

Curative Effect and Safety of Tolvaptan Combined with Traditional Diuretics in Treatment of Patients with Cirrhotic Ascites and Relevant Research on its Dose: A Systematic Review with Meta-Analysis of Randomized Controlled Trials

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Abstract

Background Tolvaptan is a receptor antagonist of highly selective vasopressin V2, and it can promote excretion of water without electrolyte.

Aims To evaluate curative effect and safety of Tolvaptan in treatment of cirrhotic ascites, and its relationship with drug dose.

Methods Computer retrieval of PubMed, EMBASE and The Cochrane Library was carried out to search the clinical trials of cirrhotic ascites treatment by Tolvaptan. The time limit of retrieval is from the database setup to May 31, 2019. 2 researchers independently screened studies, extracted the data and crosschecked. RevMan 5.3 software was used for Meta-analysis.

Results Finally, 6 articles and 848 patients were included in the study. Meta-analysis indicates that after the intervention for 7 days, serum sodium ion concentration of the combined diuretic group obviously increased, compared with the traditional diuretic group (WMD=2.92mmol/L, 95%CI [2.15, 3.70], P<0.001). In addition, Tolvaptan also can decrease patients' ascites amount through increasing liquid discharge. However, the drug dose has no obvious correlation with the reduction degree of ascites amount. The rise of blood uric acid is the major adverse event in the treatment of cirrhotic ascites patients by Tolvaptan (OR=6.01, 95%CI [1.11, 32.56], P=0.04). When the dose of Tolvaptan rose to 15mg or 30mg, the total incidence of adverse events was obviously higher than it of traditional diuretic group.

Conclusion Tolvaptan combined with traditional diuretics has good curative effect for the patients with cirrhotic ascites. As its adverse reactions, the recommended dose of Tolvaptan is 7.5mg in the combined therapy.

Registration number: The meta-analysis was registered prospectively on the PROSPERO database (ID: CRD42019143480).

Background

Ascites and hyponatremia are the major complications of patients with liver cirrhosis. Ascites will occur to 60% of patients in the compensatory phase of cirrhosis within 10 years, and the proportion of patients with ascites in the decompensatory phase is higher [1]. This also leads to all kinds of subjective symptoms of liver cirrhosis patients, thus reducing their living quality [2]. The one-year survival rate of the patients with ascites and hyponatremia in the phase of decompensated liver cirrhosis is only 60% [3]. Liver transplantation is the only method to radically cure decompensation of liver cirrhosis, but most patients still adopt conservative medication and palliative surgery. Traditional diuretics represented by furosemide are the main drugs to treat cirrhotic ascites [4].

However, traditional diuretics will cause hyponatremia and about 15% of patients have no response to traditional diuretics, which are the main problems faced by cirrhotic ascites treatment [5–6]. Different

from traditional diuretics, Tolvaptan is a receptor antagonist of highly selective vasopressin V2, and it can promote excretion of water without electrolyte. Besides, it neither influences in vivo electrolyte content except for serum sodium ion, nor easily results in kidney failure [7]. Tolvaptan has been approved by many countries around the world to treat autosomal dominant polycystic kidney disease, cardiac failure and hyponatremia [8–9]. But most of studies about the curative effect of Tolvaptan in treatment of cirrhotic ascites was retrospective or observational researches, and the safety of Tolvaptan in treatment of cirrhotic ascites is still questioned, including the occurrence rate of adverse reactions such as liver injury. Thus, Tolvaptan is only approved to treat cirrhotic ascites in a minority of regions including Japan [8, 10].

At present, there are only a few meta-analyses for vaptans drugs (including Tolvaptan, Satavaptan and Lixivaptan), and there are very little results about Torvalptan, let alone a comprehensive analysis on the efficacy and safety of Torvalptan [11, 12]. A most recent meta analysis for retrospective cohort studies of Tolvaptan reported total survival after application, but no detailed data were available on treatment outcomes and complications [13]. Besides, we found a meta analysis for Tolvaptan (in Chinese) [14], but most (5/8) of the studies included were single-center clinical trials published in Chinese journals. These trials were not registered and did not describe explicit hidden allocation method and detailed experimental process, so we thought the results of this paper are doubtful.

To evaluate curative effect and safety of Tolvaptan in treatment of cirrhotic ascites, and its relationship with drug dose, this study reviews the randomized controlled trial (RCT) of cirrhotic ascites treatment by Tolvaptan.

Method

Data and method

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses and registered prospectively on the PROSPERO database (ID: CRD42019143480).

Type of study

RCT study on Tolvaptan combined with traditional diuretics (loop diuretic and/or anti-aldosterone agent) and pure traditional diuretics (with/without placebo) in treatment of liver cirrhosis combined with ascites.

Object of study

The patients diagnosed with ascites which is only caused by liver cirrhosis and received the treatment by traditional diuretics.

Intervention measure

The patients received the treatment by Tolvaptan combined with traditional diuretics or pure traditional diuretics (with/without placebo).

Outcome indicators

Major indicator of curative effect: the changes of serum sodium ion. Minor indicator of curative effect: ascites changes (weight, abdominal girth and ascites amount) and urine volume changes on the first day after medication. Major indicator of safety: total incidence of adverse events. Minor indicator of safety: total incidence of severe adverse events (including death or the events endangering life, continuous or severe disability, and the increase in the times of hospitalization) and incidence of various common adverse events (increase of blood uric acid, frequency of urination, thirst, constipation, hepatic encephalopathy, diarrhea, fever, insomnia, renal function damage and hypokalemia). In addition, the changes in the above indicators under different dose were evaluated.

Exclusion criteria

(1) Non-RCT study; (2) articles published repeatedly; (3) articles from which the data cannot be extracted.

