral-related cirrhosis: 15 (32.6%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 3 (6.5%) Other causes for cirrhosis: 6 (13%) Follow-up in months: 1 Years of recruitment: 2009-2011 Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no

Singh 2012 *(Continued)*

	Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: yes Other causes for cirrhosis: yes Other important exclusion criteria • History of coronary artery disease • History of cardiomyopathy • History of ventricular arrhythmia • History of obstructive arterial disease of the limbs
Interventions	Participants were randomly assigned to two groups. Group 1: noradrenaline and albumin (n = 23) Further details: patients received terlipressin as an intravenous bolus of 0.5 mg every 6 h. If a significant reduction in serum creatinine level was not observed during a 3-day period, the dose of terlipressin was increased in a stepwise fashion every 3 days to a maximum of 2 mg every 6 h. Patients in either group received treatment with terlipressin or noradrenaline with 20 g albumin/day. Albumin was withheld if central venous pressure was more than 18 cm of saline. Group 2: terlipressin and albumin (n = 23) Further details: patients received a continuous infusion of noradrenaline at an initial dose of 0.5 mg/h, designed to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in 4 h urine output of more than 200 mL. When one of these goals was not achieved, the noradrenaline dose was increased every 4 h in steps of 0.5 mg/h, up to the maximum dose of 3 mg/h. Patients in either group received treatment with terlipressin or noradrenaline with 20 g albumin/day. Albumin was withheld if central venous pressure was more than 18 cm of saline.
Outcomes	The outcomes reported were: • Mortality • Adverse events • Recovery from hepatorenal syndrome • Costs
Notes	Reasons for post-randomisation dropouts: severe coronary artery disease in three, sepsis in nine, hepatocellular carcinoma in one and diabetic nephropathy in one patient.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer made the randomization code with 46 envelopes".
Allocation concealment (selection bias)	Unclear risk	Quote: "with 46 envelopes, half for terlipressin...". Comment: Further details of how the allocation was concealed were not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and investigators were not blinded to the treatment assignments".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Patients and investigators were not blinded to the treatment assignments".

Singh 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: abstracts presented information on 60 patients while full article presented data only on 46. It was not clear from the full text whether the exclusions were after randomisation. If they were, the outcomes were related to the dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Solanki 2003

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 24 Post-randomisation dropouts: 0 (0%) Revised sample size: 24 Average age: 52 years Females: 7 (29.2%) Hepatorenal syndrome type 1: 24 (100%) Hepatorenal syndrome type 2: 0 (0%) Alcohol-related cirrhosis: 8 (33.3%) Viral-related cirrhosis: 9 (37.5%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): 0 (0%) Other causes for cirrhosis: 7 (29.2%) Follow-up in months: 0.5 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: no Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: no Other causes for cirrhosis: yes Other important exclusion criteria • Shock • Ongoing bacterial infection • Fluid losses • Treatment with nephrotoxic drugs • No improvement in renal function following diuretic withdrawal and plasma volume expansion • Proteinuria < 500 mg/day • No ultrasonographic evidence of renal parenchymal disease or urinary tract obstruction
Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 12)

Solanki 2003 *(Continued)*

	Further details: patients received terlipressin 1 mg IV at 12 h intervals The patients from both groups received IV albumin infusion, 20 g/day and fresh frozen plasma 150 mL every 8 h, until central venous pressure reached the upper normal range (10–12 cm of H_2O). Group 2: albumin (n = 12) Further details: patients received placebo (distilled water) 1 mL IV at 12 h intervals for the study period (15 days). The patients from both groups received IV albumin infusion, 20 g/day and fresh frozen plasma 150 mL every 8 h, until central venous pressure reached the upper normal range (10–12 cm of H_2O).
Outcomes	The outcomes reported were: • Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random-number table"
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "single-blind" Comment: Further information on whether outcome assessors were blinded was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Stine 2018

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 12 Post-randomisation dropouts: 0 (0%) Revised sample size: 12 Average age: 59 years Females: 5 (41.7%) Hepatorenal syndrome type 1: 12 Hepatorenal syndrome type 2: 0 Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated

Stine 2018 *(Continued)*

Other causes for cirrhosis: not stated
Follow-up in months: 6
Years of recruitment: 2014-2016
Prophylactic antibiotics for subacute bacterial peritonitis: not stated
Additional treatment for ascites: not stated

Important inclusion and exclusion criteria

Patients with hepatorenal syndrome type I: not stated

Patients with hepatorenal syndrome type II: not stated

Alcoholic cirrhosis: not stated

Viral-related cirrhosis: not stated

Autoimmune disease-related cirrhosis: not stated

Other causes for cirrhosis: not stated

Other important exclusion criteria

- Patients with labelled contraindications to pentoxifylline (allergy or hypersensitivity to pentoxifylline or intolerance to methylxanthines (e.g. caffeine, theophylline))
- Recent cerebral or retinal haemorrhage
- Recent pregnancy
- Concurrent use of nephrotoxic drugs
- Uncontrolled bacterial infection
- Renal parenchymal disease (e.g. acute tubular necrosis, glomerular disease, interstitial nephritis, urinary obstruction)
- Shock
- TNFα antagonist use
- Severe or poorly controlled comorbid disease as determined by the principal investigator to hinder the ability of the subject to adhere to study protocols

Interventions	Participants were randomly assigned to two groups. Group 1: midodrine, octreotide, pentoxifylline and albumin (n = 6) Further details: 14-day course of pentoxifylline 400 mg three times a day or the equivalent dose adjusted for renal impairment [400 mg twice a day for estimated glomerular filtration rate 10-50 mg/dL and 400 mg once a day for eGFR < 10 mg/ dL] Group 2: midodrine, octreotide and albumin (n = 6) Further details: not provided
Outcomes	The outcomes reported were: • Mortality • Liver transplantation • Recovery from hepatorenal syndrome
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.

