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Research article

Assessing the effectiveness of Renzhu Jianwei Granula in managing precancerous lesions of gastric cancer: A meta-analysis of randomized clinical trials

Tu Chen [a,b,1], Lingling Zhou [c,1], Zixuan Wang [a,1], Tianhao Wu [d,e,1], Guiling Wang [c,*], Heng Zhang [d,**]

[a] Clinical Metabolomics Center, China Pharmaceutical University, Nanjing, 211198, China
[b] Department of Cardiology, Pukou Hospital of Chinese Medicine affiliated to China Pharmaceutical University, Nanjing, 210000, China
[c] Department of Traditional Chinese Medicine, Children's Hospital of Nanjing Medical University, Nanjing, 210008, China
[d] Department of Hematology and Oncology, Children's Hospital of Nanjing Medical University, Nanjing, 210008, China
[e] Department of Pediatrics, The First People's Hospital of Lianyungang, Lianyungang, 222002, China

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ABSTRACT

Background: Renzhu Jianwei Granula (RJG) is a traditional Chinese medicine compound initially formulated to address precancerous lesions for gastric cancer. The aim of this study was to assess RJG's efficacy in treating precancerous lesions of gastric cancer through a comprehensive meta-analysis of randomized clinical trials.

Methods: Two authors separately conducted an exhaustive search across three databases (PubMed, CNKI and Wanfang) without imposing any restrictions on publication year or language. Eligible studies, spanning from the inception of databases to July 18th, 2024, were included. Valid data were summarized and those with a group size of 3 or more were preserved. R software and Cochrane collaboration tools were employed for sensitivity analysis and assessing the quality of the included studies. The data from selected studies were transformed into risk ratios (RRs) and subjected to meta-analysis. This study was prospectively registered in PROSPERO.

Results: Data from 9 studies encompassing 912 participants revealed that the RJG group exhibited superior clinical efficacy compared to the control group, with an RR of 0.36 (95 % confidence interval (CI): 0.25 to 0.52). RJG demonstrated enhanced efficacy over the control group in both comprehensive efficacy (RR: 0.42, 95 % CI: 0.31 to 0.55) and gastroscopy efficacy (RR: 0.56, 95 % CI: 0.46 to 0.69). Moreover, significant improvements in pathological features such as atrophy (RR: 0.58, 95 % CI: 0.45 to 0.73), dysplasia (RR: 0.41, 95 % CI: 0.27 to 0.61), and intestinal metaplasia (RR: 0.54, 95 % CI: 0.43 to 0.69) in precancerous lesions of gastric cancer were observed following RJG administration.

Conclusion: This study's synthesized data provide compelling evidence of RJG's substantial therapeutic impact in ameliorating symptoms associated with precancerous lesions of gastric cancer.

Trial registration number: The study protocol was registered at PROSPERO (CRD42024572606)

* Corresponding author. Department of Traditional Chinese Medicine, Hospital of Nanjing Medical University, China.
** Corresponding author. Department of Hematology and Oncology, Children's Hospital of Nanjing Medical University, China.
E-mail addresses: wgl1575@163.com (G. Wang), zhangheng0513@126.com (H. Zhang).
[1] These authors contributed equally to this work.

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1. Introduction

Gastric cancer (GC) is a global and significant disease, ranking fifth both among the most prevalent cancers and in cancer-related fatalities worldwide in the latest published cancer stastics [1]. Although it is possible to recognize and diagnose early, most patients are unfortunately diagnosed at the advanced stage and finally die of the cancer [2]. The process of intestinal-type gastric adenocarcinoma, from the inflammation-atrophy-metaplasia-dysplasia-carcinoma sequence, is called the Correa cascade [2]. Atrophic gastritis, metaplasia, and dysplasia associated with chronic inflammation could promote the development of GC [3]. Chronic atrophic gastritis (CAG) manifests as a condition characterized by the atrophy of the gastric mucosa, often remaining asymptomatic and easily overlooked. It's well-established that CAG has the potential to advance to gastric cancer [4].

