BMC Gastroenterology

SYSTEMATIC REVIEW Open Access

Efficacy analysis of folic acid in chronic atrophic gastritis with Helicobacter pylori infection: a systematic review and meta-analysis

Hui Li[1†], Jincheng Li[1†] and Mingyu Lai[1*]

Abstract

Background Current data indicate that supplements such as folic acid play a significant role in treating chronic atrophic gastritis (CAG). However, no meta-analysis article evaluates its efficacy comprehensively. Therefore, we conducted a meta-analysis to compare the effectiveness and safety of folic acid in the treatment of CAG with Helicobacter pylori (H. pylori) infection.

Methods Using a systematic review method, consider randomized controlled trials (RCT), including clinical trial reports, unpublished clinical trial data, and conference papers. A comprehensive search of the literature was conducted from all years up to June 2024. We searched PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Vip, and Wanfang databases. Data were extracted using a pre-designed extraction tool and analysis was undertaken using RevMan5.4 and STAT15.1. Efficacy and safety outcomes were evaluated using risk ratio (RR) and 95% confidence intervals (CI).

Results 16 randomized controlled trials with 1364 patients were included. Compared with conventional therapy, folic acid therapy had a higher total effective rate (95.09% vs.79.06%, pooled RR = 1.19, 95% CI: 1.12–1.26, $p < 0.00001$) and lower incidence of adverse events (11.64% vs. 14.04%, RR = 0.86, 95% CI: 0.46–1.60, $p = 0.64$). Moreover, folic acid can better improve gastric function and repair gastric mucosa (MD = 27.20, 95%CI:23.84–30.56, $p < 0.00001$).

Conclusions For HP-related CAG, anti-HP treatment and folic acid supplementation should be started as early as possible. Gastric mucosal protective agents can improve the curative effect and can be selected according to the condition of patients with obvious adverse reactions. Our study provided evidence for their potential clinical use in the management of CAG. However, CAG-related studies in other countries and regions need to be further studied.

Registration The logn number of our Meta-analysis on PROSPERO is 42,024,571,785.

Keywords Chronic atrophic gastritis, Folic acid, Helicobacter pylori, Effective rate, Adverse events, Meta-analysis

[†]Hui Li and Jincheng Li contributed equally to this work.

*Correspondence:
Mingyu Lai
2194857720@qq.com

[1]Department of Gastroenterology, The First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Guangxi Zhuang Autonomous Region, Nanning 530000, People's Republic of China

Background

Chronic atrophic gastritis (CAG) is a global digestive system disease and one of the important causes of gastric cancer, the incidence of CAG has been increasing yearly worldwide [1]. Chronic atrophic gastritis refers to a chronic digestive system disease with atrophy of gastric mucosal epithelium and glands and thinning of gastric mucosa, accompanied by pyloric and intestinal metaplasia, which can be diagnosed by gastroscopy and gastric mucosal biopsy [2–3]. Its main symptoms include nonspecific dyspepsia, such as epigastric pain, bloating, satiety, and versatility, which can be aggravated or alleviated when eating [4]. The disease will affect the digestive function of patients, thus affecting the work and life of patients, and may develop into gastric cancer in severe cases [5–10]. Therefore, treatment and evaluation of the efficacy of drugs in chronic atrophic gastritis are crucial in the prevention and treatment of stomach cancer.

Helicobacter pylori infection is a vital factor in the carcinogenesis of stomach mucosa in chronic atrophic gastritis [11], which makes it an environmental risk factor for gastric cancer [12]. H. pylori eradication has the potential to alleviate gastric inflammation, facilitate the mending of the mucosa, cure peptic ulcers, and substantially decrease the risk of gastric cancer [13–14]. Therefore, H. pylori-positive chronic gastritis patients should receive H. pylori eradication therapy regardless of symptoms and complications [13].