Stine 2018 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, placebo-controlled, triple blinded pilot study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, placebo-controlled, triple blinded pilot study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Tavakkoli 2012

Methods	Randomised clinical trial
Participants	Country: Iran Number randomised: 23 Post-randomisation dropouts: 0 (0%) Revised sample size: 23 Average age: 52 years Females: 8 (34.8%) Hepatorenal syndrome type 1: 15 (65.2%) Hepatorenal syndrome type 2: 8 (34.8%) Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 3 Years of recruitment: 2011-2012 Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: yes Patients with hepatorenal syndrome type II: yes Alcoholic cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • Evidence of hepatocellular carcinoma

Tavakkoli 2012 *(Continued)*

- Recent history of related complications of cirrhosis

Interventions	Participants were randomly assigned to two groups. Group 1: noradrenaline and albumin (n = 11) Further details: patients received a continuous infusion of noradrenaline at an initial dose of 0.1 µg/kg/min, aimed to attain an increase in mean arterial pressure of at least 10 mmHg. In case of lack of increase in baseline mean arterial pressure of at least 10 mmHg, noradrenalin was increased every 4 hours in steps of 0.05 µg/kg/min up to the maximum dose of 0.7 µg/kg/min. Noradrenaline was administered either until hepatorenal syndrome reversal or for a maximum of 15 days. Noradrenaline doses were subsequently tapered to 0 over 3 days. In addition, an amount of 20 to 60 g/d of albumin was infused in all patients to maintain central venous pressure in the range of 10 to 15 mmHg. Group 2: midodrine, octreotide and albumin (n = 12) Further details: octreotide was administered subcutaneously at an initial dose of 100 µg 3 times daily and then, if necessary, increased to 200 µg 3 times daily. Midodrine was administered orally at an initial dose of 5 mg 3 times daily, and in case of lack of increase in baseline mean arterial pressure of at least 15 mmHg, midodrine was increased every 24 hours in steps of 5 mg 3 times daily up to the maximum dose of 15 mg 3 times daily, if needed. In addition, an amount of 20 to 60 g/d of albumin was infused in all patients to maintain central venous pressure in the range of 10 to 15 mmHg.
Outcomes	The outcomes reported were: • Mortality • Recovery from hepatorenal syndrome
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no post-randomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Yang 2001

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 15 Post-randomisation dropouts: not stated Revised sample size: 15 Average age: 48 years Females: 3 (20%) Hepatorenal syndrome type 1: not stated Hepatorenal syndrome type 2: not stated Alcohol-related cirrhosis: 4 (26.7%) Viral-related cirrhosis: 13 (86.7%) Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: 2 (13.3%) Follow-up in months: 0.2 Years of recruitment: 2000 Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: not stated Patients with hepatorenal syndrome type II: not stated Alcoholic cirrhosis: yes Viral-related cirrhosis: yes Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: yes Other important exclusion criteria • Shock • Persistent bacterial infection before and during treatment • Use of nephrotoxic drugs • Urinary tract obstruction • No renal parenchymal lesions in either kidney
Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 8) Further details: terlipressin given by intravenous infusion once every 12 h for a total of 5 days; control group: spironolactone 80mg and furosemide 40 mg, 3 times a day, for five days. Infusion of albumin was not restricted during the observation period of the two groups. Group 2: albumin (n = 7) Further details: infusion of albumin was not restricted during the observation period of the two groups.
Outcomes	No outcomes of interest for this review were reported.
Notes	Reasons for post-randomisation dropouts: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.

Yang 2001 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: This information was not available.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

Zafar 2012

Methods	Randomised clinical trial
Participants	Country: Pakistan Number randomised: 50 Post-randomisation dropouts: not stated Revised sample size: 50 Average age: not stated Females: not stated Hepatorenal syndrome type 1: not stated Hepatorenal syndrome type 2: not stated Alcohol-related cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis (for example, PSC, PBC, AIH): not stated Other causes for cirrhosis: not stated Follow-up in months: 3 Years of recruitment: not stated Prophylactic antibiotics for subacute bacterial peritonitis: not stated Additional treatment for ascites: not stated **Important inclusion and exclusion criteria** Patients with hepatorenal syndrome type I: not stated Patients with hepatorenal syndrome type II: not stated Alcoholic cirrhosis: not stated Viral-related cirrhosis: not stated Autoimmune disease-related cirrhosis: not stated Other causes for cirrhosis: not stated Other important exclusion criteria • Bacterial infection

Zafar 2012 *(Continued)*

- Cardiovascular diseases
- Organic nephropathy
- Hepatocellular carcinoma

Interventions	Participants were randomly assigned to two groups. Group 1: terlipressin and albumin (n = 25) Further details: terlipressin (1 mg/4 hourly, IV), and albumin (1 g/kg followed by 20-40 g/day) Group 2: albumin (n = 25) Further details: albumin (1 g/kg followed by 20-40 g/day)
Outcomes	The outcomes reported were: • Mortality
Notes	Reasons for post-randomisation dropouts: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: This information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Authors mentioned intention-to-treat analysis, but not clear if they imputed any data.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol was available.
Other bias	Low risk	Comment: No other bias noted

AIH: autoimmune hepatitis
CVP: central venous pressure
EVLWI: extravascular lung water index
GEDVI: global end-diastolic volume index
HDF: haemodiafiltration
HRS: hepatorenal syndrome
IV: intravenous
MARS: molecular adsorbent recirculating system
PBC: primary biliary cholangitis
PICCO: pulse contour cardiac output
pO2/FiO2: partial pressure of oxygen/fractional inspired oxygen
PSC: primary sclerosing cholangitis
SNOSE: sequentially numbered opaque sealed envelopes

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abutaleb 2007	Not a randomised controlled trial
Ackerman 2002	Patients did not have hepatorenal syndrome
Angeli 1999	Not a randomised controlled trial
Angeli 2015	Not a randomised controlled trial
Antoniades 2003	Not a randomised controlled trial
Casado Caballero 1996	Not a randomised controlled trial
Clewell 1994	Not a randomised controlled trial
Conn 2000	Not a randomised controlled trial
Duhamel 2000	Not a randomised controlled trial
Durkin 1995	Not a randomised controlled trial
Elia 2015	Not a randomised controlled trial
Gines 2005	Not a randomised controlled trial
Giostra 1995	Not a randomised controlled trial
Hadengue 1998	In this cross-over trial, the duration of treatment was 48 hours and the wash-out period was 24 hours. No meaningful data could be obtained from this study.
Kaffy 1999	Not a randomised controlled trial
Kalambokis 2005	Not a randomised controlled trial
Kalambokis 2017	Not a randomised controlled trial
Mullen 2002	Not a randomised controlled trial
Ortega 2002	Not a randomised controlled trial
Pauwels 2008	Not a randomised controlled trial
Pomier-Layrargues 2003	In this cross-over trial, the duration of treatment was 96 hours without any wash-out period. No meaningful data could be obtained from this study
Robertson 2014	Not a randomised controlled trial
Srivastava 2015	Not a randomised controlled trial
Sugerman 1970	Not a randomised controlled trial
Sugerman 1971	Not a randomised controlled trial

Study	Reason for exclusion
Testro 2009	Not a randomised controlled trial
Valer-Fandó 2004	Unclear if study was a randomised controlled trial and no further information available
Varajic 2017	Variations of different forms of goal-directed therapy