As an effective solution for primary health care, traditional Chinese medicine (TCM) is also a good natural drug resource for innovation and discovery [5].Due to its diverse bioactivities and different natural compounds or their synthetic derivatives, TCM included Chinese medicine compound has been highly regarded for its efficacy in chronic diseases and discovering antitumor drug candidates [6,7]. Drawing from the extensive clinical experience of Professor Shan Zhaowei, a distinguished veteran practitioner of Chinese medicine, it is posited that gastric precancerous lesions stem from a combination of positive deficiency, evil excess, and a mix of deficiency and excess. The central pathogenic factor is considered to be "qi-deficiency and blood-stasis," resulting in damage to the spleen and stomach, as well as the internal accumulation of stagnant heat syndrome [8]. Renzhu Jianwei Granula, a traditional Chinese medicine compound containing traditional Chinese medicine (TCM) ingredients as following: *Astragali radix* (AR), *Atractylods macrocephalae rhizoma* (AMR), *Coicis semen* (CS), *Scutellariae radix* (SR), *Agrimoniae herba* (AH), *Curcumae rhizoma* (CR), *Lobelize chinensis herba* (LCH), and *Scleromitrion diffusum herba* (SDH), has the efficacy of nourishing the spleen and stomach by replenishing qi and invigorating serum while clearing heat away from the perspective of Traditional Chinese Medicine [9].

Nevertheless, there remains a scarcity of substantiating evidence regarding the effectiveness of RJG on Chronic Atrophic Gastritis (CAG) in clinical settings. This purpose of this study was to assess the clinical efficacy of RJG through a meta-analysis of randomized clinical trials.

2. Material and methods

This study was prospectively registered in PROSPERO and the PROSPERO ID is CRD42024572606.

2.1. Data sources

Two authors independently conducted searches using a combination of subject headings or free key terms on PubMed, the China National Knowledge Infrastructure (CNKI), and WanFang databases without restrictions on publication year or language. The Chinese search terms used were "仁术健胃颗粒", "仁术健胃颗粒 OR (仁术健胃颗粒 AND ((胃癌) OR (癌前病变)))", while in English, the search terms used were(Renzhu Jianwei Granula) AND ((gastric cancer) OR (Precancerous Lesions of Gastric Cancer) OR (chronic atrophic gastritis)). Eligible studies from the inception of these databases until July 18, 2024, were included.

2.2. Eligible criteria and study selection

The documents considered for inclusion in this study were required to meet specific criteria: (1) their admitted patients met the diagnostic criteria of chronic atrophic gastritis with intestinal metaplasia and (or) dysplasia syndrome of qi deficiency and blood stasis. (2) their research direction was the effect of RJG on human body; (3) involved any outcomes about distinct efficacy of RJG against placebo or any other drugs proven to be effective in clinic; (4) were randomized control trials. Furthermore, academic seminar reports, reviews, academic forum reports, and duplicate data within searched articles were excluded. In the case of duplicate results by the same authors, the dataset with more valid information was selected while excluding the other. To validate the reliability of the data screening and selection process, a kappa (κ) statistic was used for verifying agreement between two authors. Referred to the study of Keramati M [10], the selection of included studies of this study was carried out under the guideline of PRISMA guidelines [11].

2.3. Data extraction and synthesis

Basic information, including author name, study period, country of participants, treatment, and sample size of the experimental and control groups, were extracted from eligible studies. A summary of valid outcome data from all included studies was complied, and valid data with a group size of 3 or more were preserved.

2.4. Quality evaluation of included studies

Given that the study primarily involved randomized clinical trials, the Cochrane bias score evaluation tool was utilized to assess the quality of the literature. The content of the evaluation included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) also with other bias. The evaluation levels were categorized into three tiers: high risk, unclear risk and low risk. Two authors independently completed the evaluation, and any disparities were resolved

through comparison and discussion before consolidation.

2.5. Data analysis

The Risk Ratio (RR) was employed as the combined effect size indicator, accompanied by its corresponding 95 % Confidence Interval (CI). Heterogeneity was assessed using both Q-value statistics and I^2 statistics. The selection between the fixed-effect model and the random-effect model was contingent upon the p-value of the Q′ test and I^2 statistics. Specifically, if the p-value of the Q′ test was greater than 0.05 and I^2 was less than 50 %, the fixed-effect model was employed; otherwise, the random-effect model was utilized. Sensitivity analysis, performed using R software, ensured the robustness and stability of the final results. Additionally, an assessment of publication bias was conducted to ascertain the potential bias affecting the study's efficacy. The grading of recommendations assessment, development and evaluation (GRADE) approach for meta-analysis was applied for evaluating the certainty and strength of the evidence for each outcome in this study.