Study retrieval strategy

Computer retrieval of PubMed, EMBase and The Cochrane Library was carried out to search the clinical trials of cirrhotic ascites treatment by Tolvaptan. The time limit of retrieval is from the database setup to August 31, 2019. Meanwhile, supplementary retrieval of research data was conducted, including WHO clinical trial registry platform (<http://apps.who.int/trialsearch>), Chinese clinical trial registry platform (<http://www.chictr.org.cn>) and American clinical trial registry library (<https://clinicaltrials.gov>). Moreover, the references included in the papers were traced to supplement and gain relevant studies. The subject terms and free words were combined for the retrieval. The search terms include Tolvaptan, Samsca, Jinarc, Jynarque, OPC41061, OPC 41061, OPC-41061, and Ascites. The search algorithm is ((Tolvaptan or Samsca or Jinarc or Jynarque or OPC41061 or OPC 41061 or OPC-41061) and Ascites). There was no language restriction during literature search.

Study screening and data extraction

2 researchers independently screened studies, extracted the data and crosschecked. In case of any divergence, it should be solved by discussion and consensus. During study screening, the title was first read. After obviously irrelevant studies were excluded, the abstract and the full text were further read to determine whether the article was included. If necessary, the original authors could be contacted by email and telephone to gain the uncertain but very important information for this study. The extracted data include (1) research features, including the first author, publication year, country, random method, blind method and duration of mediation (research period); (2) general features of patients, including the number, age and gender in each research group; (3) therapeutic evaluation indexes, including the changes of serum sodium ion, bodyweight abdominal girth, and ascites amount as well as the change in urine volume on the first day of medication; (4) safety evaluation indexes, including total incidence of adverse

events, total incidence of severe adverse events, and the incidence of various common adverse events (diarrhea, frequency of urination, fever, hepatic encephalopathy, insomnia, increase of blood uric acid, and hypokalemia); (6) dose-related safety evaluation indexes and therapeutic evaluation indexes: the occurrence rates of safety evaluation indexes and therapeutic evaluation indexes under different dose were collected.

Methodological quality evaluation

The 2 researchers evaluated within-study risk of bias for the searched studies. According to the Cochrane Handbook for Systematic Reviews of Interventions, 2011)[15], the evaluation indexes include: ☒ selection bias, random sequence generation and allocation concealment; ☒ implementation, the blind method was implemented for the researchers and subjects; ☒ measurement, evaluation of research results with the blind method; ☒ follow-up visit, integrity of result data; ☒ reporting, selective reporting of research results; ☒ others. If the above indexes are of low risks, the study is evaluated as low bias risk, and other results are considered to have high bias risk.

Statistical method

RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for Meta-analysis. For the continuous outcome data, weighted mean difference (WMD) was used as the effect size. For the dichotomous outcome data, the odds ratio (OR) was used as the effect size. The point estimate and 95% credibility interval (95% CI) were given for each effect size. The heterogeneity of research results was analyzed by χ^2 test, and the heterogeneity degree was quantitatively judged by combining I^2 . A $P < 0.10$ or $I^2 > 50\%$ were considered as significant heterogeneity. The publication bias of all end points was first judged by the funnel plot. Then, Egger test was adopted for quantitative assessment. $P < 0.05$ means the difference has statistical significance.

Results

Study screening and bias analysis

Based on the above search method, 220 references which may conform to the conditions were found out in total. After abstract reading and elimination of the researches which did not conform to the inclusion criteria, 46 references were retrieved. They were downloaded, read and further assessed. Among them, 32 references are non-RCT researches; 6 references have no objective outcome indicators; 2 references are of abstract form, without objective outcome indicators. The detailed screening process is shown in Fig 1. Finally, 6 articles [16-21] and 848 patients were included in the study (Table 1). Among them, 530 patients received Tolvaptan treatment, and there were 318 persons in the control group.

3 studies do not explain the detailed and specific randomization methods, and the other 3 studies interpret the randomization methods, including random number generated by the computer and center randomization. 4 articles describe the specific allocation scheme hiding method. 5 studies involve double

blind method, and 1 study involves triple blind method. 5 articles report the changes of serum sodium ion, and 5 articles report the total incidence of adverse events. All articles describe the specific follow-up visit, including the number and reasons of patients without follow-up visit. All studies are registered in the clinical database. The risk of bias within studies is shown in Supplement Fig 1.

Curative effect

To evaluate the curative effect, the changes in serum sodium concentration, average body weight, average waistline and average ascites amount after the intervention for 7 days as well as the change of urine volume on the first day of intervention compared with the last day were compared for both groups.

5 studies report the change of serum sodium concentration (including 758 patients) [16-18, 20-21]. Meta analysis indicates that after the intervention for 7 days, serum sodium ion concentration of the combined diuretic group obviously increased, compared with the traditional diuretic group (WMD=2.92mmol/L, 95%CI [2.15, 3.70], $P<0.001$, Fig 2D). There was a significant heterogeneity ($I^2=61\%$, Fig 2D), sensitivity analysis showed that I^2 was 4% when *Isao 2014* was removed (Supplement Fig 2A).

In the aspect of minor indexes, the changes in the average weight, average waistline and average ascites amount are reported in 4 studies (499 patients) [17-20], 3 studies (440 patients) [17-18, 20], and 2 studies (216 patients) [17, 19], respectively. The changes of urine volume on the first day of intervention compared with the last day are reported in 4 studies (498 patients) [16-17, 19-21]. After the intervention for 7 days, the reduction of average weight (WMD=-1.51Kg, 95%CI [-1.86, -1.16], $P<0.001$, Fig 2A), average abdominal girth (WMD=-2.05cm, 95%CI [-2.67, -1.43], $P<0.001$, Fig 2B), and the average ascites amount (WMD=-293.43mL, 95%CI [-502.53, -84.34], $P=0.006$, Fig 2C) of combined diuretic group was obviously better than that of traditional diuretic group. Besides, the increment in the urine volume of the combined diuretic group on Day 1 of intervention was more than that of traditional diuretic group (WMD=1.09L, 95%CI [0.85, 1.33], $P<0.001$, Fig 2E).