Characteristics of ongoing studies *[ordered by study ID]*

NCT02770716

Trial name or title	A multi-center, randomized, placebo controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with hepatorenal syndrome type 1 (the CONFIRM Study)
Methods	Randomised controlled trial
Participants	Inclusion Criteria: • Written informed consent by subject or legally authorised representative • At least 18 years of age • Cirrhosis and ascites • Rapidly progressive worsening in renal function to a serum creatinine (SCr) at least 2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks • No sustained improvement in renal function (less than 20% decrease in SCr and SCr at least 2.25 mg/dL) at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin Exclusion Criteria: • Serum creatinine level greater than 7.0 mg/dL • At least 1 event of large volume paracentesis (LVP) at least 4 L within 2 days of randomisation • Sepsis and/or uncontrolled bacterial infection (e.g. persisting bacteraemia, persisting ascitic fluid leucocytosis, fever, increasing leucocytosis with vasomotor instability) • Fewer than 2 days anti-infective therapy for documented or suspected infection • Shock • Current or recent (within 4 weeks) treatment with or exposure to nephrotoxic agents: e.g. aminoglycosides, amphotericin, cyclosporine A, cisplatin, nonsteroidal anti-inflammatory drugs (NSAIDs: e.g. ibuprofen, naproxen, diclofenac), significant exposure to radiographic contrast agents (large doses or multiple injections of iodinated contrast media; e.g, during coronary or abdominal angiogram) • Estimated life expectancy of fewer than 3 days • Superimposed acute liver injury due to drugs (e.g. acetaminophen), dietary supplements, herbal preparations, viral hepatitis, or toxins (e.g. Amanita toxin with mushroom poisoning carbon tetrachloride), with the exception of acute alcoholic hepatitis • Proteinuria greater than 500 mg/day • Evidence of obstructive uropathy or parenchymal renal disease on ultrasound or other imaging • Tubular epithelial casts, heme granular casts, hematuria or microhematuria (greater than 50 red blood cells per high power field in the absence of recent catheterisation) on urinalysis Note: Urine sediment examination is required to exclude presence of heme granular casts and other clinically significant casts. • Subjects known to be pregnant; all women of child-bearing age and potential must have a negative pregnancy test. • Severe cardiovascular disease, including, but not limited to, unstable angina, pulmonary edema, congestive heart failure requiring increasing doses of drug therapy, or persisting symptomatic

NCT02770716 *(Continued)*

	peripheral vascular disease, myocardial infarction or stable chronic angina within the past 12 months, or any other cardiovascular disease judged by the investigator to be severe • Current or recent (within 4 weeks) renal replacement therapy (RRT) • Participation in other clinical research involving investigational medicinal products within 30 days of randomisation • Transjugular intrahepatic portosystemic shunt (TIPS) within 30 days of randomisation • Use of vasopressors (e.g. norepinephrine, epinephrine or vasopressin dopamine or other vasopressors) of at least 3 consecutive days within the prior 14-day screening period. Patients receiving a vasopressor other than midodrine within 24 hours of qualifying SCr are excluded, i.e. a 24-h washout is required prior to enrolment. Note: Patients receiving midodrine and octreotide may be enrolled. Midodrine and octreotide treatment must be stopped prior to randomisation. * Known allergy or sensitivity to terlipressin or another component of the study treatment
Interventions	Participants are randomly assigned to two groups. Group 1: terlipressin acetate Further details: lyophilised terlipressin acetate 1 mg by intravenous bolus injection every 6 hours Group 2: placebo Further details: 11 mg mannitol reconstituted with 5 mL of sterile 0.9% sodium chloride solution
Outcomes	The outcomes to be reported are: • Recovery from hepatorenal syndrome
Starting date	12 May 2016
Contact information	Lisa Fitzgerald 800-556-3314 clinicaltrials@mnk.com
Notes	

NCT03455322

Trial name or title	Pros & cons of norepinephrine infusion versus midodrine & octreotide in patients with hepatorenal syndrome type 1 in intensive care unit
Methods	Randomised controlled trial
Participants	Inclusion Criteria: • All patients that will be included in the study have cirrhosis as diagnosed by clinical, biochemical, and ultrasound findings, with HRS type 1, the absence of bacterial infections; however, patients with bacterial infections could be included in the study if renal failure persisted after infection resolution by clinical, laboratory indices up to 48 hours. Exclusion Criteria: • Patients will be excluded if there are advanced cardiovascular diseases due to poor prognosis or any extrahepatic disease that could affect the short-term prognosis, the presence of advanced hepatocellular carcinoma or presence of contraindication to norepinephrine as hypotension due to blood volume deficits except emergency measure, mesenteric or peripheral vascular thrombosis unless there is life-saving procedure, profound hypoxia, or hypercarbia.
Interventions	Participants are randomly assigned to two groups. Group 1: noradrenaline

NCT03455322 *(Continued)*	
	Further details: intravenous infusion noradrenaline in a dose of 0.05-0.3 µg/Kg/min to keep mean arterial pressure ≥ 80-100 mmHg and continued either until hepatorenal syndrome reversal or for maximum 10 days Group 2: midodrine and octreotide Further details: oral midodrine 5 mg three times/day and can be increased every 24 h up to 12.5 mg three times daily plus octreotide 100 µg/ 6h subcutaneous & if needed increased to 200µg/6h
Outcomes	The outcomes to be reported are: • Mortality • Recovery from hepatorenal syndrome • Adverse events • Hospital stay • Costs
Starting date	8 March 2018
Contact information	Eman El-Desoki 01227409501 eman18350@gmail.com
Notes	

ADDITIONAL TABLES

Table 1. Criteria for diagnosis of hepatorenal syndrome

- Diagnosis of cirrhosis and ascites
- Diagnosis of acute kidney injury (AKI) according to International Club of Ascites AKI criteria (ICA-AKI) criteria*
- No response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
- Absence of shock
- No current or recent use of nephrotoxic drugs (nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, iodinated contrast media, etc.)
- No macroscopic signs of structural kidney injury, defined as: absence of proteinuria (> 500 mg/day), absence of microhaematuria (> 50 red blood cells per high-power field), and normal findings on renal ultrasonography. Individuals who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between hepatorenal syndrome and acute tubular necrosis.

*Increase in serum creatinine ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours or ≥ 50% increase in serum creatinine from baseline which is known or presumed to have occurred within the previous seven days.