3. Results

3.1. Study selection and quality evaluation

Upon an initial database search, a total of 90 studies were retrieved. The PRISMA flow diagram mapping out the number of records identified, included, excluded, the reasons for exclusions and the score of kappa analysis (κ) which ranged in 0.98–1.00 is represented in Fig. 1. Before screening, 58 repetitive studies were removed. Among remainers, there were 9 studies focusing on topics unrelated to human body efficacy. Further examination and comparison revealed duplicate and ineffective data across 14 excluded studies, including 1 review and 6 academic reports. Subsequently, 9 eligible studies meeting the criteria with valid data were included in the final analysis. Characteristics of the included studies are summarized in Table 1 [12–20], reflecting a total sample size of 912 participants. The quality assessment of these studies, evaluated using the Cochrane Collaboration tool, is presented in Fig. 2. The report of the GRADE assessment is displayed in.

3.2. Analysis of outcomes

3.2.1. Clinical efficacy

Among the eight included studies that reported clinical efficacy, a fixed-effect model was employed due to the absence of significant heterogeneity ($I^2 = 0$ %, $p = 0.95$). The combined data indicated that RJG demonstrated superior clinical efficacy compared to the control group (RR:0.36, 95%CI:0.24 to 0.52, Fig. 3A).

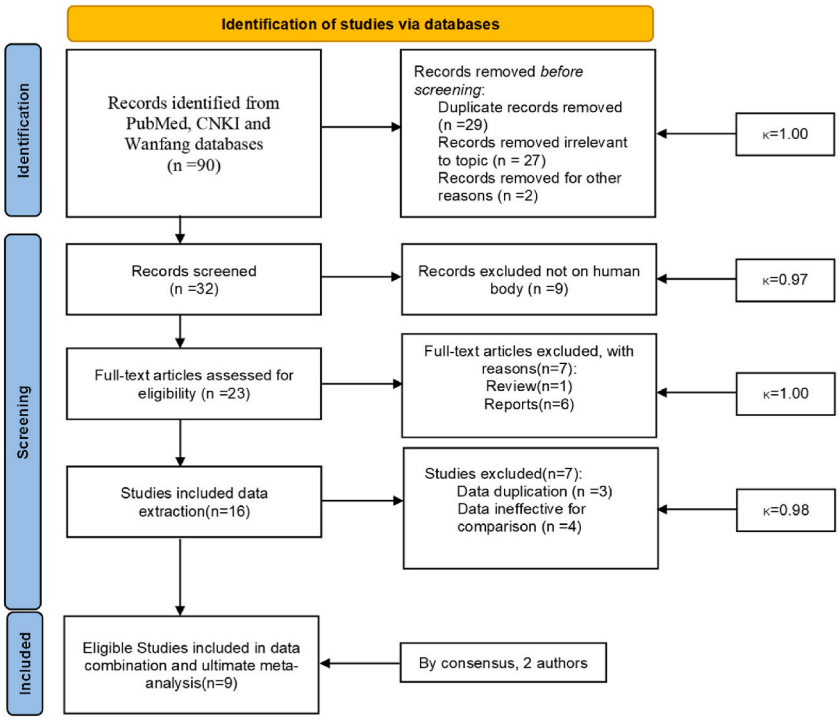

Fig. 1. PRISMA Flow diagram of study identification, screening and inclusion process of the studies. κ: score of kappa analysis.

Table 1
Characteristics of the studies included in the meta-analysis.

