



# Efficacy and safety of Chinese medicine combined with balloon dilatation vs. balloon dilatation alone for achalasia patients: a systematic review and meta-analysis

Junqian Chen<sup>1#^</sup>, Xiaoxun Huang<sup>2#</sup>, Yingting Li<sup>1^</sup>, Haomeng Wu<sup>1^</sup>, Shumin Qin<sup>1^</sup>, Huan Zheng<sup>1^</sup>, Jianhua Li<sup>1^</sup>, Haiyan Zhang<sup>1^</sup>, Lijuan Hu<sup>1^</sup>, Shaogang Huang<sup>1^</sup>

<sup>1</sup>Department of Gastroenterology, Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, China; <sup>2</sup>Department of Critical Care Medicine, Zhongshan Hospital of Traditional Chinese Medicine, Zhongshan, China

**Contributions:** (I) Conception and design: J Chen, X Huang, S Huang; (II) Administrative support: J Chen, X Huang, S Huang; (III) Provision of study materials or patients: Y Li, X Huang, S Qin; (IV) Collection and assembly of data: H Zheng, J Li, H Zhang, L Hu; (V) Data analysis and interpretation: J Chen, X Huang, Y Li, S Huang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

**Correspondence to:** Shaogang Huang, Department of Gastroenterology, Guangdong Provincial Hospital of Traditional Chinese Medicine, 55 Neihuanxi Road, Panyu District, Guangzhou 510006, China. Email: huangshaogang@gzucm.edu.cn.

**Background:** Balloon dilatation is widely used for patients with achalasia; however, the efficacy and safety of Chinese medicine combined with balloon dilatation for achalasia patients is still unclear. Therefore, we conducted a meta-analysis to compare the treatment effectiveness of treatment with Chinese medicine plus balloon dilatation versus balloon dilatation alone for patients with achalasia.

**Methods:** Randomized controlled trials (RCTs) compared the effectiveness of Chinese medicine plus balloon dilatation with balloon dilatation as examined in studies in the PubMed, Springer, Embase, Wiley-Blackwell, Chinese Journal Full-text Database, and the Cochrane library from their inception up to May 2019. The odds ratios (ORs) and weighted mean differences (WMDs) with corresponding 95% confidence intervals (CIs) were used to calculate categories and continuous outcomes using the random-effects model. The inclusion of studies according to the PICOS (participants, interventions, comparisons, outcomes) criteria, the assessment of risk of bias of included studies adhered to the Cochrane criteria guidelines.

**Results:** The initial electronic searches produced 378 records, and 10 RCTs that recruited 504 achalasia patients were included in the final quantitative analysis. Except for other potential biases with moderate to high-risk bias of 20–40%, the other six items had a low-risk bias of 80–90%. Overall, we noted that patients who received the Chinese medicine plus balloon dilatation treatment had a greater incidence of improvement at 1 year (OR: 2.20; 95% CI: 1.45–3.33;  $P < 0.001$ ), and 5 years (OR: 1.83; 95% CI: 1.23–2.74;  $P = 0.003$ ), and reduced the risk of gastroesophageal reflux (OR: 0.42; 95% CI: 0.24–0.76;  $P = 0.004$ ) than patients who underwent balloon dilation only. However, patients who received the Chinese medicine plus balloon dilatation treatment did not have a greater risk of perforation (OR: 0.53; 95% CI: 0.24–1.19;  $P = 0.123$ ) compared with patients undergoing balloon dilation. Finally, Chinese medicine plus balloon dilatation was associated with high esophageal sphincter pressure (WMD: 2.01; 95% CI: 1.19–2.84;  $P < 0.001$ ) compared with patients who underwent balloon dilatation only.

**Conclusions:** Chinese medicine plus balloon dilatation had better effects after treatment than balloon dilatation alone for achalasia patients. Given the risk of bias of included studies, the conclusion should be made with cautions.

<sup>^</sup> ORCID: Junqian Chen, 0000-0001-8342-7322; Yingting Li, 0000-0003-4014-1564; Haomeng Wu, 0000-0001-8091-5603; Shumin Qin, 0000-0003-2507-6274; Huan Zheng, 0000-0003-1061-341X; Jianhua Li, 0000-0003-1537-282X; Haiyan Zhang, 0000-0002-0379-0939; Lijuan Hu, 0000-0002-9340-3778; Shaogang Huang, 0000-0002-5507-1194.

**Keywords:** Chinese medicine; balloon dilatation; achalasia

Submitted Jan 14, 2022. Accepted for publication Mar 14, 2022.

doi: 10.21037/atm-22-744

View this article at: <https://dx.doi.org/10.21037/atm-22-744>

## Introduction

Achalasia is a kind of esophageal motor dysfunction caused by lesions on the primary esophageal nerve and smooth muscles. The main clinical manifestations of achalasia are dysphagia, post-sternal pain, and food reflux (1-3). Research shows that potential reasons for these manifestations are: (I) the damage of the nerve plexus in the esophageal wall, which causes dysfunction of the autonomic nervous system and the sympathetic nervous system; (II) the degeneration of the myenteric plexus caused by a neurotoxic virus; and (III) the lower esophageal sphincter contains vasoactive intestinal peptide that is significantly lower than normal level, leading to an increase of the tension of the esophageal smooth muscle in achalasia (4-6).

Balloon dilatation is an endoscopic treatment method for ruptures of the esophageal lower sphincter muscle fibers, which uses inflatable balloon dilatation to reduce tension caused by the rupture (7-9). In doing so, endoscopic balloon dilation may improve the symptoms of achalasia. However, dilatation therapy mainly solves swallowing difficulties, and uncontrolled complications are inevitable. Therefore, additional treatment strategies should be employed to obtain greater benefits and avoid any potential adverse complications. To improve the treatment methods for achalasia, traditional Chinese medicine was used and added to the balloon dilatation method for patients with achalasia (10-12). The traditional Chinese medicine treatment of achalasia is mainly based on regulating qi to open depression, resolving phlegm to disperse knot, promoting blood circulation to remove stasis, nourishing Yin to moisten dryness, and stimulating diaphragm to have an appetite. In light of syndrome differentiation and targeted treatment, the traditional Chinese medicine combined with acupuncture and moxibustion and massage achieved a good effect (13).

Several existing studies compared the treatment effectiveness of Chinese medicine plus balloon dilatation *vs.* balloon dilatation only for patients with achalasia, but the observed results were inconsistent (13,14). Therefore, this study used a quantitative meta-analysis to systematically

evaluate the effectiveness of treatment with Chinese medicine plus balloon dilatation compared to balloon dilatation only for achalasia patients. We present the following article in accordance with the PRISMA reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-744/rc>).