In the subgroup analysis, as the daily dose of Tolvaptan rose (7.5mg-15mg-30mg), the increase degree of serum sodium ion concentration in the combined diuretic group was also larger (Fig 3A). But the rise of Tolvaptan dose did not bring obvious change in the weight (Fig 3B) and abdominal girth (Fig 3C). In general, the rise of Tolvaptan dose brings the limited improvement of curative effect for patients.

Safety

In safety evaluation, total incidence of adverse events, total incidence of severe adverse events, and the incidence of various common adverse events (diarrhea, frequency of urination, fever, hepatic encephalopathy, insomnia, increase of blood uric acid, and hypokalemia) in the both groups were mainly compared in the intervention process. And, the occurrence rates of total adverse events, diarrhea and frequency of urination were evaluated under different dose.

5 studies report the total incidence of adverse events (including 620 patients) in the intervention process [16-20]. Meta-analysis result shows that in the intervention process, the total incidence of adverse events was obviously higher than that of traditional diuretic group (OR=1.98, 95%CI [1.11, 3.52], P=0.02, Fig 5A). There was a significant heterogeneity ($I^2=50\%$, Fig 4A), sensitivity analysis showed that I^2 was 0% when *Haruki 2017* was removed (Supplement Fig. 1B).

In the subgroup analysis of adverse events, we found that when the daily dose of Tolvaptan was maintained at 7.5mg in the combined diuretic group, the total incidences of adverse events in the combined diuretic group and traditional diuretic group had no statistical difference (OR=1.28, 95%CI [0.66, 2.47], P=0.46, Fig 4C 7.5mg). But, when the daily dose of Tolvaptan rose to 15mg (OR=2.99, 95%CI [1.03, 8.69], P=0.04, Fig 4C) or 30mg (OR=3.54, 95%CI [1.73, 7.24], P<0.001, Fig 4C), the total incidence of adverse events in the combined diuretic group was significantly higher than that of traditional diuretic group. In terms of the incidence of severe adverse events, there was no statistical difference between the two groups (OR=1.05, 95%CI [0.60, 1.84], P=0.88, Fig 4B).

Various common adverse events include the increase of blood uric acid, frequency of urination, thirst, constipation, hepatic encephalopathy, diarrhea, fever, insomnia, renal function damage and hypokalemia. The detailed Meta-analysis results are shown in Supplement Table 1. 2 articles (282 patients) [18, 20] report the occurrence rate of blood uric acid rise in the intervention process. The combined diuretic group was significantly higher than that of traditional diuretic group (OR=6.01, 95%CI [1.11, 32.56], P=0.04, Fig 5A). Although the occurrence rates of frequency of urination and thirst in both groups had no statistical difference (Supplement Table 1), the subgroup analysis shows that when the daily dose of Tolvaptan reached 15mg or 30mg, the occurrence rates of frequency of thirst (Fig 5B) and urination (Fig 5C) in the combined diuretic group were obviously higher than those of traditional diuretic group.

Discussions

It is found in this study that, compared with traditional diuretic group, Tolvaptan combined with traditional diuretic can effectively improve serum sodium level in treatment of cirrhotic ascites. With the dose increases, the increase degree of serum sodium level also rises. In addition, Tolvaptan also can decrease patients' ascites amount (weight, abdominal girth and ascites amount decrease, while the urine volume on the first day increases) through increasing liquid discharge. However, the drug dose has no obvious correlation with the reduction degree of ascites amount. Meanwhile, the rise of blood uric acid is the major adverse event in the treatment of cirrhotic ascites patients by Tolvaptan combined with traditional diuretics. The rise of Tolvaptan dose did not increase the occurrence rates of severe adverse events and various common adverse events. When the dose of Tolvaptan was controlled at 7.5 mg, the total incidences of adverse events in both groups had no abnormality. But when the dose of Tolvaptan rose to 15 mg or 30 mg, the total incidence of adverse events, and the occurrence rates of frequency of urination and thirst were obviously higher than those of traditional diuretic group.

Although the meta analysis of changes of overall serum sodium in our study showed high heterogeneity, the sensitivity analysis found that it was mainly caused by Isao 2014, which only focused on 7.5 mg Tolvaptan, while changes of overall serum sodium combined the results of 7.5–30 mg Tolvaptan in the other four studies. This high heterogeneity can also be explained by subgroup analysis results that Isao 2014 did not cause heterogeneity at 7.5 mg tolvaptan. Similarly, Haruki 2017 also only focused on 7.5 mg Tolvaptan. Due to its low therapeutic dose, the incidence of total adverse events was reduced, resulting in high heterogeneity in meta analysis of total adverse events.

The common complications of liver cirrhosis include refractory ascites, hyponatremia and hepatic encephalopathy, etc. Especially when the above complications happen to the patients with liver cirrhosis, the death rate will also increase greatly [22]. Tolvaptan is a drug approved by FDA to treat hyponatremia. But multiple countries including China still have not approved it to treat cirrhotic ascites. At present, there are only 6 RCT studies on the patients with cirrhotic ascites who are treated by Tolvaptan [16–21]. The curative effect and safety of Tolvaptan in treatment of cirrhotic ascites are still unclear, and the use dose is not recommended with solid evidence. Moreover, hyponatremia caused by traditional diuretics are also denounced all the time. Some studies also verify that the patients with cirrhotic ascites combined with hyponatremia are closely related to the high death rate [23–24]. Thus, serum sodium level is an important index which cannot be ignored in treatment of cirrhotic ascites by diuretics. The data results of this study show that the application of Tolvaptan can obviously improve patients' hyponatremia. Besides, with the increase of Tolvaptan dose (7.5–30 mg), the increase degree of patients' serum sodium level also rises.