Study id	Study period	Country	Treatment		Sample size			Outcome Indicators
			Experimental	Control	Experimental	Control	Total	
Li 1999	1996/06–1999/03	China	Renzhu Jianwei Granula	Weifuchun Capsule	80	40	120	a b c d e f
Lu 2001	1996/06–2000/12	China	Renzhu Jianwei Granula	Weifuchun Capsule	128	62	190	a b c d e f
Lu et al., 2003	–	China	Renzhu Jianwei Granula	Weifuchun Capsule	85	43	128	b c
Luo 2006	–	China	Renzhu Jianwei Granula	Weifuchun Capsule	29	29	58	a b c d f
Sun 2011	–	China	Renzhu Jianwei Granula	Weifuchun Capsule	42	30	72	a b c
Wang 2001	1996/06–2000/12	China	Renzhu Jianwei Granula	Weifuchun Capsule	88	42	130	a b c d e f
Wang 2012	2009/01–2010/12	China	Renzhu Jianwei Granula	Weifuchun Capsule	46	30	76	a c
Wang et al., 2010	2005/12–2006/10	China	Renzhu Jianwei Granula	Weifuchun Capsule	36	36	72	a b c
Zhang et al., 2009	2004/10–2006/02	China	Renzhu Jianwei Granula	Weifuchun Capsule	35	31	66	a

[a] Clinical efficacy.
[b] Comprehensive efficacy.
[c] Gastroscopy efficacy.
[d] Pathological efficacy (Atrophy).
[e] Pathological efficacy (Dysplasia).
[f] Pathological efficacy (Intestinal metaplasia).

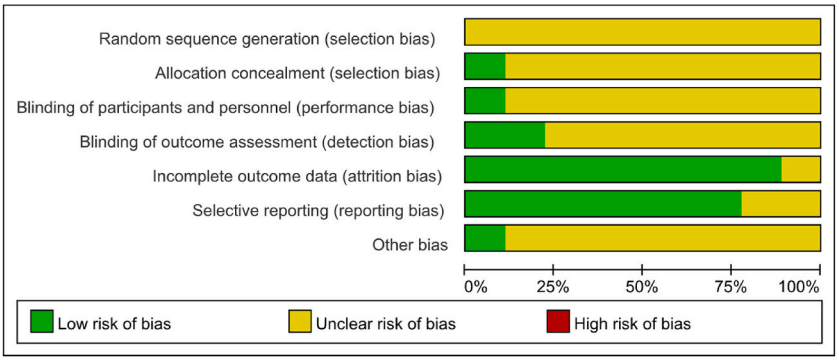

Fig. 2. Risk of bias assessment for included studies using the Cochrane Collaboration's tool.

3.2.2. Comprehensive efficacy

Seven eligible trials comprising 770 total sample size have reported the comprehensive efficacy. As the p-value of Q' test and I^2 regarding the heterogeneity showed that $p = 0.55$ and $I^2 = 0$ %, the fixed effect model was applied to the meta-analysis. Compared with the control group, RJG had better comprehensive improvement effect on CAG (RR:0.42, 95%CI:0.31 to 0.55, Fig. 3B).

3.2.3. Gastroscopy efficacy

Eight eligible trials, with a total sample size of 846, reported gastroscopy efficacy. Given the insignificant heterogeneity ($p = 0.93$, $I^2 = 0$ %), the meta-analysis employed a fixed-effect model. Results indicated that compared to the control group, RJG exhibited superior gastroscopy improvement effects on CAG (RR:0.56, 95%CI:0.46 to 0.69, Fig. 3C).

3.2.4. Pathological efficacy

A total of four studies were included that reported changes in pathological efficacy, encompassing atrophy (four studies), intestinal metaplasia (four studies), and dysplasia (three studies). Heterogeneity analysis for all three aspects showed no significance (atrophy: $I^2 = 0$ %, $p = 0.76$; dysplasia: $I^2 = 0$ %, $p = 0.85$; intestinal metaplasia: $I^2 = 0$ %, $p = 0.95$), warranting the use of a fixed-effect model. Fig. 3D and E illustrate substantial improvements in RJG's effectiveness for managing atrophy symptoms (RR: 0.58, 95 % CI: 0.45 to 0.73) and dysplasia symptoms (RR: 0.41, 95 % CI: 0.27 to 0.61). Regarding intestinal metaplasia symptoms, the RJG group exhibited significant improvement compared to the control group (RR: 0.54, 95 % CI: 0.43 to 0.69) Fig. 3F.