Folic acid is a water-soluble vitamin composed of pteridine, aminobenzoic acid, and L-glutamic acid. The one-carbon group provided by folic acid is essential for DNA synthesis, which can maintain DNA methylation and protein synthesis, to accelerate the repair of epithelial cells and improve gastric mucosal injury [15–18]. When patients with gastric precancerous conditions were treated with folic acid, the apoptotic rate of gastric mucosal epithelial cells and the expression of tumor suppressor gene P53 were significantly increased, while the expression of certain oncogenic proteins was reduced to prevent further abnormal DNA methylation [19–20]. A meta-analysis reveals that folic acid has a beneficial impact on the treatment of pathological changes in gastric precancerous conditions (GPC) [21]. In conventional therapy for H. pylori eradication, folic acid supplementation may benefit the prevention and treatment of CAG. However, the current guidelines have not clarified the standard treatment of folic acid in Helicobacter pylori infection complicated with CAG.

Studies have confirmed that folic acid has a certain therapeutic effect on chronic atrophic gastritis with Helicobacter pylori Infection, but there is still a lack of systematic reviews. Consequently, we carried out a prospective meta-analysis to analyze folic acid's efficacy and safety in treating chronic atrophic gastritis with Helicobacter pylori Infection. In the present study, we collected clinical studies on the use of folic acid in the treatment of CAG in various cities from all years up to June 2024 analyzed its curative effect, and provided guidance for chronic atrophic gastritis even gastric cancer prevention and treatment.

Methods

This review was pre-registered on the PROSPERO platform (registration number: 42024571785), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [22].

Data sources and literature search strategy

Without language restrictions from the beginning to June 2024, a comprehensive electronic search of the literature was conducted from PubMed, Embase, Web of Science (WOS), Cochrane.

Library, ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI), VIP, and Wanfang.

Databases. We conducted a search using MeSH headings and text word terms for: "chronic atrophic gastritis", "folic acid", "helicobacter pylori", and their types. In addition, other data sources were considered, such as the possible references cited in included studies and relevant review articles.

Study selection

The inclusion criteria for this meta-analysis were by the PICOS principles. We formulated the inclusion and exclusion criteria before searching the database. The inclusion criteria were as follows:

Participants (P): Adults with H. pylori infection who were diagnosed using the following tests: 13 C-/14 C-urea breath test, rapid urease test, histological examination, H. pylori culture, stool antigen test, or anti-H. pylori antibody test(blood).

Intervention (I): the use of folic acid.

Comparator (C): lack of the use of folic acid.

Outcomes (O): (i)Primary outcome: efficacy of the use of folic acid. (ii)Secondary outcome: gastric function, and incidence of adverse events.

Study design (S): Randomized controlled trials.

The exclusion criteria were as follows: The exclusion criteria included non-RCTs, conference abstracts, editorials, letters, comments, trial protocols, reviews, meta-analyses, ongoing trials, studies without sufficient data, and duplicate publications were all excluded.

Two researchers (HL and JCL) independently screened titles and abstracts and reviewed the full text based on the inclusion and exclusion criteria from the databases. Subsequently, the two reviewers evaluate the full-text article based on the established criteria for inclusion. When a disagreement occurred, another investigator

(MYL) participated with others in the discussion of the disputed study until a consensus was reached.

Data extraction

Using a prepared form, the following key items were extracted by two authors (HL and JCL) independently: study ID (first author and publication year), trial number, country, study design, medication of experimental group and control group, duration of treatment, and outcomes assessed. When necessary, missing data was added by emailing the corresponding author.

Quality assessment

Two reviewers (HL and JCL) independently assessed the risk of bias and quality of evidence of each study, and discrepancies were discussed and reconciled. The Cochrane Collaboration tool was used to determine the potential risk of bias in the studies included in this review [23–24]. The domains of evaluation included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain was evaluated as either low risk, high risk, or uncertain risk. Most studies were of low risk.