Source: Angeli 2015a

AKI: acute kidney injury

ICA: international club of ascites

NSAIDs: nonsteroidal anti-inflammatory drugs

Table 2. Potential effect modifiers

Study name	Intervention 1	Intervention 2	Intervention 1: number of participants	Intervention 2: number of participants	Hepatorenal syndrome type 1	Hepatorenal syndrome type 2	Alcohol-related cirrhosis: number of participants	Viral-related cirrhosis: number of participants	Autoimmune disease-related cirrhosis (example, PSC, PBC, AIH): number of participants	Other causes for cirrhosis: number of participants	Additional treatment for ascites	Years of randomisation	Average follow-up in months	Risk of bias
Alessandria 2007	Albumin plus terlipressin	Albumin plus noradrenaline	12	10	9	13	6	Not stated	Not stated	Not stated	Yes	Not stated	1	High
Arora 2018	Albumin plus terlipressin	Albumin plus noradrenaline	60	60	120	0	87	18	5	10	Not stated	2015-2016	1	High
Badawy 2013	Albumin plus terlipressin	Albumin plus noradrenaline	26	25	51	0	5	47	7	11	No	2009-2012	0.5	High
Ghosh 2013	Albumin plus terlipressin	Albumin plus noradrenaline	23	23	0	46	31	8	2	5	Yes	2009-2011	3	High
Goyal 2008	Albumin plus terlipressin	Albumin plus noradrenaline	16	16	10	22	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	0.5	High
Goyal 2016	Albumin plus terlipressin	Albumin plus noradrenaline	20	21	41	0	28	7	Not stated	7	Not stated	Not stated	0.5	High
Indrabi 2013	Albumin plus terlipressin	Albumin plus noradrenaline	30	30	60	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	3	High

Table 2. Potential effect modifiers *(Continued)*

Saif 2018	Albumin plus terlipressin	Albumin plus noradrenaline	30	30	60	0	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	3	High
Sharma 2008	Albumin plus terlipressin	Albumin plus noradrenaline	20	20	40	0	26	9	1	4	Yes	2005-2006	0.5	High
Singh 2012	Albumin plus terlipressin	Albumin plus noradrenaline	23	23	46	0	22	15	3	6	Not stated	2009-2011	1	High
Boyer 2016	Albumin plus terlipressin	Albumin	97	99	196	0	103	95	9	55	Not stated	2010-2013	3	High
Martin-Llahi 2008	Albumin plus terlipressin	Albumin	23	23	35	11	33	Not stated	Not stated	Not stated	Not stated	Not stated	3	High
Neri 2008	Albumin plus terlipressin	Albumin	26	26	52	0	7	45	0	0	Not stated	2002-2005	3	High
Sanyal 2008	Albumin plus terlipressin	Albumin	56	56	112	0	40	46	3	17	Not stated	Not stated	6	Low
Solanki 2003	Albumin plus terlipressin	Albumin	12	12	24	0	8	9	0	7	Yes	Not stated	0.5	High
Yang 2001	Albumin plus terlipressin	Albumin	8	7	Not stated	Not stated	4	13	Not stated	Not stated	Not stated	2000	0.2	High
Zafar 2012	Albumin plus terlipressin	Albumin	25	25	Not stated*	Not stated*	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	3	High
Cavallin 2015	Albumin plus terlipressin	Albumin plus midodrine plus octreotide	27	21	44	4	0	18	Not stated	Not stated	Not stated	2008-2012	3	High
Copaci 2013	Albumin plus terlipressin	Albumin plus octreotide	20	20	36	4	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	1	High

Table 2. Potential effect modifiers *(Continued)*

Tavakkoli 2012	Albumin plus noradrenaline	Albumin plus midodrine plus octreotide	11	12	15	8	Not stated	Not stated	Not stated	Not stated	Not stated	2011-2012	3	High
Stine 2018	Albumin plus midodrine plus octreotide	Albumin plus midodrine plus octreotide plus pentoxifylline	6	6	12	0	Not stated	Not stated	Not stated	Not stated	Not stated	2014-2016	6	High
Chelarescu 2003	Captopril plus octreotide	Octreotide	13	12	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	0.2	High
Koch 2016	Goal-directed therapy	No goal-directed therapy	16	9	Not stated	Not stated	22	2	1	0	Not stated	Not stated	1	High
Mitzner 2000	Haemofiltration	MARS	5	8	13	0	7	4	1	1	Yes	Not stated	1	High
Daskalopoulos 1985	Peritoneovenous shunt	Medical (no further details)	11	15	Not stated	Not stated	28	Not stated	Not stated	Not stated	Not stated	1978-1983	0.5	High

*Number of participants not stated, but both participants with type I and type II HRS included in the study
MARS: molecular adsorbent recirculating system

Table 3. Risk of bias (arranged by intervention)

Study name	Intervention 1	Intervention 2	Sequence generation	Allocation concealment	Blinding of patients and healthcare providers	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	Overall risk of bias
Alessandria 2007	Albumin plus terlipressin	Albumin plus noradrenaline	unclear	unclear	high	high	low	unclear	High

Table 3. Risk of bias (arranged by intervention) *(Continued)*

Arora 2018	Albumin plus terlipressin	Albumin plus noradrenaline	unclear	low	high	high	low	low	High
Badawy 2013	Albumin plus terlipressin	Albumin plus noradrenaline	unclear	unclear	high	high	high	unclear	High
Ghosh 2013	Albumin plus terlipressin	Albumin plus noradrenaline	low	unclear	high	high	unclear	low	High
Goyal 2008	Albumin plus terlipressin	Albumin plus noradrenaline	unclear	unclear	high	high	unclear	unclear	High
Goyal 2016	Albumin plus terlipressin	Albumin plus noradrenaline	low	unclear	high	high	low	low	High
Indrabi 2013	Albumin plus terlipressin	Albumin plus noradrenaline	unclear	unclear	unclear	unclear	low	unclear	High
Saif 2018	Albumin plus terlipressin	Albumin plus noradrenaline	low	unclear	unclear	unclear	low	unclear	High
Sharma 2008	Albumin plus terlipressin	Albumin plus noradrenaline	low	unclear	high	high	low	unclear	High
Singh 2012	Albumin plus terlipressin	Albumin plus noradrenaline	low	unclear	high	high	unclear	unclear	High
Boyer 2016	Albumin plus terlipressin	Albumin	low	low	low	low	low	low	Low
Martin-Llahi 2008	Albumin plus terlipressin	Albumin	low	low	high	high	low	low	High
Neri 2008	Albumin plus terlipressin	Albumin	low	low	unclear	unclear	low	unclear	High
Sanyal 2008	Albumin plus terlipressin	Albumin	low	low	low	low	low	low	Low
Solanki 2003	Albumin plus terlipressin	Albumin	low	unclear	high	unclear	low	unclear	High
Yang 2001	Albumin plus terlipressin	Albumin	unclear	unclear	unclear	unclear	unclear	unclear	High
Zafar 2012	Albumin plus terlipressin	Albumin	unclear	unclear	unclear	unclear	unclear	unclear	High