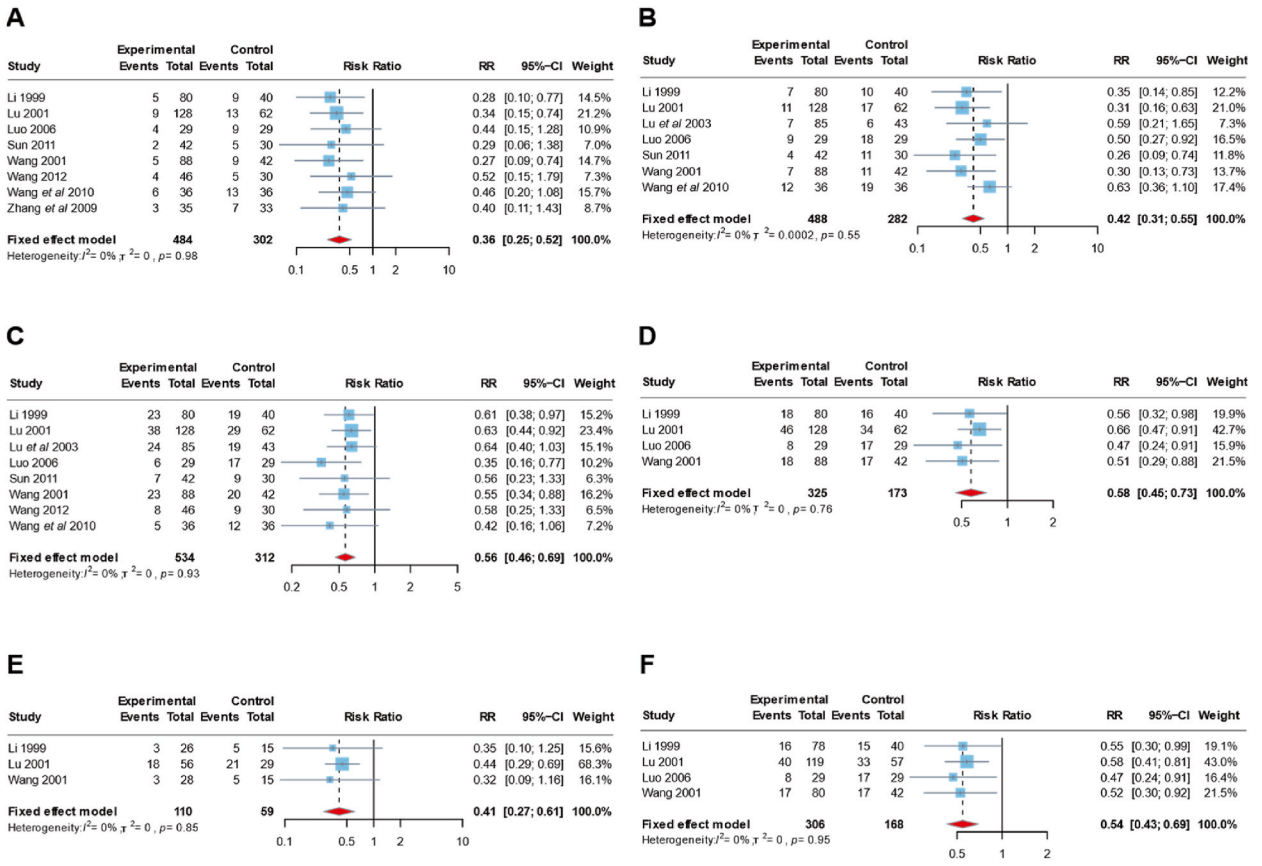

Fig. 3. Forest plots depicting the diverse efficacy of Renzhu Jianwei Granula: (A) Clinical efficacy, (B) Comprehensive efficacy, (C) Gastroscopy efficacy, (D) Pathological efficacy (Atrophy), (E) Pathological efficacy (Dysplasia), and (F) Pathological efficacy (Intestinal metaplasia).

3.2.5. Sensitivity analysis and publication bias

Fig. 4(A–F) presented the sensitivity analysis showed the results evaluated in this study are stable and have no potential bias. The analysis of publication bias in Fig. 5(A–F) also revealed that none of included studies published one-sided results.