Statistical analysis

We extracted and analyzed the data of folic acid treatment for the clinical treatment of CAG, including efficiency, adverse events rate, and gastric function changes for meta-analysis. Data were summarized across studies by using mean difference (MD) with 95% confidence intervals (CIs) for the individual Pepsinogen I (PGI) and Pepsinogen I/II Ratio (PGR). Standard mean difference (SMD) was used when microbial effects were measured by inconsistent scales. A risk ratio (RR) with 95% CI was also calculated to estimate effective and adverse effects rates. Intention-to-treat (ITT) analyses were undertaken to evaluate the H. pylori eradication rate. Q tests and I^2 statistics were utilized to evaluate statistical heterogeneity, with a p-value of <0.05 indicating statistical significance. I^2 scores of 0–25% indicate insignificant heterogeneity, while 26–50% signify low heterogeneity, 51–75% show moderate heterogeneity, and values higher than 75% demonstrate high heterogeneity [25]. A random-effect model was applied when $I^2 \geq 50\%$, signifying the presence of study heterogeneity. When the results are similar, the random effect model is preferred, because some researchers believe that the random-effect model is a more natural choice than the fixed effect model in medical decision-making [23–26]. Subgroup analyses and meta-regression were used to investigate any factors that could affect the overall results, as well as any sources of heterogeneity. In order to guarantee the dependability of the results, sensitivity analyses were executed by omitting one study at a time. Results were considered statistically significant with two-sided p values <0.05. All analyses were performed using Revman 5.4 and Stata 15.1.

Results

Literature search and study selection process

After conducting an electronic search, 1634 records were identified, 916 of which were kept after removing duplicates. After assessing the titles and abstracts, a further 891 records were excluded, leaving 25 articles to be retrieved for full-text evaluation. In the end, 16 RCTs [27–42] fulfilled the inclusion criteria. Figure 1 displays a flowchart of the study selection process.

Characteristics of included studies

In total, 1364 patients were involved in 16 RCTs published were included. All studies were conducted in China. Among these studies, the sample size spanned from 50 to 140, the follow-up time spanned from 1 week to 12 weeks. Of the included RCTs, 13 RCTs were patients of mean age <65, and 3 RCTs >65. Besides, a total of 7 RCTs use triple therapy, 7 RCTs use quadruple therapy, and 2 RCTs use other therapy for anti-helicobacter pylori. Out of the 16 included studies, the regime of folic acid, 9 RCTs only use folic acid, 4 RCTs combined with VB12, and 3 RCTs combined with Other gastric mucosal protectants. The main characteristics of the included studies are outlined in Table 1(Table 1: Characteristics of the studies enrolled in the meta-analysis).

Risk of bias

Figure 2 displays the details regarding the risk of bias. 2 authors independently estimated the risk of bias of all contained studies with the Cochrane tool and any differences will be resolved through negotiation. (Figure.2: Risk of bias summary)

Selection bias

In 13 studies because they describe the use of sturdy random methods to generate random sequences (such as the use of a computer random number generator), the selection bias is low. 2 studies did not describe the method of randomization, so the selection bias is unclear. The remaining 1 study had a high risk of selection bias because the random sequence generation method was grouped according to the order in which they came for diagnosis.

Allocation concealment

15 studies mentioned the method of hiding the allocation to the study group, the selection bias is low. The remaining 1 study did not describe the method of randomization, the selection bias was unclear.