## Methods

### *Data sources, search strategy, and selection criteria*

This meta-analysis was planned and performed in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis statement (15). We systematically searched PubMed, Springer, Embase, Wiley-Blackwell, Chinese Journal Full-text Database, and the Cochrane library to identify the studies to compare Chinese medicine plus balloon dilatation with balloon dilatation alone for achalasia patients from their inception up to May 2019. The following search terms were used as medical subject headings and free words: Chinese medicine, balloon dilatation, and achalasia. The hand-searches of reference lists from retrieved studies were also reviewed to select any new eligible study.

The literature search and study selection were conducted by two authors, and any disagreement was resolved by group discussion. A study was included if it met the following inclusion criteria: (I) patients: patients diagnosed with achalasia; (II) intervention: Chinese medicine plus balloon dilatation; (III) control: balloon dilatation alone; (IV) outcomes: the study reported at least 1 of following outcome: improvement at 1 year and 5 years, perforation, gastroesophageal reflux, and esophageal sphincter pressure; and (V) study design: the study had to have a randomized controlled trial (RCT). The exclusion criteria were the following: (I) a study with an observational design; (II) patients received other treatment strategies; (III) Control group was not balloon dilatation; and/or (IV) study reported outcomes other than the treatment effectiveness of balloon dilation. If results from a study were published more than once, data from the most recent publication was considered

eligible for this study.

### **Data collection**

The two reviewers read the full text and extracted the relevant data of each study into the coding table in Microsoft Excel software. The characteristics extracted in this study included the first author's name, publication year, year of onset, sample size (Chinese medicine with balloon dilatation/balloon dilatation), mean range of patients, intervention, and control.

### **Quality assessment**

The quality of included studies was assessed according to the Cochrane criteria guidelines (16). The data collection and quality assessment were assessed by two authors, and inconsistencies were resolved by an additional author referring to the original article. The items assessed were as follows: selection bias, selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential sources of bias.

### **Statistical analysis**

The summary odds ratio (OR) and 95% confidence interval (CI) were used to calculate the incidence of improvement of perforation and gastroesophageal reflux at 1 year and 5 years after treatment, while the pooled weighted mean difference (WMD) and 95% CI were used to assess esophageal sphincter pressure after treatment with Chinese medicine plus balloon dilatation and balloon dilatation only. The summary results were calculated using the random-effects model (17,18). Heterogeneity among included studies was assessed using the I-square and Q statistic, and  $P < 0.10$  was regarded as significant heterogeneity (19,20). Sensitivity analyses were conducted for investigated outcomes to assess the impact of a single study (21). Subgroup analyses were also conducted to assess improvement in perforation, gastroesophageal reflux, and esophageal sphincter pressure at 1 year and 5 years after treatment based on publication year and the mean age of patients. Moreover, the treatment effects between subgroups were also assessed (22). Analysis of publication bias was conducted by funnel plots, Egger (23), and Begg test results (24). The inspection level for pooled results was 2-sided, and  $P < 0.05$  was regarded as statistically significant. All statistical analyses were conducted using RevMan (version 5.3.5, Nordic Cochrane

Center, Copenhagen, Denmark) and STATA software (version 10.0; Stata Corporation, College Station, TX, USA).

## **Results**

### **Search results**

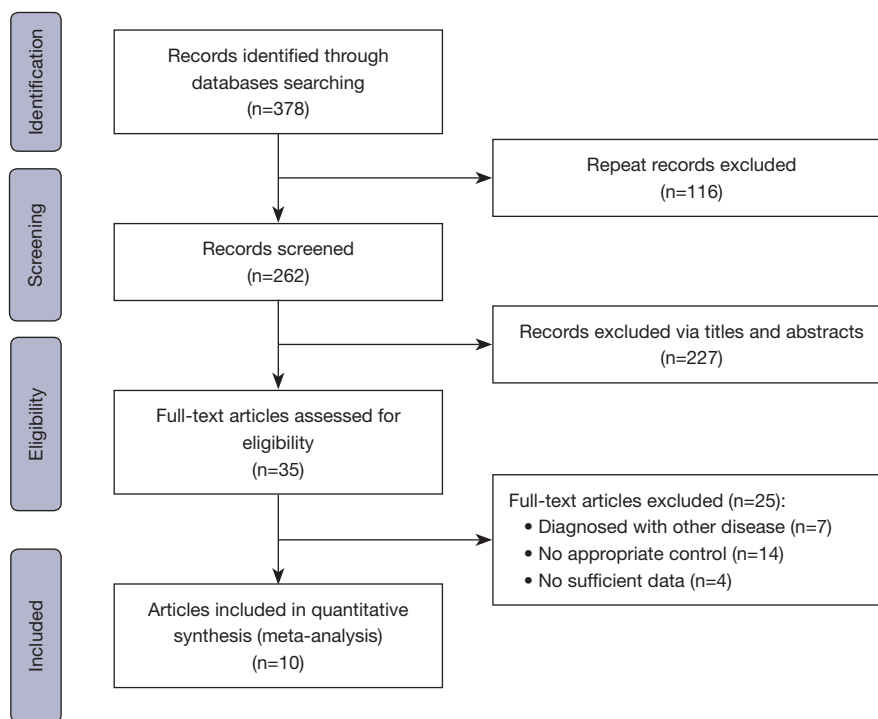
An initial electronic search produced 378 records, and 343 were excluded because they were duplicates or were about an irrelevant topic. The remaining 35 studies were retrieved for detailed evaluations, and 25 were excluded because the patients were diagnosed with diseases other than achalasia, the studies did not contain an appropriate control, or the study reported outcomes other than the treatment effectiveness of balloon dilation. Finally, 10 RCTs were selected for final analysis (13,14,25-32). *Figure 1* shows a flowchart of the identification, inclusion, and exclusion process.

### **Characteristics of included studies**

*Table 1* lists the first author's name, year of publication, age of onset, sample size (Chinese medicine with balloon dilatation *vs.* balloon dilatation), age range of patients, and outcome parameters for each study. All included articles were published from 2000 to 2018. The sample size was between 12 and 142 patients. The included studies contained 504 patients with achalasia, including 250 who underwent treatment with Chinese medicine plus balloon dilatation and 254 who underwent treatment with balloon dilatation only. The deviation table in the Review Manager 5.0 tutorial was used to assess the risk of each study by applying the criteria for evaluating design-related deviations. The risk of bias and the details of each article are shown in *Figure 2*. Except for other potential biases with moderate to high-risk bias of 20–40%, the other six items had a low-risk bias of 80–90%.