4. Discussion

Gastric cancer, a complex disease caused by combined action of the microenvironment and the host, is a malignant cancer [21]. Although the treatment methods for gastric cancer were increasing and various, many patients with advanced gastric cancer still had a low survival rate while most patients were diagnosed at an advanced stage because of inconspicuous symptoms in the early stages [22]. It is promising to inhibit or slow the progression of CAG to GC in case that the CAG, a significant part of gastric cancer precancerous lesions, could be effectively improved. The RJG is a proprietary Chinese medicine developed by Professor Shan Zhaowei based on clinical experience to improve the treatment effect of gastric cancer precancerous lesions. The present meta-analysis, found that RJG was effective in improving comprehensive, clinical, gastroscopic, and pathological (including atrophy, dysplasia and intestinal metaplasia symptoms) outcomes in patients. Furthermore, the results of this assessment have a certain degree of persuasiveness, as no outliers were observed in the sensitivity analysis or publication bias analysis.

Most of the included traditional Chinese medicine (TCM) in RJG have been proved to be the important part in anti-cancer or anti-inflammatory [2,15,21–25]. For example, Astragaloside IV, which is one of the main active components of AR, could inhibit pro-inflammatory agents by NF-κB, alter the expression of following growth factors: vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β, and hepatocyte growth factor (HGF) and more other pathways to participate in the inhibition of various cancers, such as liver, lung, breast and gastric cancers [23]. As a main active ingredient of AMR, Atractylenolide III (AT-III) treatment benefited the remission of gastric precancerous lesions and the attenuation of angiogenesis in rats [24]. Furthermore, the ethanolic extract of AMR exerted an anti-inflammatory through suppressing the AKT/IκBα/NF-κB pathway [25]. Besides, RJG could significantly improve the levels of gastric mucosal carcinoembryonic antigen (CEA) and cyclooxygenase 2 (COX-2) in patients with gastric cancer precancerous lesions [26]. A joint study on the p53 gene polymorphism and the efficacy of RJG in clinical patients showed that the efficacy of those with p53 gene polymorphisms in RJG was significantly better than that of the control group after 6 months of treatment [17]. So, it was plausible to suppose that the human p53 gene polymorphisms were closely related to the efficacy