Table 3. Risk of bias (arranged by intervention) *(Continued)*

Cavallin 2015	Albumin plus terlipressin	Albumin plus midodrine plus octreotide	low	low	unclear	unclear	high	low	High
Copaci 2013	Albumin plus terlipressin	Albumin plus octreotide	unclear	unclear	unclear	unclear	unclear	unclear	High
Tavakkoli 2012	Albumin plus noradrenaline	Albumin plus midodrine plus octreotide	unclear	unclear	unclear	unclear	low	unclear	High
Stine 2018	Albumin plus midodrine plus octreotide	Albumin plus midodrine plus octreotide plus pentoxifylline	unclear	unclear	low	low	low	unclear	High
Chelarescu 2003	Captopril plus octreotide	Octreotide	unclear	unclear	unclear	unclear	unclear	unclear	High
Koch 2016	Goal directed therapy	No goal-directed therapy	unclear	unclear	unclear	unclear	unclear	unclear	High
Mitzner 2000	Haemofiltration	MARS	low	low	unclear	unclear	unclear	unclear	High
Daskalopoulos 1985	Peritoneovenous shunt	Medical (no further details)	unclear	unclear	unclear	unclear	high	unclear	High

MARS: molecular adsorbent recirculating system

Table 4. Model fit

All-cause mortality	Fixed-effect model	Random-effects model	Inconsistency model
Dbar	176.9	153.6	153.7
DIC	199.9	184.8	185.7
pD	22.93	31.22	31.95
Serious adverse events (proportion)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	31.03	31.57	31.6
DIC	36.04	37.3	37.35
pD	5.01	5.72	5.76
Serious adverse events (number per participant)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	21.16	21.17	21.15
DIC	25.12	25.13	25.09
pD	3.95	3.96	3.94
Any adverse events (proportion)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	33.95	34.58	34.57
DIC	40.9	42.16	42.14
pD	6.96	7.58	7.57
Any adverse events (number per participant)	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	46.84	46.83	47.86
DIC	53.71	53.67	55.86
pD	6.87	6.84	8.01
Liver transplantation	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	29.12	29.77	29.79
DIC	34.12	35.48	35.51
pD	4.99	5.71	5.72
Recovery from hepatorenal syndrome	**Fixed-effect model**	**Random-effects model**	**Inconsistency model**
Dbar	169.2	161.1	159

Table 4. Model fit *(Continued)*

DIC	191.9	189.9	187.3
pD	22.64	28.85	28.3

Abbreviations
DBar = posterior mean of deviance
DIC = deviance information criteria
pD = effective number of parameters or leverage

Table 5. Effect estimates

All-cause mortality	**Albumin + Terlipressin**	**Albumin + Noradrenaline**	**Albumin**	**Albumin + Midodrine + Octreotide**	**Albumin + Midodrine + Octreotide + Pentoxyfylline**	**Albumin + Octreotide**
Albumin + Terlipressin	-	1.36 [0.92,1.91]	1.19 [0.46,4.61]	1.62 [0.68,3.82]	-	1.45 [0.49,4.49]
Albumin + Noradrenaline	1.33 [0.87,2.00]	-	-	0.88 [0.26,2.94]	-	-
Albumin	1.06 [0.69,1.80]	0.80 [0.44,1.60]	-	-	-	-
Albumin + Midodrine + Octreotide	1.42 [0.52,3.79]	1.07 [0.39,2.89]	1.33 [0.42,3.91]	-	0.36 [0.06,1.66]	-
Albumin + Midodrine + Octreotide + Pentoxyfylline	0.50 [0.06,4.07]	0.38 [0.04,3.07]	0.47 [0.05,3.98]	0.36 [0.05,2.21]	-	-
Albumin + Octreotide	1.46 [0.35,6.49]	1.10 [0.25,5.26]	1.37 [0.29,6.44]	1.03 [0.18,6.32]	2.92 [0.23,42.06]	-
Serious adverse events (proportion)	**Albumin + Terlipressin**	**Albumin + Noradrenaline**	**Albumin**	-		
Albumin + Terlipressin	-	0.81 [0.21,2.93]	0.80 [0.50,1.26]			
Albumin + Noradrenaline	0.82 [0.21,2.98]	-	-			
Albumin	0.80 [0.50,1.26]	0.98 [0.25,3.99]	-			
Serious adverse events (number per participant)	**Albumin + Terlipressin**	**Albumin + Noradrenaline**	**Albumin**	-		
Albumin + Terlipressin	-	0.82 [0.23,2.82]	0.92 [0.51,1.63]			
Albumin + Noradrenaline	0.83 [0.23,2.83]	-	-			
Albumin	0.91 [0.51,1.65]	1.11 [0.28,4.53]	-			

Table 5. Effect estimates *(Continued)*

Any adverse events (proportion)	**Albumin + Terlipressin**	**Albumin + Noradrenaline**	**Albumin**	**Albumin + Midodrine + Octreotide**	-
Albumin + Terlipressin	-	0.16 [0.01,1.46]	0.58 [0.25,1.28]	1.14 [0.30,4.30]	
Albumin + Noradrenaline	0.16 [0.01,1.44]	-	-	-	
Albumin	0.58 [0.25,1.25]	3.65 [0.36,113.18]	-	-	
Albumin + Midodrine + Octreotide	1.14 [0.30,4.27]	7.40 [0.53,262.96]	1.95 [0.42,9.21]	-	

Any adverse events (number per participant)	**Albumin + Terlipressin**	**Albumin + Noradrenaline**	**Albumin**	-
Albumin + Terlipressin	-	*0.51 [0.28,0.87]*	0.79 [0.52,1.21]	
Albumin + Noradrenaline	*0.50 [0.28,0.88]*	-	-	
Albumin	0.80 [0.52,1.22]	1.59 [0.78,3.20]	-	

Liver transplantation	**Albumin + Terlipressin**	**Albumin + Noradrenaline**	**Albumin**	-
Albumin + Terlipressin	-	1.09 [0.36,3.23]	1.01 [0.68,1.52]	
Albumin + Noradrenaline	1.09 [0.36,3.31]	-	-	
Albumin	1.01 [0.68,1.52]	0.93 [0.28,3.06]	-	