### **Improvement at 1 year after treatment**

After pooling all included studies, we noted that treatment with Chinese medicine plus balloon dilatation was associated with an increased incidence of improvement at 1 year (OR: 2.20; 95% CI: 1.45–3.33;  $P < 0.001$ ; *Figure 3*), and no evidence of heterogeneity was detected. The conclusions of subgroup analyses in all subsets were consistent with the overall analysis and reported a



**Figure 1** Flow diagram of the study identification, inclusion, and exclusion.

significantly high incidence of improvement at 1 year in patients who received Chinese medicine plus balloon dilatation treatment (*Table 2*). The results of sensitivity analysis for all indicators are shown in the *Figure S1*. Sensitivity analysis for improvement at 1 year indicated that this pooled conclusion was stable because the result was not altered by excluding any particular trial (*Figure S1A*). The funnel plots of publication bias for all indicators are shown in the *Figure S2*. No significant publication bias for improvement at 1 year was detected (P value for Egger: 0.442; P value for Begg: 0.721; *Figure S2A*).

#### **Improvement at 5 years after treatment**

After pooling all included studies, results showed that patients who received the Chinese medicine plus balloon dilatation treatment had a significantly increased incidence of improvement at 5 years after treatment than those who received balloon dilatation only (OR: 1.83; 95% CI: 1.23–2.74;  $P=0.003$ ; *Figure 4*), and no evidence of heterogeneity was observed. Sensitivity analysis indicated that the pooled conclusion for improvement at 5 years was not changed by sequential exclusion of any individual trial (*Figure S1B*).

Subgroup analyses indicated that the significant differences for improvement at 5 years were mainly detected if the pooled studies were published in or after 2010 and if the mean age of patients was greater than 40.0 years (*Table 2*). No significant publication bias was detected (P value for Egger: 0.305; P value for Begg: 0.721; *Figure S2B*).

#### **Perforation**

After pooling all included studies, results showed there was no significant difference in the risk of perforation between patients treated with Chinese medicine plus balloon dilatation and those treated with balloon dilatation alone (OR: 0.53; 95% CI: 0.24–1.19;  $P=0.123$ ; *Figure 5*), and no evidence of heterogeneity was observed. Sensitivity analysis was conducted, and this conclusion was not altered after sequentially excluding individual studies (*Figure S1C*). Subgroup analyses indicated that there were no significant differences between patients treated with Chinese medicine plus balloon dilatation and patients treated with balloon dilatation alone for the risk of perforation in all subsets (*Table 2*). Finally, no significant publication bias was observed (P value for Egger: 0.189; P

**Table 1** Characteristics of the included studies

First author	Year	Country	Age range (mean)	Groups	Number	Years of onset
Huang (25)	1997	China	49.3±4.6	Chinese medicine and balloon dilatation	10	January 2007 to January 2017
				Balloon dilatation	9	
Ma (26)	2004	China	21.8±3.8	Chinese medicine and balloon dilatation	6	January 2004 to November 2009
				Balloon dilatation	6	
Qin (27)	2009	China	47.7±8.7	Chinese medicine and balloon dilatation	16	November 2011 to September 2015
				Balloon dilatation	14	
Tan (28)	2012	China	42.5±11.3	Chinese medicine and balloon dilatation	11	August 2013 to February 2014
				Balloon dilatation	12	
Tao (29)	2003	China	35.4±13.1	Chinese medicine and balloon dilatation	10	December 2000 to December 2002
				Balloon dilatation	10	
Wei (13)	2017	China	35.3±11.3	Chinese medicine and balloon dilatation	12	January 2001 to December 2003
				Balloon dilatation	10	
Yu (14)	2016	China	46.8±2.3	Chinese medicine and balloon dilatation	38	January 2012 to August 2015
				Balloon dilatation	42	
Zhang (30)	2001	China	32.8±8.2	Chinese medicine and balloon dilatation	72	January 2004 to June 2010
				Balloon dilatation	70	
Zhao (31)	2018	China	44.1±7.9	Chinese medicine and balloon dilatation	34	October 1989 to December 2006
				Balloon dilatation	42	
Zhou (32)	2018	China	47.8±6.3	Chinese medicine and balloon dilatation	41	October 2004 to October 2016
				Balloon dilatation	39	

value for Begg: 0.174; [Figure S2C](#)).

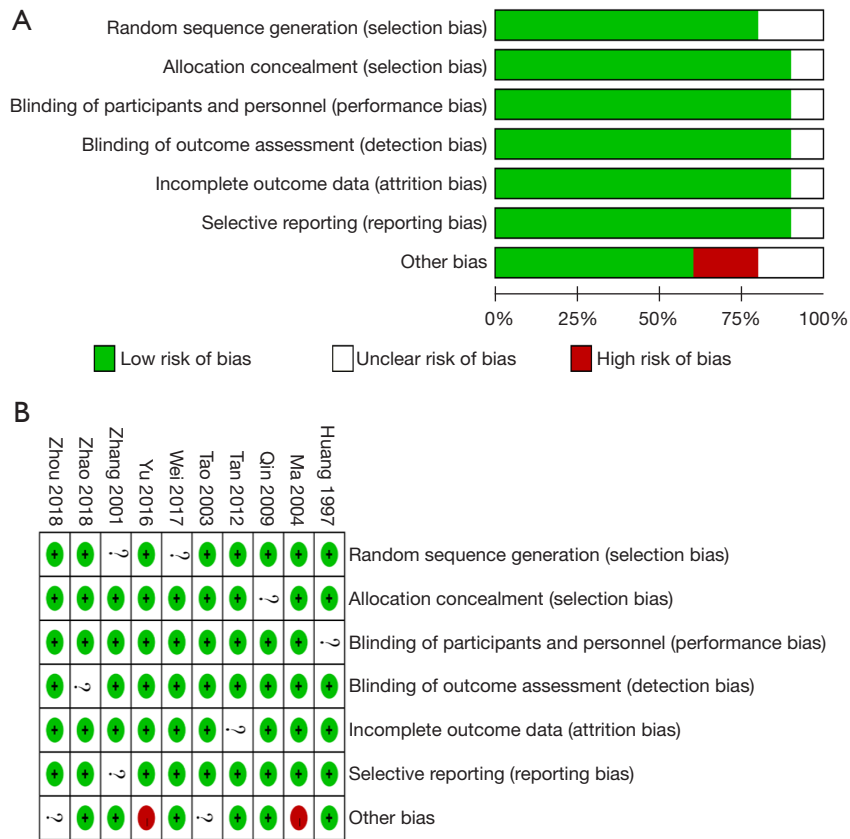
### ***Gastroesophageal Reflux***

After pooling all included studies, we noted that Chinese medicine plus balloon dilatation treatment was associated with a reduced risk of gastroesophageal reflux compared with balloon dilatation alone (OR: 0.42; 95% CI: 0.24–0.76;  $P=0.004$ ; [Figure 6](#)), and no evidence of heterogeneity was observed. The pooled conclusion was stable and did not change by excluding any specific trial ([Figure S1D](#)). Subgroup analyses indicated that the significant differences in the risk of gastroesophageal reflux for patients who were treated with Chinese medicine plus balloon dilatation compared with patients treated with balloon dilatation alone were mainly observed if the pooled studies were published in or after 2010 and if the mean age of patients was greater than 40.0 years ([Table 2](#)). No significant publication bias for