At the same time, after the use of traditional diuretics, the diuresis effect is not obvious (refractory ascites), which is another problem of cirrhotic ascites treatment [25–26]. In particular, inappetence, abdominal distension, dyspnea and other symptoms resulting from lots of ascites seriously affect patients' daily life [2]. So, for the patients with cirrhotic ascites, Tolvaptan combined with traditional diuretics is considered to be a new target for cirrhotic ascites treatment, and its liquid discharge curative effect receives much attention. The results of this study show that compared with pure use of traditional diuretics, Tolvaptan combined with traditional diuretics can significantly increase patients' urine volume (liquid discharge) to reduce ascites amount, indicating that the combined therapy has excellent curative effect on reduction of ascites. In particular, we should encourage using it to treat the patients with refractory ascites. But for reduction of ascites amount, the increase in daily dose of Tolvaptan fails to improve curative effect.

The complications caused by Tolvaptan also receive much attention, apart from the good curative effect. Existing RCT researches report the daily application of low-dose Tolvaptan (7.5 mg or 15 mg) promotes 6-month survival rate of patients with cirrhotic ascites [21], and a latest meta analysis also reported that Tolvaptan could significantly improve overall survival [13]. However, the concrete complications in the use process are not verified by lots of data. This study demonstrates that it is safe when the daily dose of Tolvaptan is maintained at 7.5 mg. The total incidence of adverse events, the incidence of severe adverse events and the incidence of various complications excluding the rise of blood uric acid have no significant differences with those of traditional diuretic group. When the daily dose of Tolvaptan exceeds

15 mg, the total incidence of adverse events is obviously higher than that of traditional diuretic group. Especially, the occurrence rates of frequency of urination and thirst rise obviously. Although a previous meta analysis reported that Tolvaptan did not affect mortality and complications in patients with cirrhosis[11] and our study showed that the incidence of severe adverse events has no obvious difference with that of traditional diuretic group, it should be more prudent to apply high-dose Tolvaptan combined with traditional diuretics in treatment of patients with cirrhotic ascites. Furthermore, regardless of Tolvaptan dose, the rise of blood uric acid is the major complication of Tolvaptan combined with traditional diuretics. The specific mechanism still remains to be further demonstrated.

Early meta studies for Vaptan drugs (including Tolvaptan, Satavaptan and Lixivaptan) reported that Vaptan drugs was not associated with prolonged survival in patients with cirrhosis [11–12]. In contrast, a recent meta analysis based on retrospective studies showed that Tolvaptan significantly improves overall survival in patients with cirrhosis and refractory ascites, but this paper has not a high level of evidence [13]. Due to the good efficacy and safety of 7.5 mg Tolvaptan demonstrated in this study, more RCT studies to study Tolvaptan and survival rates in patients with cirrhotic ascites should be performed to support the prognostic role of tolvaptan.

The limitations of this study are mainly as follows: 1. Currently, there are still few RCT studies on the treatment of cirrhotic ascites with Tolvaptan, and indicators of each study are not completely consistent; 2. Some studies did not research the relationship between dose and efficacy or safety, so the sample size of dose-related studies was small. In the future, we expect to conduct a larger sample of RCT study on the treatment of cirrhotic ascites with Tolvaptan.

Tolvaptan combined with traditional diuretics has good curative effect for the patients with cirrhotic ascites. When the dose of Tolvaptan is low (7.5 mg), it is safe. But in view of safety result of high-dose use (≥ 15 mg) and dose-related research results, high-dose Tolvaptan fails to bring the better curative effect, but causes the higher incidence of adverse events. In the combined therapy, the recommended dose of Tolvaptan is 7.5 mg. For the patients without response on 7.5 mg Tolvaptan, the data do not support application of higher dose Tolvaptan. Besides, it is required to pay close attention to the changes of patients' blood uric acid in the drug use process.

Conclusions

Tolvaptan combined with traditional diuretics has good curative effect for the patients with cirrhotic ascites. As its adverse reactions, the recommended dose of Tolvaptan is 7.5mg in the combined therapy. No matter whether the dose of Tolvaptan rises, the changes of blood uric acid should be monitored in the whole treatment process.

Abbreviations

RCT: randomized controlled trial; WMD: weighted mean difference; OR: odds ratio; 95% CI: 95% credibility interval.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: The manuscript is approved by all authors for publication. We would like to declare that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

Availability of data and materials: We have uploaded relevant meta-analysis data to the submission system as a supplementary file.

Competing interests: None.

Funding: None.

Authors' contributions:

XL was responsible for data extraction, data processing and original manuscript writing. SL was responsible for data extraction and the registration of research scheme. HZ was responsible for methodology guidance. FL was responsible for the management of original document screening. LM was responsible for the review and revision of draft. HX and ZZ were responsible for the screening of original document. WZ was responsible for research design and management. All authors read and approved the final manuscript.

Acknowledgments: None.

Ethics approval and consent to participate: Not applicable.

Consent for publication: The manuscript is approved by all authors for publication. We would like to declare that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

Availability of data and materials: We have uploaded relevant meta-analysis data to the submission system as a supplementary file.

Competing interests: None.

Funding: None.

Authors' contributions:

XL was responsible for data extraction, data processing and original manuscript writing. SL was responsible for data extraction and the registration of research scheme. HZ was responsible for methodology guidance. FL was responsible for the management of original document screening. LM was responsible for the review and revision of draft. HX and ZZ were responsible for the screening of original document. WZ was responsible for research design and management. All authors read and approved the final manuscript.