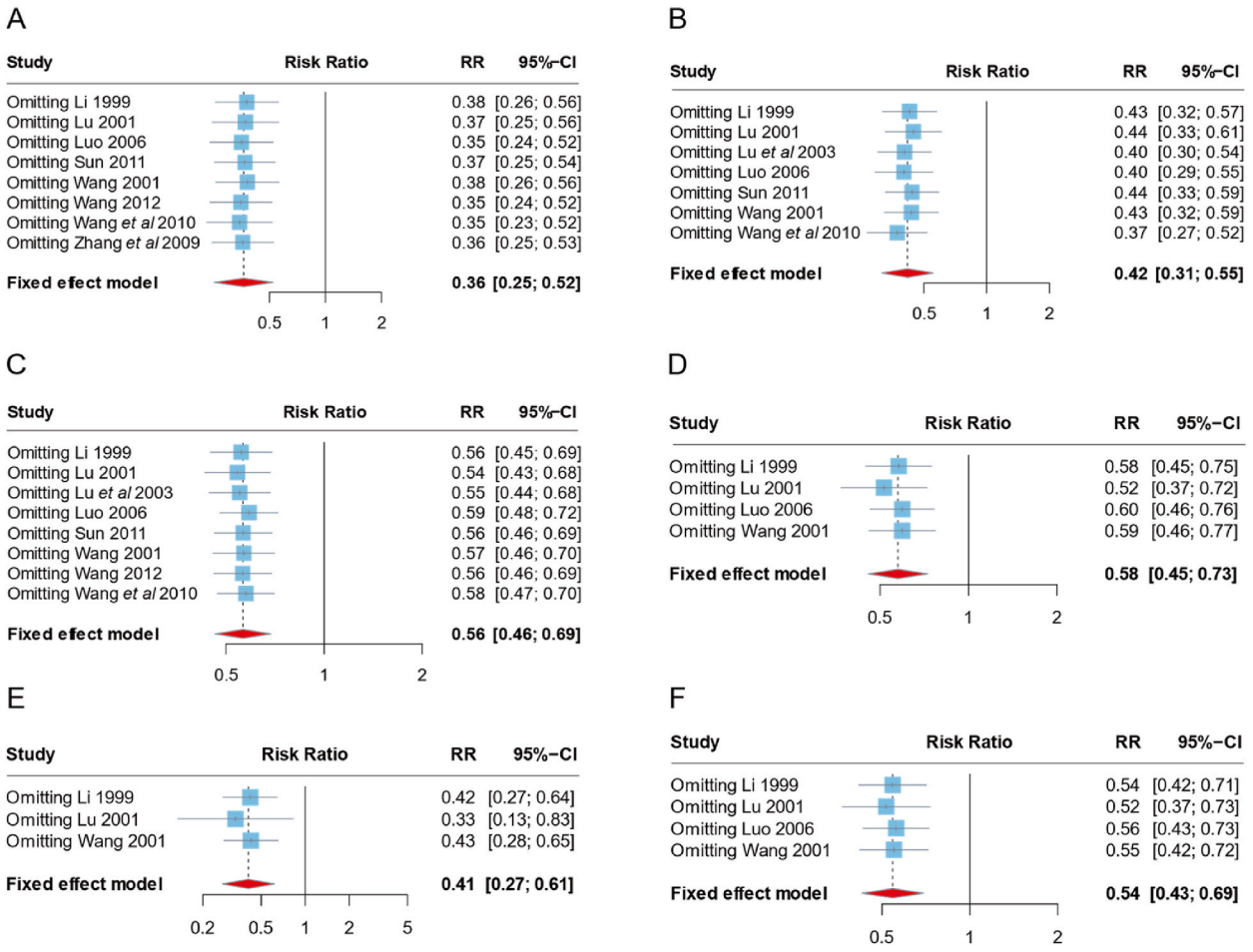

Fig. 4. Sensitivity analysis for included studies (A) Clinical efficacy, (B) Comprehensive efficacy, (C) Gastroscopy efficacy, (D) Pathological efficacy (Atrophy), (E) Pathological efficacy (Dysplasia), (F) Pathological efficacy (Intestinal metaplasia).

of RJG. RJG could adjust the abnormal changes pf gastric mucosal damage factors included ET, NOS, MTL, and gastric mucosal protection factors GAS, SS and SIgA to close to or return to normal levels [27]. The drug-containing serum of RJG was proved to inhibit the proliferation of Human embryo gastric mucosal epithelial cell malignant transformation (MC) cells as well as the expression of CDK4, Bcl-2, p53 protein, and promote the expression P16 and Fas protein to play a role of anti-proliferation and pro-apoptosis, which might be one of the mechanisms of influencing the precancerous lesions of gastric cancer [2]. All of the above mentioned are the possible mechanisms by which RJG exerts its effect on precancerous gastric lesions, but its actual mechanism of action in human body still remains to be investigated.

There were mainly several limitations in this actual meta-analysis as following. Firstly, all of the included studies were published in Chinese. Secondly, there were only a few assessed studies reporting the pathological efficacy of RJG with four on atrophy and intestinal metaplasia while just three on dysplasia. Besides, the involved studies had uncleared methodological reviews. Although there was no obvious high risk of bias in the evaluation of selection bias or detection bias, it may exist potential risks. The validation of the effectiveness of RJG in this study provided comprehensive evidence of efficacy for physicians in clinical use, while providing new options for new drug development, and it is demonstrated by this study that to explore the mechanism of RJG has a long-term significance. However, more clinical trials about RJG are still needed not only reporting in distinct aspects of clinical efficacy but also in different countries.

5. Conclusion

In conclusion, these results based on meta-analysis offer valuable evidence supporting the efficacy of RJG in improving precancerous lesions of gastric cancer. The findings indicate promising prospects for the continued development and utilization of RJG.