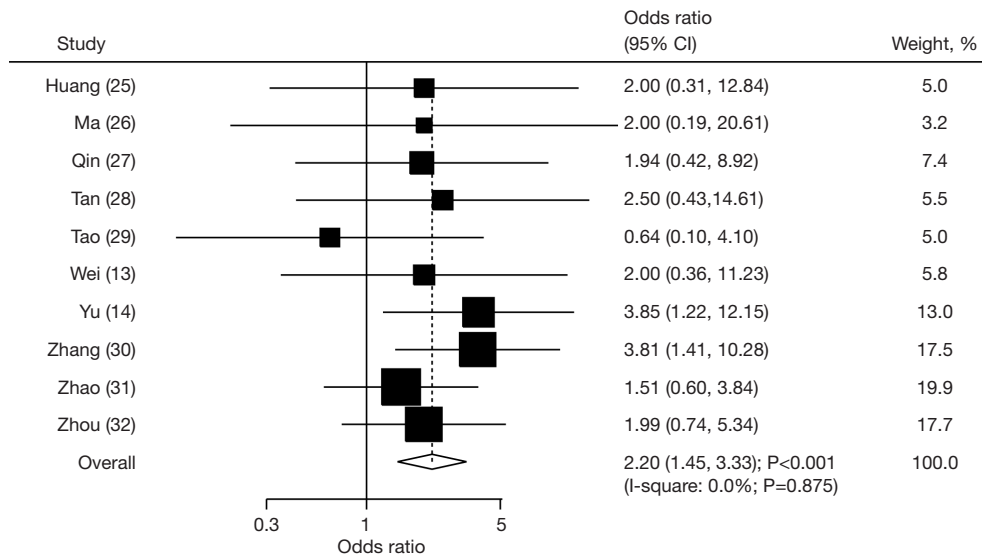
gastroesophageal reflux was detected (P value for Egger: 0.166; P value for Begg: 0.371; [Figure S2D](#)).

### ***Esophageal sphincter pressure***

After pooling all included studies, results showed that patients who were treated with Chinese medicine plus balloon dilatation had significantly increased esophageal sphincter pressure as compared with patients treated with balloon dilatation alone (WMD: 2.01; 95% CI: 1.19–2.84;  $P<0.001$ ; [Figure 7](#)), and no evidence of heterogeneity among included trials. The results of sensitivity analysis indicated that the pooled result was stable after excluding any particular study ([Figure S1E](#)). Subgroup analyses indicated that these significant differences were mainly detected if the pooled studies were published in or after 2010 and if the mean age of patients was greater than 40.0 years ([Table 2](#)). There was no significant publication bias detected (P value



**Figure 2** Quality assessment of the included studies. (A) Risk of bias graph; (B) summary risk of bias. “+”, low risk of bias; “?”, unclear risk of bias; “-”, high risk of bias.



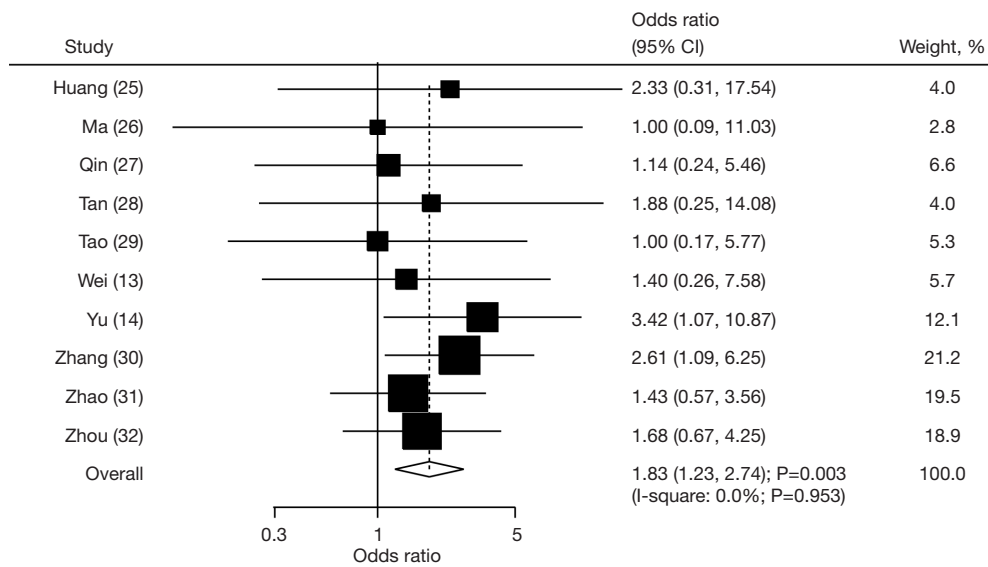
**Figure 3** The effect of Chinese medicine plus balloon dilatation vs. balloon dilatation alone on the incidence of improvement at 1 year (13,14,25-32). CI, confidence interval.