Recovery from hepatorenal syndrome	**Albumin + Terlipressin**	**Albumin + Noradrenaline**	**Albumin**	**Albumin + Midodrine + Octreotide**	**Albumin + Midodrine + Octreotide + Pentoxyfylline**	**Albumin + Octreotide**
Albumin + Terlipressin	-	0.90 [0.64,1.29]	0.27 [0.05,1.17]	*0.04 [0.00,0.25]*	-	*0.26 [0.07,0.80]*
Albumin + Noradrenaline	0.85 [0.58,1.28]	-	-	0.87 [0.26,2.91]	-	-
Albumin	*0.28 [0.14,0.53]*	*0.33 [0.14,0.69]*	-	-	-	-
Albumin + Midodrine + Octreotide	*0.26 [0.08,0.79]*	*0.30 [0.09,0.92]*	0.92 [0.24,3.53]	-	1.00 [0.02,38.67]	-
Albumin + Midodrine + Octreotide + Pentoxyfylline	0.25 [0.00,12.85]	0.30 [0.01,14.78]	0.91 [0.02,48.76]	1.06 [0.02,46.34]	-	-

Table 5. Effect estimates *(Continued)*

Albumin + Octreotide	0.26 [0.05,1.12]	0.31 [0.06,1.40]	0.95 [0.16,4.78]	1.03 [0.14,6.98]	1.03 [0.01,65.17]	-

The table provides the effect estimates (proportion of people with serious adverse events and any adverse events; hazard ratio for all-cause mortality, and recovery from hepatorenal syndrome; and rate ratio for number of serious adverse events and any adverse events, other than decompensation) of each pairwise comparison for the different outcomes. The top half of the table indicates the effect estimates from the direct comparisons. The bottom half of the table indicates the effect estimates from the network meta-analysis. For network meta-analysis, to identify the effect estimate of a comparison, say A versus B, look at the cell that occupies the row corresponding to intervention A and the column corresponding to intervention B for the direct effect estimate. If that cell is empty (indicated by a '-'), look at the row corresponding to intervention B and the column corresponding to intervention A. Take the inverse of this number (i.e. 1/number) to arrive at the treatment effect of A versus B. For direct comparisons, this is exactly the opposite; look at the cell that occupies the column corresponding to intervention A and the row corresponding to intervention B for the direct effect estimate. If that cell is empty, look at the column corresponding to intervention B and the row corresponding to intervention A. Take the inverse of this number to arrive at the treatment effect of A versus B. If the cell corresponding to B versus A is also missing in direct comparisons, this means that there was no direct comparison.
Except for the differences shown in italics for number of adverse events (lower with albumin + noradrenaline versus albumin + terlipressin) (direct comparison and network meta-analysis) and for recovery from hepatorenal syndrome (lower with albumin + midodrine + octreotide versus albumin + terlipressin in direct comparison and network meta-analysis; lower with albumin + octreotide versus albumin + terlipressin in direct comparison only; and lower with albumin alone versus albumin + terlipressin and albumin + noradrenaline and albumin + midodrine + octreotide versus albumin + noradrenaline in network meta-analysis only), there was no evidence of a difference in any of the other comparisons in direct comparisons or network meta-analysis.

APPENDICES

Appendix 1. Glossary of terms

Analogue - something which is different but very similar to something else. In the context of drugs, this is usually a drug which acts in the same way as a molecule produced by the body.

Ascites - buildup of protein-containing fluid in the abdomen, most commonly as a result of liver disease

Coagulopathy - disorder of blood clotting which causes a tendency towards prolonged or excessive bleeding

Decompensated cirrhosis - the liver can accommodate for some loss of function which occurs at the beginning of the cirrhosis. However, eventually the scarring means the liver cannot perform its essential functions and the patient develops symptoms, this is then termed decompensated cirrhosis

Fibrous septa - sheets of tissue made of collagen which divide two areas

Hepatic - of, or relating to, the liver

Hepatic encephalopathy - a lowered level of consciousness or other neurological symptoms as a results of liver failure. It is caused by build-up of ammonia in the blood, something which is normally prevented by the liver

Intravascular - contained by blood vessels

Nephrotoxic - damaging to the kidneys

Oncotic - a form of pressure exerted on liquid by proteins

Portal - a venous system which occurs when a capillary bed pools into another capillary bed through veins without going through the heart; most notably in humans, this occurs in the liver creating the hepatic portal system

Parenchymal nodules - a small mass of tissue made up of the functional tissue of an organ

Transjugular - through the internal jugular vein, which is a large neck vein

Variceal bleeding - loss of blood from dilated veins just below the gut lining, most commonly occurring in the lower portion of the oesophagus or upper stomach

Vasocontrictor - a substance that causes the narrowing of blood vessels

Appendix 2. Search strategies

Database	Time span	Search strategy
Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 12, 2018	#1 MeSH descriptor: [Hepatorenal Syndrome] explode all trees #2 hepatorenal syndrom* #3 #1 or #2
MEDLINE Ovid	January 1947 to December 2018	1. exp Hepatorenal Syndrome/ 2. hepatorenal syndrom*.ti,ab. 3. 1 or 2 4. randomized controlled trial.pt. 5. controlled clinical trial.pt. 6. randomized.ab. 7. placebo.ab. 8. drug therapy.fs. 9. randomly.ab. 10. trial.ab. 11. groups.ab. 12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 13. exp animals/ not humans.sh. 14. 12 not 13 15. 3 and 14
Embase Ovid	January 1974 to December 2018	1. exp hepatorenal syndrome/ 2. hepatorenal syndrom*.ti,ab. 3. 1 or 2 4. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 5. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af. 6. 4 or 5 7. 3 and 6
Science Citation Index Expanded (Web of Science)	January 1945 to December 2018	#1 TS= (hepatorenal syndrom*) #2 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #3 #1 AND #2

(Continued)

World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx)	December 2018	Condition: hepatorenal syndrome
ClinicalTrials.gov	December 2018	Interventional Studies | Hepatorenal Syndrome | Phase 2, 3, 4
European Medicines Agency (www.ema.europa.eu/ema/) and US Food and Drug Administration (www.fda.gov)	December 2018	Hepatorenal syndrome