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Tables

Table 1: Characteristics of included studies

Country	Multicenter	Conventional diuretic	Treatment Duration	Treatment	N	Age (year)	Female (n, %)	Child-Pugh Grade (n, %)		
								A	B	C
USA	Yes	Yes	4d	Tolvaptan 15-60 mg/d	57	52±8	13(22.8)	6(10.5)	28(49.1)	19(33.3)
				Placebo	63	55±9	19(30.2)	11(17.5)	33(52.4)	16(25.4)
Japan	Yes	Yes	7d	Tolvaptan 7.5 mg/d	25	65±9	7(28.0)	1(4.0)	13(52.0)	11(44.0)
				Tolvaptan 15 mg/d	25	65±10	4(16.0)	0(0)	15(60.0)	10(40.0)
				Tolvaptan 30 mg/d	25	63±10	10(40.0)	2(8.0)	13(52.0)	10(40.0)
				Placebo	26	64±10	9(34.6)	0(0)	16(61.5)	10(38.5)
Japan	Yes	Yes	7d	Tolvaptan 7.5 mg/d	82	68(31-80)	30(36.6)	0(0)	44(53.7)	38(46.3)
				Placebo	80	69(46-78)	31(38.8)	0(0)	54(67.5)	26(32.5)
Japan	Yes	Yes	7d	Tolvaptan 7.5 mg/d	28	69.3±11.8	11(39.3)	0(0)	16(57.1)	12(42.9)
				Placebo	28	69.4±12.6	13(46.4)	0(0)	15(53.6)	13(46.4)
China	Yes	Yes	7d	Tolvaptan 15 mg/d	57	49.9±9.2	11(19.3)	2(3.6)	29(51.8)	25(44.6)
				Tolvaptan 30 mg/d	63	63.0±10.0	15(23.8)	2(3.2)	40(63.5)	21(33.3)
				Placebo	62	48.3±10.5	18(29.0)	3(4.8)	35(56.5)	24(38.7)
China	Yes	Yes	7d	Tolvaptan 15-60 mg/d	169	54.6±8.6	33(19.5)	2(1.2)	113(66.8)	54(32.0)
				Placebo	61	51.6±10.7	12(19.7)	1(1.6)	45(73.8)	15(24.6)

Appendices

Supplement Table 1: The detailed Meta analysis results of various common adverse events.

Supplement Fig 1: The risk of bias within studies.

Supplement Fig 2: A: The result of sensitivity analysis for the comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of

serum sodium concentration (mmol/L) after 7-days intervention. B: The result of sensitivity analysis for the comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about total adverse events.

Figures

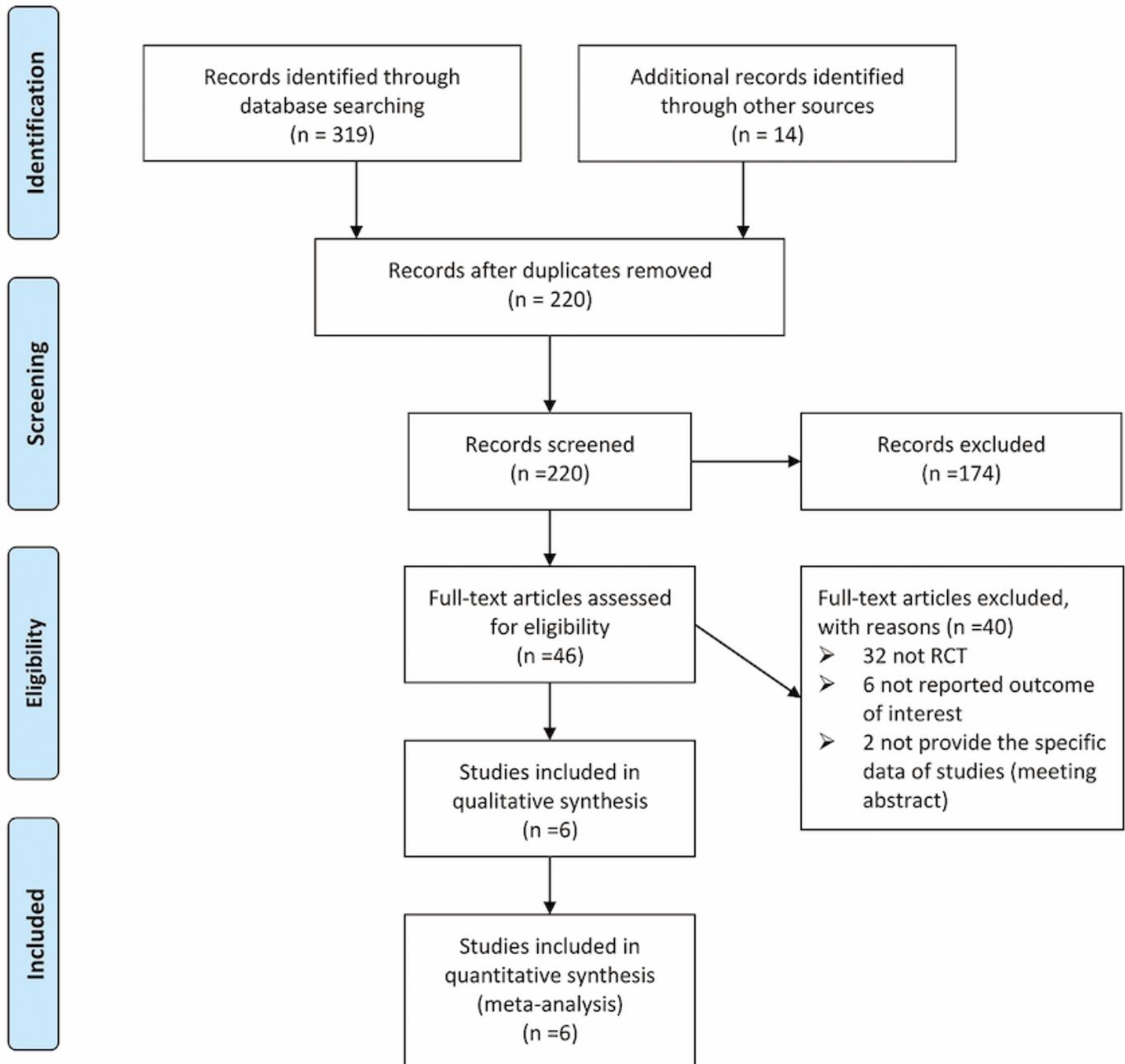


Figure 1

Identification process of the included studies.