Table 2 Subgroup analyses for investigated outcomes

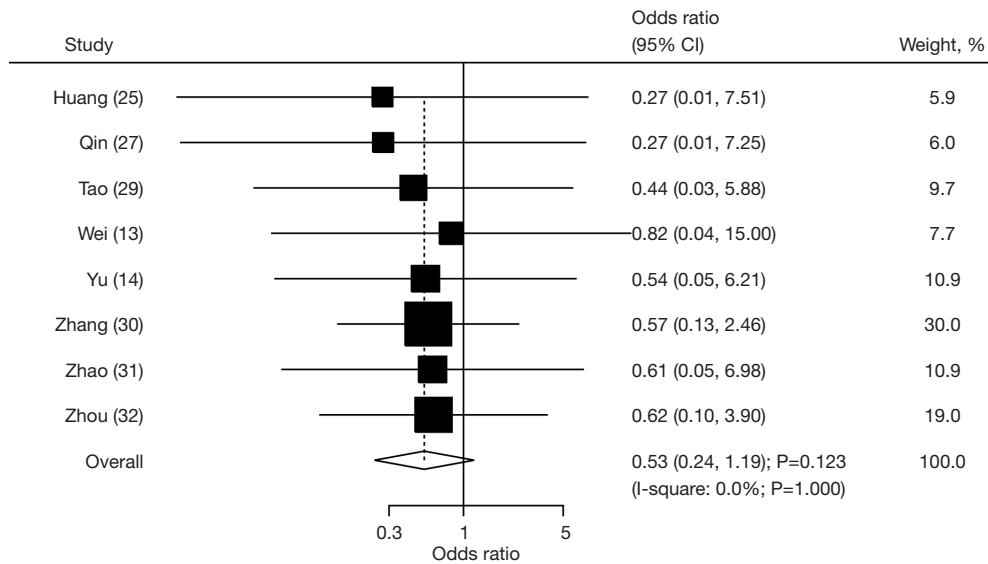
Outcomes	Group	Number of studies	OR/WMD and 95% CI	P value	Heterogeneity (%)/ P value	P value between subgroups
Improvement at 1 year	Publication year					0.865
	Before 2010	5	2.30 (1.17–4.51)	0.015	0.0/0.576	
	2010 or after	5	2.14 (1.26–3.62)	0.005	0.0/0.811	
	Mean age (years)					0.793
	≥40.0	6	2.12 (1.28–3.50)	0.003	0.0/0.901	
	<40.0	4	2.39 (1.14–5.00)	0.021	0.0/0.417	
Improvement at 5 years	Publication year					0.969
	Before 2010	5	1.85 (0.98–3.50)	0.059	0.0/0.784	
	2010 or after	5	1.82 (1.08–3.06)	0.024	0.0/0.821	
	Mean age (years)					0.915
	≥40.0	6	1.80 (1.09–2.97)	0.021	0.0/0.871	
	<40.0	4	1.89 (0.96–3.73)	0.067	0.0/0.701	
Perforation	Publication year					0.704
	Before 2010	4	0.46 (0.15–1.40)	0.170	0.0/0.965	
	2010 or after	4	0.62 (0.20–1.98)	0.423	0.0/0.997	
	Mean age (years)					0.865
	≥40.0	5	0.50 (0.16–1.51)	0.216	0.0/0.987	
	<40.0	3	0.57 (0.18–1.84)	0.348	0.0/0.954	
Gastroesophageal reflux	Publication year					0.643
	Before 2010	5	0.50 (0.20–1.22)	0.127	0.0/0.715	
	2010 or after	5	0.37 (0.17–0.81)	0.012	0.0/0.795	
	Mean age (years)					0.811
	≥40.0	6	0.40 (0.19–0.83)	0.015	0.0/0.853	
	<40.0	4	0.47 (0.18–1.20)	0.113	0.0/0.578	
Esophageal sphincter pressure	Publication year					0.095
	Before 2010	5	1.11 (–0.23 to 2.46)	0.103	0.0/0.777	
	2010 or after	5	2.56 (1.51 to 3.61)	<0.001	0.0/0.687	
	Mean age (years)					0.338
	≥40.0	6	2.33 (1.28 to 3.37)	<0.001	0.0/0.923	
	<40.0	4	1.57 (–0.19 to 3.32)	0.080	33.3/0.212	

OR, odds ratios; WMD, weighted mean differences; CI: confidence interval.





**Figure 4** The effect of Chinese medicine plus balloon dilatation *vs.* balloon dilatation alone on the incidence of improvement at 5 years (13,14,25-32). CI, confidence interval.



**Figure 5** The effect of Chinese medicine plus balloon dilatation *vs.* balloon dilatation alone on the risk of perforation (13,14,25,27,29-32). CI, confidence interval.

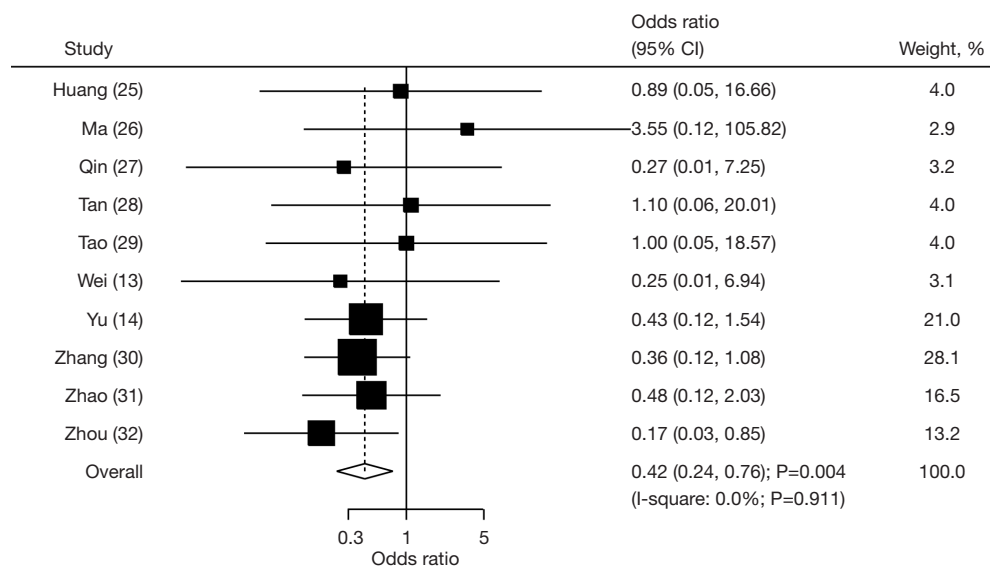
for Egger: 0.745; P value for Begg: 0.858; [Figure S2E](#)).

**Discussion**

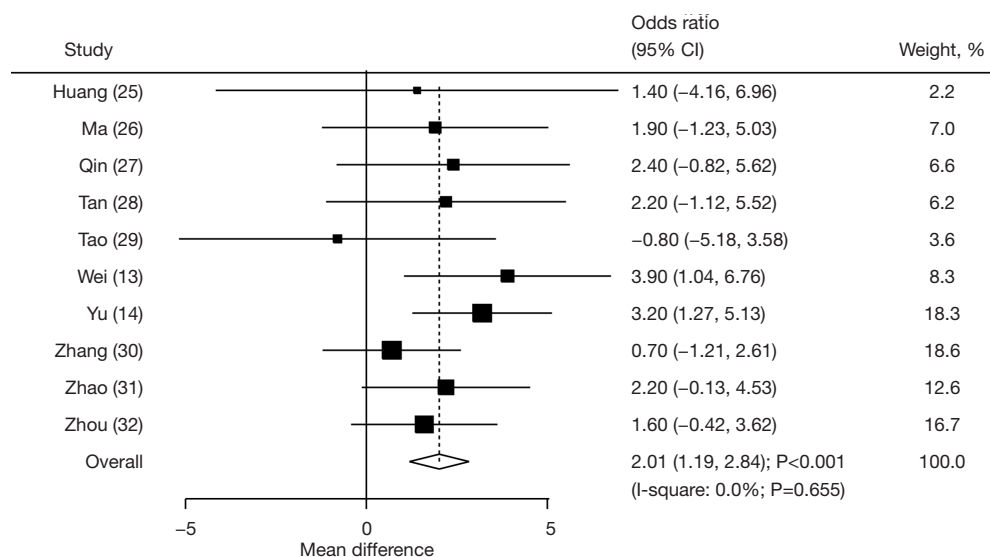
Cardiac achalasia presents as cardia spasm, esophageal peristalsis, and megaesophagus because it causes motor

dysfunction of esophageal nerves and muscles, high pressure in the lower esophageal sphincter, and weakens the relaxation response when swallowing (33-35). All of this can cause flaccidity and prevent food from passing smoothly. This subsequently result in the esophageal tension and peristalsis. Therefore, effective treatment strategies should





**Figure 6** The effect of Chinese medicine plus balloon dilatation *vs.* balloon dilatation alone on the risk of gastroesophageal reflux (13,14,25-32). CI, confidence interval.