Appendix 3. Data

#Mortality; 1 = Albumin plus terlipressin; 2 = Albumin plus noradrenaline; 3 = Albumin; 4 = Albumin plus midodrine plus octreotide; 5 = Albumin plus midodrine plus octreotide plus pentoxyfylline; 6 = Albumin plus octreotide

list(nt=6,ns.a=18,ns2=1,ns3=0,ns4=0)

t.a[,1]	t.a[,2]	t.a[,3]	t.a[,4]	r.a[,1]	r.a[,2]	r.a[,3]	r.a[,4]	n.a[,1]	n.a[,2]	n.a[,3]	n.a[,4]	na.a[]	time.a[]	#study
1	2	NA	NA	4	3	NA	NA	12	10	NA	NA	2	1	#Alessandria 2007
1	2	NA	NA	12	13	NA	NA	26	25	NA	NA	2	0.5	#Badawy 2013
1	2	NA	NA	8	9	NA	NA	23	23	NA	NA	2	3	#Ghosh 2013
1	2	NA	NA	11	11	NA	NA	20	21	NA	NA	2	0.5	#Goyal 2016
1	2	NA	NA	28	29	NA	NA	30	30	NA	NA	2	3	#Indrabi 2013
1	2	NA	NA	9	9	NA	NA	20	20	NA	NA	2	0.5	#Sharma 2008
1	2	NA	NA	16	15	NA	NA	23	23	NA	NA	2	1	#Singh 2012
1	2	NA	NA	31	48	NA	NA	60	60	NA	NA	2	1	#Arora 2018
1	2	NA	NA	24	29	NA	NA	30	30	NA	NA	2	3	#Saif 2018
1	3	NA	NA	40	43	NA	NA	97	99	NA	NA	2	3	#Boyer 2016
1	3	NA	NA	17	19	NA	NA	23	23	NA	NA	2	3	#Martin-Llahi 2008
1	3	NA	NA	32	35	NA	NA	56	56	NA	NA	2	6	#Sanyal 2008
1	3	NA	NA	7	12	NA	NA	12	12	NA	NA	2	0.5	#Solanki 2003
1	3	NA	NA	19	20	NA	NA	25	25	NA	NA	2	3	#Zafar 2012
1	4	NA	NA	11	12	NA	NA	27	21	NA	NA	2	3	#Cavallin 2015
1	6	NA	NA	6	8	NA	NA	20	20	NA	NA	2	1	#Copaci 2013
2	4	NA	NA	6	6	NA	NA	11	12	NA	NA	2	3	#Tavakkoli 2012

(Continued)

4	5	NA	NA	5	3	NA	NA	6	6	NA	NA	2	6	#Stine 2018
END														
t[,1]	t[,2]	t[,3]	t[,4]	y[,2]	y[,3]	y[,4]	se[,2]	se[,3]	se[,4]	na[]	V[]	#study		
1	3	NA	NA	-0.83	NA	NA	0.18	NA	NA	2	NA	#Neri 2008		
END														
#Mortality; 1 = Captopril plus octreotide; 2 = Octreotide														
list(nt=2,ns=1)														
t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	n[,1]	n[,2]	n[,3]	n[,4]	na[]	time[]	#study
1	2	NA	NA	1	2	NA	NA	13	12	NA	NA	2	0.1	#Chelarescu 2003
END														
#Mortality; 1 = Haemofiltration; 2 = MARS														
list(nt=2,ns=1)														
t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	n[,1]	n[,2]	n[,3]	n[,4]	na[]	time[]	#study
1	2	NA	NA	5	6	NA	NA	5	8	NA	NA	2	1	#Mitzner 2000
END														
#Mortality; 1 = Medical; 2 = Surgical														
list(nt=2,ns=1)														
t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	n[,1]	n[,2]	n[,3]	n[,4]	na[]	time[]	#study
1	2	NA	NA	13	8	NA	NA	15	11	NA	NA	2	0.5	#Daskalopoulos 1985
END														
#SAE_Num; 1 = Albumin plus terlipressin; 2 = Albumin plus noradrenaline; 3 = Albumin														

(Continued)

list(nt=3,ns=2)

t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	E[,1]	E[,2]	E[,3]	E[,4]	na[]	time[]	#study
1	2	NA	NA	6	5	NA	NA	60	60	NA	NA	2	1	#Arora 2018
1	3	NA	NA	24	22	NA	NA	23	23	NA	NA	2	3	#Martin-Llahi 2008
END														

#SAE_Prop; 1 = Albumin plus terlipressin; 2 = Albumin plus noradrenaline; 3 = Albumin

list(nt=3,ns=3)

t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	n[,1]	n[,2]	n[,3]	n[,4]	na[]	time[]	#study
1	2	NA	NA	6	5	NA	NA	60	60	NA	NA	2	1	#Arora 2018
1	3	NA	NA	59	53	NA	NA	97	99	NA	NA	2	3	#Boyer 2016
1	3	NA	NA	37	36	NA	NA	56	56	NA	NA	2	6	#Sanyal 2008
END														

#AE_Num; 1 = Albumin plus terlipressin; 2 = Albumin plus noradrenaline; 3 = Albumin

list(nt=3,ns=5)

t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	E[,1]	E[,2]	E[,3]	E[,4]	na[]	time[]	#study
1	2	NA	NA	5	3	NA	NA	20	21	NA	NA	2	0.5	#Goyal 2016
1	2	NA	NA	5	3	NA	NA	20	20	NA	NA	2	0.5	#Sharma 2008
1	2	NA	NA	6	2	NA	NA	23	23	NA	NA	2	1	#Singh 2012
1	2	NA	NA	19	10	NA	NA	60	60	NA	NA	2	1	#Arora 2018
1	3	NA	NA	50	40	NA	NA	23	23	NA	NA	2	3	#Martin-Llahi 2008
END														

(Continued)

#AE_Prop; 1 = Albumin plus terlipressin; 2 = Albumin plus noradrenaline; 3 = Albumin; 4 = Albumin plus midodrine plus octreotide

list(nt=4,ns=4)

t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	n[,1]	n[,2]	n[,3]	n[,4]	na[]	time[]	#study
1	2	NA	NA	4	1	NA	NA	23	23	NA	NA	2	3	#Ghosh 2013
1	3	NA	NA	90	88	NA	NA	97	99	NA	NA	2	3	#Boyer 2016
1	3	NA	NA	52	49	NA	NA	56	56	NA	NA	2	6	#Sanyal 2008
1	4	NA	NA	7	6	NA	NA	27	21	NA	NA	2	3	#Cavallin 2015

END

#LiverTransplant; 1 = Albumin plus terlipressin; 2 = Albumin plus noradrenaline; 3 = Albumin

list(nt=3,ns=3)

t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	n[,1]	n[,2]	n[,3]	n[,4]	na[]	time[]	#study
1	2	NA	NA	8	7	NA	NA	12	10	NA	NA	2	1	#Alessandria 2007
1	3	NA	NA	30	32	NA	NA	97	99	NA	NA	2	3	#Boyer 2016
1	3	NA	NA	18	17	NA	NA	56	56	NA	NA	2	6	#Sanyal 2008