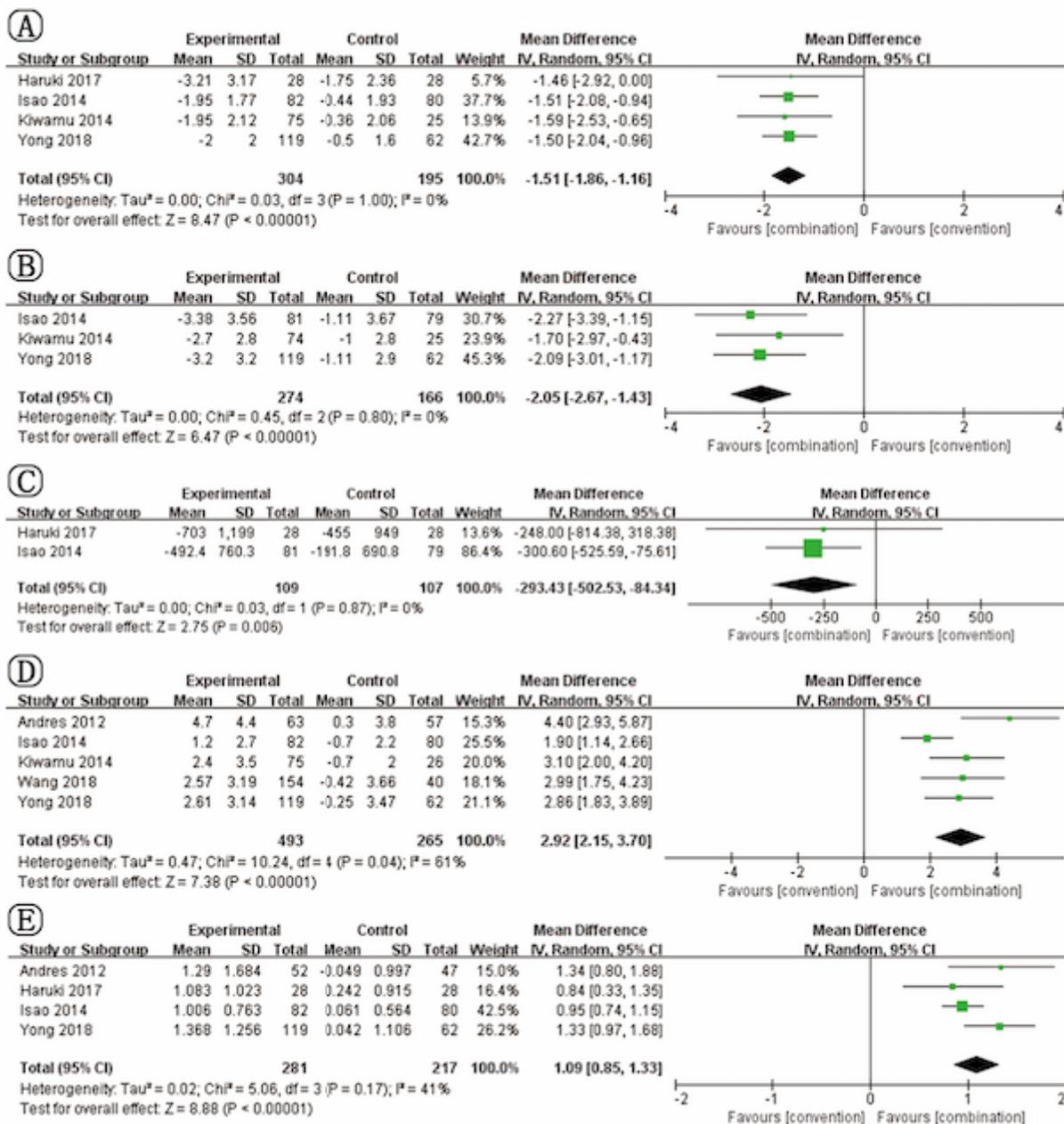


Figure 2

A: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of weight (Kg) after 7-days intervention. B: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of abdominal girth (cm) after 7-days intervention. C: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of ascites volume (mL) after 7-days intervention. D: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of serum sodium concentration (mmol/L) after 7-days intervention. E: The comparison between the

combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of urine volume (L) on Day 1 of intervention.