**Figure 7** The effect of Chinese medicine plus balloon dilatation *vs.* balloon dilatation alone on esophageal sphincter pressure (13,14,25-32). CI, confidence interval.

be employed for patients with achalasia.

This comprehensive study reviewed existing studies that together recruited 504 achalasia patients from 10 RCTs across a wide range of patient characteristics. The results of this study indicated that patients treated with Chinese medicine plus balloon dilatation had superior outcomes in terms of improvement at 1 year and 5 years,

gastroesophageal reflux, and esophageal sphincter pressure than patients treated with balloon dilatation alone. There was no significant difference between these groups for the risk of perforation.

The studies included in the meta-analysis illustrated several techniques for balloon dilatation, including using a guide wire, an endoscopic biopsy channel, and the anterior

part of the endoscope body (36-38). During balloon dilatation, the balloon could be inserted directly through the endoscopic biopsy hole of the large foramen and could be accurately located and observed during the operation. Balloon dilatation could immediately relieve dysphagia of patients. Previous studies added traditional Chinese medicine to the balloon dilatation technique, including balanced acupuncture and chiropractic therapy to balloon dilatation (39-41). However, whether these have additional benefits remains controversial.

The results of this meta-analysis showed that the improvement of symptoms at 1 year and 5 years between patients treated with Chinese medicine plus balloon dilatation and those treated with balloon dilatation alone were statistically significant. This suggests that treatment with Chinese medicine plus balloon dilatation was superior to treatment with balloon dilatation only for patients with achalasia. This result is coincident with Tan's research which showed that the clinical efficacy and esophageal function was better in patients treated with Chinese medicine plus balloon dilatation was better than those treated with only balloon dilatation (42,43).

Moreover, we noted that Chinese medicine plus balloon dilatation was associated with a lower risk of gastroesophageal reflux, but the risk of perforation between groups was not statistically significant. Although the significant reduction of the risk of gastroesophageal reflux in patients treated with Chinese medicine plus balloon dilatation was not present in most included studies, the study conducted by Zhou *et al.* (32) reported a similar result. This could be because the Zhou *et al.* (32) study reported a high incidence of gastroesophageal reflux, therefore the significant difference was easier to observe. Moreover, the risk of perforation between groups was not detected in all studies, but this may have occurred because of the low incidence of perforation in the included studies.

This study has the following limitations: (I) all included studies were conducted in China, which restricted the recommendations of the results of this study; (II) most patient characteristic were not available, which prevented a more detailed analysis; (III) many different types of traditional Chinese medicines could bias the treatment effectiveness, which needs further verification; and (IV) the results of this study were based on published articles, and unpublished data was not available, which might produce overestimation of results.

In conclusion, this meta-analysis found that achalasia patients treated with Chinese medicine plus balloon

dilatation benefited 1 year and 5 years after treatment and had greater improvements in gastroesophageal reflux and esophageal sphincter pressure than those patients who received balloon dilatation alone. However, no significant differences for the risk of perforation between patients treated with Chinese medicine plus balloon dilatation and balloon dilatation alone were observed. These results need to be verified with further large-scale RCTs.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-744/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-744/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