END

#LiverTransplant: 1 = Albumin plus midodrine plus octreotide; 2=Albumin plus midodrine plus octreotide plus pentoxyfylline

list(nt=2,ns=1)

t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	n[,1]	n[,2]	n[,3]	n[,4]	na[]	time[]	#study
1	2	NA	NA	1	1	NA	NA	6	6	NA	NA	2	6	#Stine 2018

END

#RecoveryFromHRS; 1 = Albumin plus terlipressin; 2 = Albumin plus noradrenaline; 3 = Albumin; 4 = Albumin plus midodrine plus octreotide; 5 = Albumin plus midodrine plus octreotide plus pentoxyfylline; 6 = Albumin plus octreotide

(Continued)

list(nt=6,ns=18)

t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	n[,1]	n[,2]	n[,3]	n[,4]	na[]	time[]	#study
1	2	NA	NA	6	6	NA	NA	12	10	NA	NA	2	1	#Alessandria 2007
1	2	NA	NA	12	10	NA	NA	26	25	NA	NA	2	0.5	#Badawy 2013
1	2	NA	NA	15	14	NA	NA	23	23	NA	NA	2	3	#Ghosh 2013
1	2	NA	NA	7	9	NA	NA	16	16	NA	NA	2	0.5	#Goyal 2008
1	2	NA	NA	9	10	NA	NA	20	21	NA	NA	2	0.5	#Goyal 2016
1	2	NA	NA	16	15	NA	NA	30	30	NA	NA	2	3	#Indrabi 2013
1	2	NA	NA	8	10	NA	NA	20	20	NA	NA	2	0.5	#Sharma 2008
1	2	NA	NA	9	10	NA	NA	23	23	NA	NA	2	1	#Singh 2012
1	2	NA	NA	24	10	NA	NA	60	60	NA	NA	2	1	#Arora 2018
1	2	NA	NA	16	15	NA	NA	30	30	NA	NA	2	3	#Saif 2018
1	3	NA	NA	18	12	NA	NA	97	99	NA	NA	2	3	#Boyer 2016
1	3	NA	NA	10	2	NA	NA	23	23	NA	NA	2	3	#Martin-Llahi 2008
1	3	NA	NA	21	5	NA	NA	26	26	NA	NA	2	3	#Neri 2008
1	3	NA	NA	19	7	NA	NA	56	56	NA	NA	2	6	#Sanyal 2008
1	4	NA	NA	15	1	NA	NA	27	21	NA	NA	2	3	#Cavallin 2015
1	6	NA	NA	11	4	NA	NA	20	20	NA	NA	2	1	#Copaci 2013
2	4	NA	NA	6	6	NA	NA	11	12	NA	NA	2	3	#Tavakkoli 2012
4	5	NA	NA	1	1	NA	NA	6	6	NA	NA	2	6	#Stine 2018
END														

(Continued)

#OtherDecompensation: 1 = Albumin plus terlipressin; 2 = Albumin

list(nt=2,ns=1)														
t[,1]	t[,2]	t[,3]	t[,4]	r[,1]	r[,2]	r[,3]	r[,4]	E[,1]	E[,2]	E[,3]	E[,4]	na[]	time[]	#study
1	2	NA	NA	20	22	NA	NA	23	23	NA	NA	2	3	#Martin-Llahi 2008
END														

#Costs; 1 = Albumin plus terlipressin; 2 = Albumin plus noradrenaline

list(nt=2,ns=5)														
t[,1]	t[,2]	t[,3]	t[,4]	y[,1]	y[,2]	y[,3]	y[,4]	se[,1]	se[,2]	se[,3]	se[,4]	na[]	time[]	#study
1	2	NA	NA	1895.58	132.05	NA	NA	14.2	12.1	NA	NA	2	1	#Alessandria 2007
1	2	NA	NA	340.59	83.03	NA	NA	19.6	9.5	NA	NA	2	0.5	#Badawy 2013
1	2	NA	NA	2500	750	NA	NA	436	436	NA	NA	2	0.5	#Sharma 2008
1	2	NA	NA	1290.36	363.95	NA	NA	325.6	325.6	NA	NA	2	1	#Singh 2012
1	2	NA	NA	1434.23	268.92	NA	NA	411.7	411.7	NA	NA	2	3	#Saif 2018
END														

WHAT'S NEW

Date	Event	Description
25 November 2019	Amended	Typographical error about risk of bias was noted. This was because the source of funding was removed from the risk of bias domains. As a result, two studies are now at low risk of bias. This does not alter the interpretation or conclusions in any way.

CONTRIBUTIONS OF AUTHORS

Protocol

Conceiving the protocol: KG
Designing the protocol: KG
Co-ordinating the protocol: KG
Designing search strategies: KG
Writing the protocol: LB, KG
Providing general advice on the protocol: ET, SF, AJS, NH
Securing funding for the protocol: KG
Performing previous work that was the foundation of the current study: not applicable

Review

Co-ordinating the review: KG
Study selection and data extraction: KG, LB, ELT, MC
Writing the review: LB, KG
Providing advice on the review: SF, EJM, AJS, NJ, CNH, SF, DT, CSP, BRD, ET
Securing funding for the review: KG

DECLARATIONS OF INTEREST

None known for any of the authors.

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

  Writing equipment, software, etc.

External sources

- National Institute for Health Research, UK.

  Payment for writing reviews, writing equipment, software

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We did not perform Trial Sequential Analysis (TSA), as the risk of false positive results with Bayesian meta-analysis is probably less or at least equivalent to TSA.
2. We used the latest guidance from the GRADE Working group (Yepes-Nunez 2019) rather than the previous guidance (Puhan 2014) for presenting the 'Summary of Findings' table.
3. The trials did not report the proportion of people with other episodes of decompensation, but reported the number of episodes of decompensation. Therefore, we treated this as a count outcome and used the Poisson likelihood to calculate the rate ratio.
4. In the absence of a protocol published prior to the start of the study, we have classified the risk of bias as low for selective reporting bias only when mortality, adverse events, and hepatorenal syndrome were reported, as we anticipated these outcomes to be routinely measured in clinical trials of this nature.
5. We used 30,000 iterations as a minimum for burn-in.

6. We did not present some information because of the concern about the misinterpretation of the results. We have highlighted this clearly within the text of the review along with the reasons for not presenting them.

INDEX TERMS

Medical Subject Headings (MeSH)

*Quality of Life; Bayes Theorem; Hepatorenal Syndrome [*therapy]; Liver Cirrhosis [*complications]; Liver Transplantation; Network Meta-Analysis; Randomized Controlled Trials as Topic; Vasoconstrictor Agents [therapeutic use]

MeSH check words

Adult; Female; Humans; Male; Middle Aged