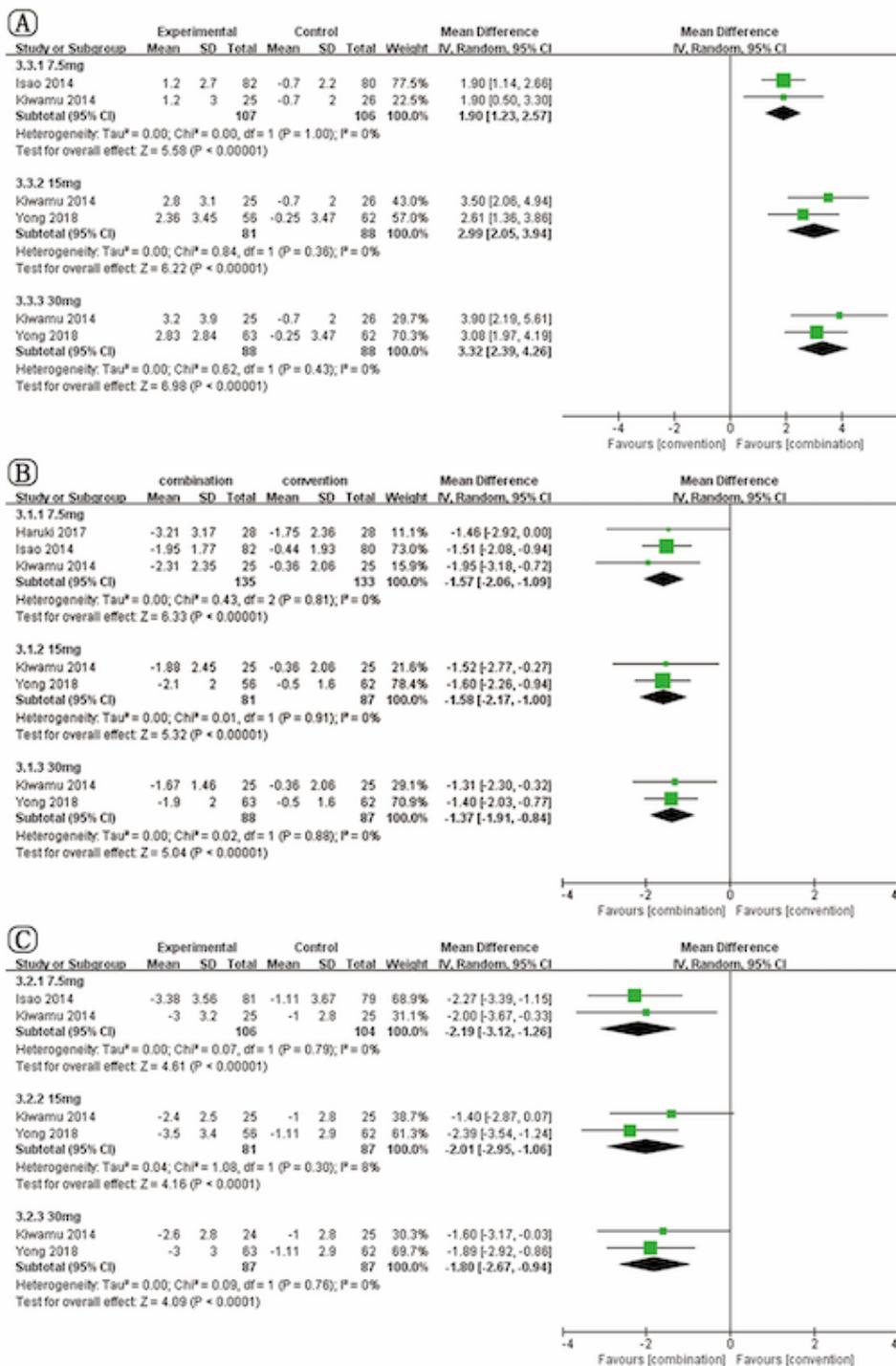


Figure 3

A: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of serum sodium concentration (mmol/L) after 7-days intervention for the different daily dose of Tolvaptan (7.5mg-15mg-30mg). B: The comparison between

the combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of weight (Kg) after 7-days intervention for the different daily dose of Tolvaptan (7.5mg-15mg-30mg). C: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about the mean change of abdominal girth (cm) after 7-days intervention for the different daily dose of Tolvaptan (7.5mg-15mg-30mg).