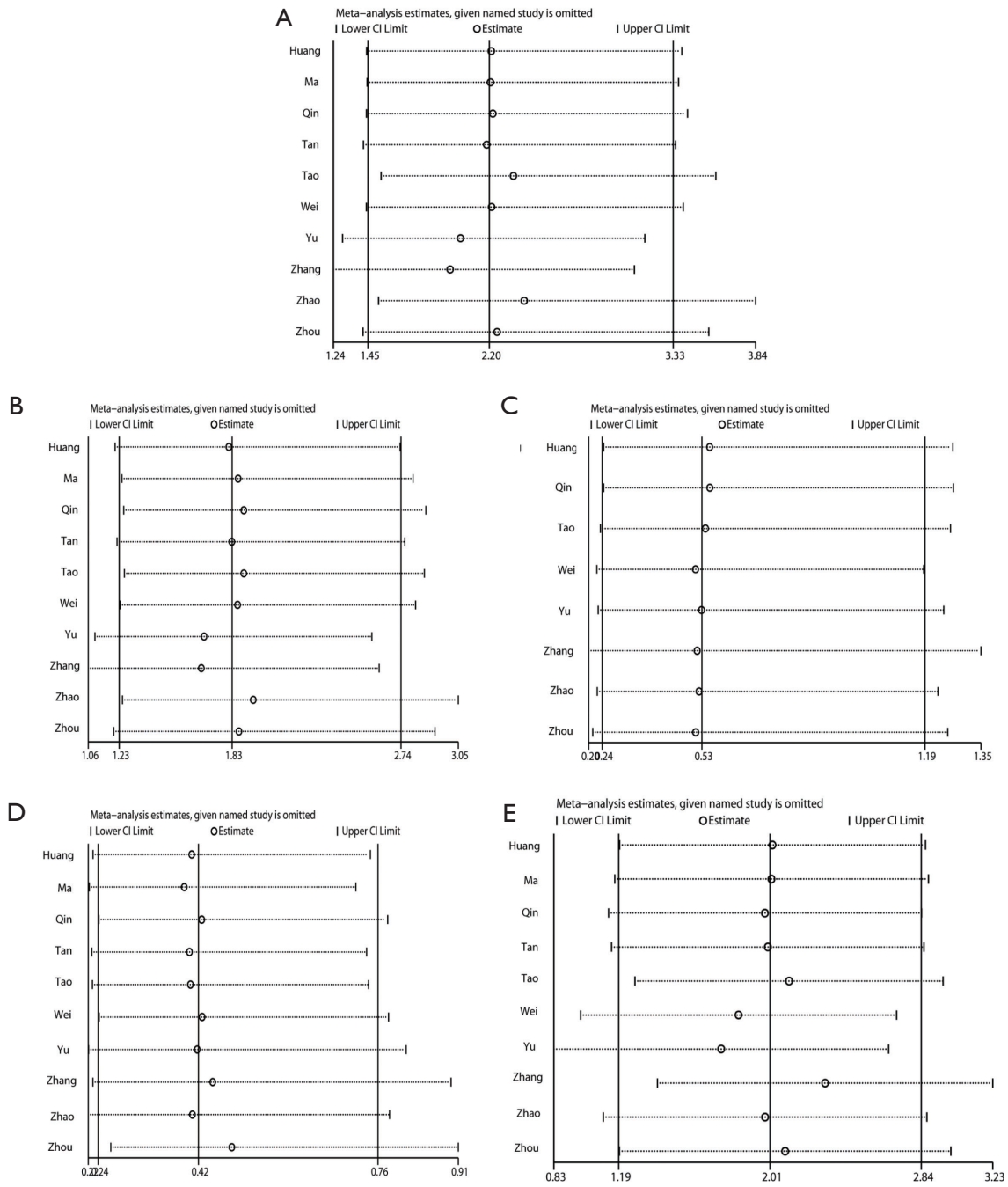
## References

1. Bonifácio P, de Moura DTH, Bernardo WM, et al. Pneumatic dilation versus laparoscopic Heller's myotomy in the treatment of achalasia: systematic review and meta-analysis based on randomized controlled trials. *Dis Esophagus* 2019;32. doi: 10.1093/dote/doy105.
2. Baniya R, Upadhaya S, Khan J, et al. Laparoscopic esophageal myotomy versus pneumatic dilation in the

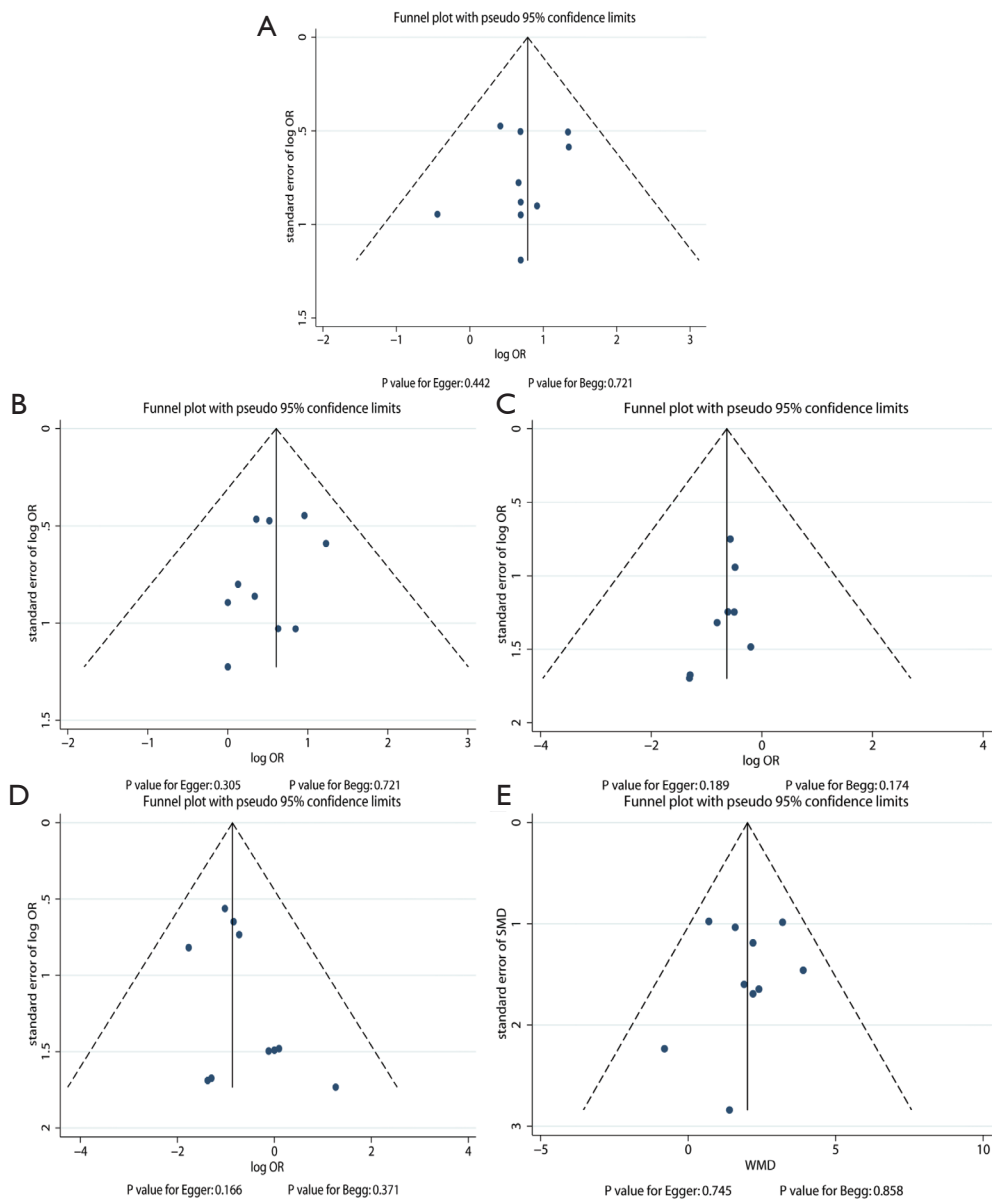
- treatment of idiopathic achalasia: a meta-analysis of randomized controlled trials. *Clin Exp Gastroenterol* 2017;10:241-8.
3. Richter JE, Jacobs J, Kumar A. Response to Elias and Castell. *Am J Gastroenterol* 2016;111:1362-3.
  4. Emami MH, Raisi M, Amini J, et al. Pneumatic balloon dilation therapy is as effective as esophagomyotomy for achalasia. *Dysphagia* 2008;23:155-60.
  5. Gomez-Larrauri A, Galloway S, Niven R. Achalasia with massive oesophageal dilation causing tracheomalacia and asthma symptoms. *Respir Med Case Rep* 2017;23:80-2.
  6. Sanaka MR, Raja S, Thota PN. Esophageal Perforation After Pneumatic Dilation for Achalasia: Successful Closure With an Over-the-Scope Clip. *J Clin Gastroenterol* 2016;50:267-8.
  7. Sánchez-Pernaute A, Aguirre EP, Talavera P, et al. Laparoscopic approach to esophageal perforation secondary to pneumatic dilation for achalasia. *Surg Endosc* 2009;23:1106-9.
  8. Souma Y, Nakajima K, Taniguchi E, et al. Mucosal perforation during laparoscopic surgery for achalasia: impact of preoperative pneumatic balloon dilation. *Surg Endosc* 2017;31:1427-35.
  9. Tuset JA, Luján M, Huguete JM, et al. Endoscopic pneumatic balloon dilation in primary achalasia: predictive factors, complications, and long-term follow-up. *Dis Esophagus* 2009;22:74-9.
  10. Zhao H, Wan XJ, Yang CQ. Comparison of endoscopic balloon dilation with metal stent placement in the treatment of achalasia. *J Dig Dis* 2015;16:311-8.
  11. Pratap N, Kalapala R, Darisetty S, et al. Achalasia cardia subtyping by high-resolution manometry predicts the therapeutic outcome of pneumatic balloon dilatation. *J Neurogastroenterol Motil* 2011;17:48-53.
  12. Mikaeli J, Bishehsari F, Montazeri G, et al. Pneumatic balloon dilatation in achalasia: a prospective comparison of safety and efficacy with different balloon diameters. *Aliment Pharmacol Ther* 2004;20:431-6.
  13. Wei W. Medical treatment of achalasia of cardia. *Psychologist* 2017;23:147-8.
  14. Yu HY, Chen X, Zhao DY, et al. Modified balloon dilatation for achalasia of cardia. *Chin J Dig Endosc* 2016;33:328-9.
  15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
  16. Manager R. (RevMan). Version 5.3. Copenhagen, Denmark: Nordic Cochrane Center, Cochrane Collaboration, 2012.
  17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
  18. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. *Med Decis Making* 2005;25:646-54.
  19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
  20. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
  21. Tobias A. Assessing the influence of a single study in meta-analysis. *Stata Tech Bull* 1999;47:15-7.
  22. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, eds. *Systematic Reviews in Health Care: Metaanalysis in Context*. 2nd ed. London: BMJ Books 2001:285-312.
  23. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
  24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.
  25. Huang HP, Yu SY. Endoscopic balloon dilatation combined with traditional Chinese medicine in the treatment of achalasia. *New Chin Med* 1997;12:33.
  26. Ma Y. Endoscopic balloon dilatation combined with traditional Chinese medicine in the treatment of cardiac arrhythmia. *Chin Folk Ther* 2004;12:34.
  27. Qin GD, Zhang F, Zhao JP. Observation on the therapeutic effect of gastroscopic balloon dilatation for achalasia. *J Changzhi Med Coll* 2009;23:364-5.
  28. Tan L, Yu HY. TCM treatment of achalasia of cardia. *Contemp Med* 2012;18:156-7.
  29. Tao KS, Xu HL, Xu LM. Treatment of achalasia of cardia with balloon dilatation combined with traditional Chinese medicine. *Shandong J Tradit Chin Med* 2003;9:540-1.
  30. Zhang XB, Huang HP, Qiu RJ, et al. Endoscopic balloon dilatation combined with traditional Chinese medicine in the treatment of achalasia of cardia. *Chin J Integ Tradit Chin Western Med* 2001;6:464.
  31. Zhao YJ, Tian ZB, Xu SQ, et al. Treatment of Magesophagus. *Wisdom and Health* 2018;1:58-9.
  32. Zhou Q, Zhu CY, Zhang SS. Recognition and treatment on achalasia of cardia in traditional Chinese medicine. *Chin J Tradit Chin Med* 2018;33:4451-3.
  33. Alderliesten J, Conchillo JM, Leeuwenburgh I, et al.