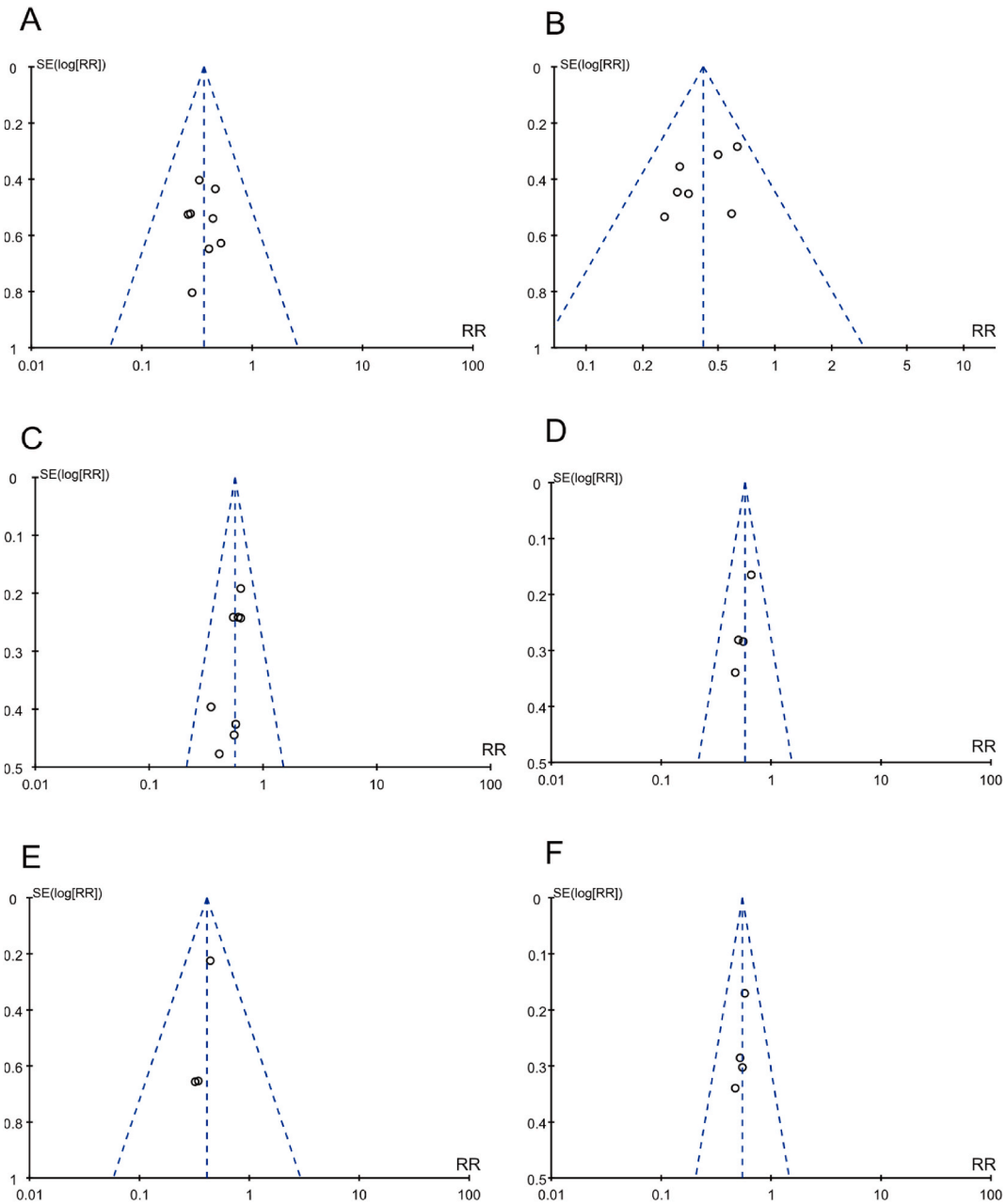

Fig. 5. Bias analyses of including studies (A) Clinical efficacy, (B) Comprehensive efficacy, (C) Gastroscopy efficacy, (D) Pathological efficacy (Atrophy), (E) Pathological efficacy (Dysplasia), (F) Pathological efficacy (Intestinal metaplasia).

CRediT authorship contribution statement

Tu Chen: Writing – review & editing, Writing – original draft, Software, Resources, Methodology. **Lingling Zhou:** Formal analysis, Data curation. **Zixuan Wang:** Writing – original draft, Software, Methodology. **Tianhao Wu:** Resources, Project administration. **Guiling Wang:** Writing – review & editing, Conceptualization. **Heng Zhang:** Writing – original draft, Funding acquisition, Conceptualization.

Data and code availability

Data included in article/supplementary material is referenced in the article.

Register information

This meta-analysis has any register information.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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