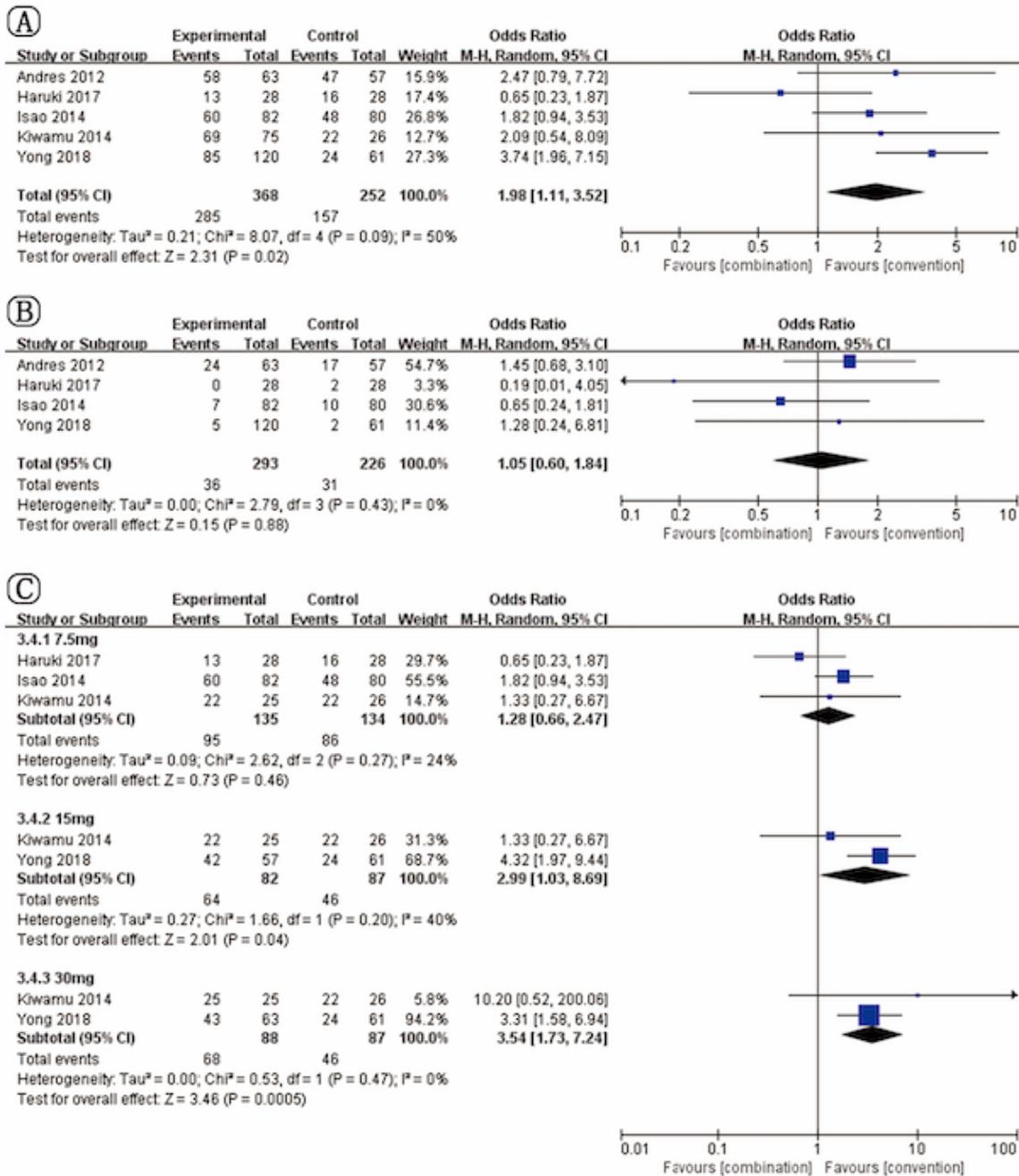


Figure 4

A: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about total adverse events. B: The comparison between the combination diuretic

treatment groups and the conventional diuretic treatment groups about serious adverse events. C: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about total adverse events with the different dose of tolvaptan.

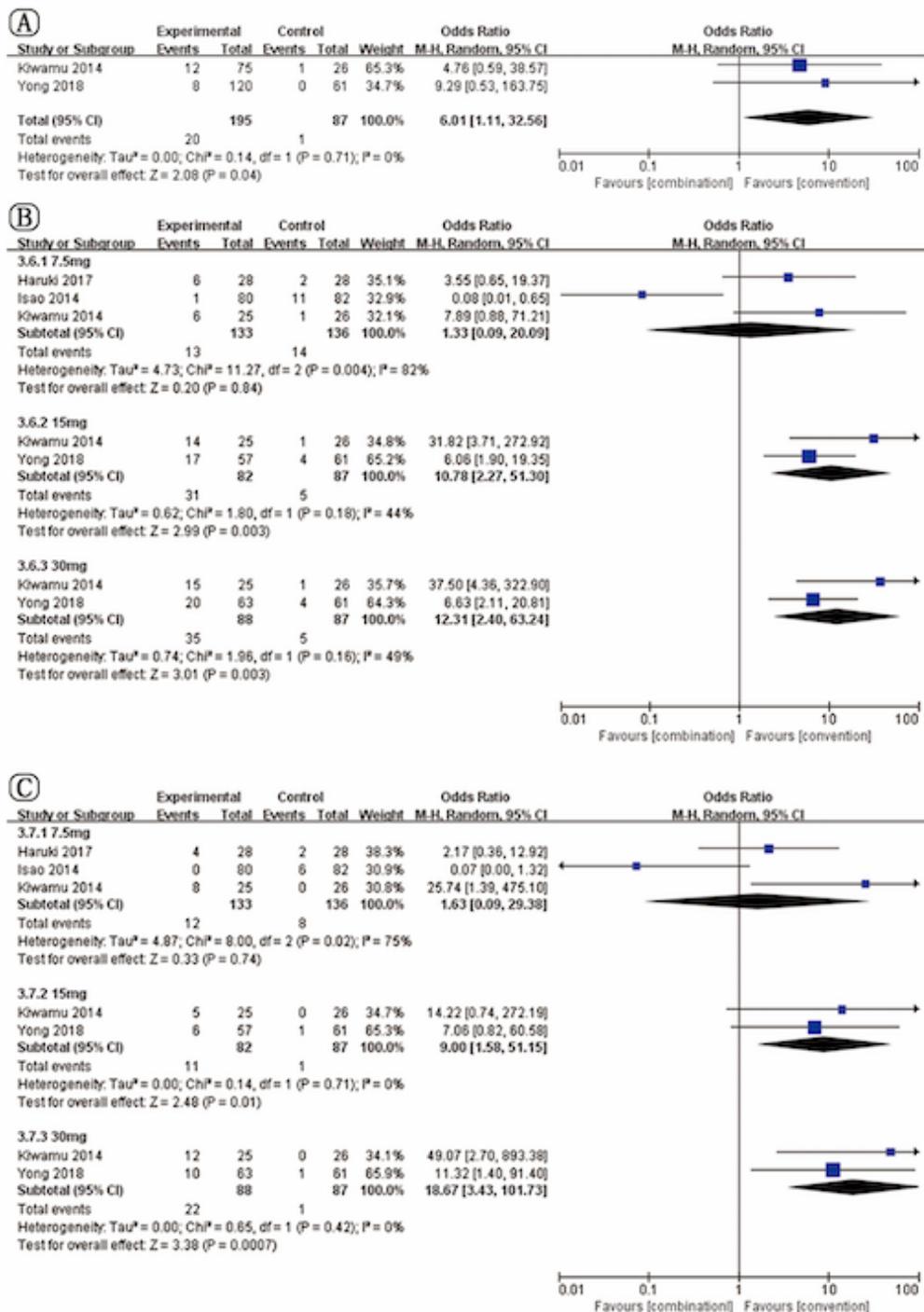


Figure 5

A: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about blood uric acid increasing as an adverse event. B: The comparison between the

combination diuretic treatment groups and the conventional diuretic treatment groups about thirst as an adverse event with the different dose of tolvaptan. C: The comparison between the combination diuretic treatment groups and the conventional diuretic treatment groups about pollakiuria as an adverse event with the different dose of tolvaptan.

Supplementary Files

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