- Predictors for outcome of failure of balloon dilatation in patients with achalasia. *Gut* 2011;60:10-6.
34. Joo YE. Can achalasia subtyping by high-resolution manometry predict the therapeutic outcome of pneumatic balloon dilatation? *J Neurogastroenterol Motil* 2011;17:203-4.
  35. Dağlı U, Kuran S, Savaş N, et al. Factors predicting outcome of balloon dilatation in achalasia. *Dig Dis Sci* 2009;54:1237-42.
  36. Boztas G, Mungan Z, Ozdil S, et al. Pneumatic balloon dilatation in primary achalasia: the long-term follow-up results. *Hepatogastroenterology* 2005;52:475-80.
  37. Khan AA, Shah SW, Alam A, et al. Efficacy of Rigiflex balloon dilatation in 12 children with achalasia: a 6-month prospective study showing weight gain and symptomatic improvement. *Dis Esophagus* 2002;15:167-70.
  38. Sabharwal T, Cowling M, Dussek J, et al. Balloon dilation for achalasia of the cardia: experience in 76 patients. *Radiology* 2002;224:719-24.
  39. Schoenberg MB, Marx S, Kersten JF, et al. Laparoscopic Heller myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. *Ann Surg* 2013;258:943-52.
  40. Di Nardo G, Rossi P, Oliva S, et al. Pneumatic balloon dilation in pediatric achalasia: efficacy and factors predicting outcome at a single tertiary pediatric gastroenterology center. *Gastrointest Endosc* 2012;76:927-32.
  41. Erdeve O, Kologlu M, Saygili B, et al. Primary cricopharyngeal achalasia in a newborn treated by balloon dilatation: a case report and review of the literature. *Int J Pediatr Otorhinolaryngol* 2007;71:165-8.
  42. Tan Y, Zhu H, Li C, et al. Comparison of peroral endoscopic myotomy and endoscopic balloon dilation for primary treatment of pediatric achalasia. *J Pediatr Surg* 2016;51:1613-8.
  43. Borhan-Manesh F, Kaviani MJ, Taghavi AR. The efficacy of balloon dilation in achalasia is the result of stretching of the lower esophageal sphincter, not muscular disruption. *Dis Esophagus* 2016;29:262-6.
- (English Language Editor: C. Mullens)

**Cite this article as:** Chen J, Huang X, Li Y, Wu H, Qin S, Zheng H, Li J, Zhang H, Hu L, Huang S. Efficacy and safety of Chinese medicine combined with balloon dilatation *vs.* balloon dilatation alone for achalasia patients: a systematic review and meta-analysis. *Ann Transl Med* 2022;10(6):275. doi: 10.21037/atm-22-744



**Figure S1** Sensitivity analysis. (A) Sensitivity analysis for improvement at 1 year; (B) sensitivity analysis for improvement at 5 years; (C) sensitivity analysis for perforation; (D) sensitivity analysis for gastroesophageal reflux; (E) sensitivity analysis for esophageal sphincter pressure. CI, confidence interval.



**Figure S2** Funnel plots to detect publication bias. (A) Funnel plot for improvement at 1 year; (B) funnel plot for improvement at 5 years; (C) funnel plot for perforation; (D) funnel plot for gastroesophageal reflux; (E) funnel plot for esophageal sphincter pressure. OR, odds ratio.