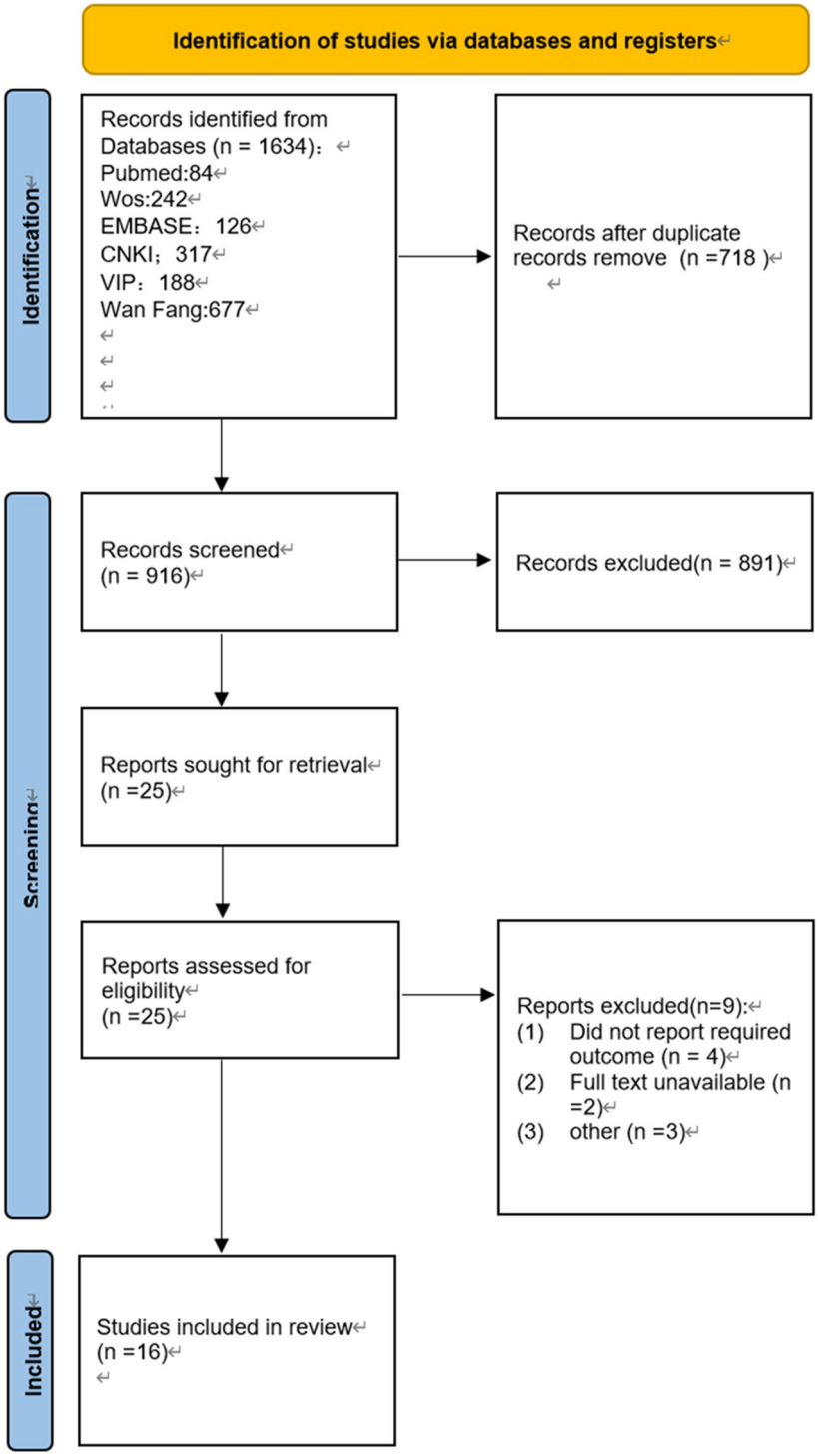

Fig. 1 PRISMA flow diagram for study selection

Detection bias: blinding of outcome assessment

All studies mentioned the method of hiding the allocation to the study group, so all studies had a low risk of bias in this field.

Performance bias: blinding participants and personnel

In 13 studies, the participants and researchers in all studies were double-blind, thus 13 studies had a low risk of bias of performance bias. 2 studies did not describe the method of blinding of methods, and the detection bias

Table 1 Characteristics of the studies enrolled in the meta-analysis. (PBQT: PPI-based bismuth-containing quadruple therapy; PAC: PPI-amoxicillinclarithromycin triple therapy; PAL: PPIamoxicillinlevofloxacin; PALM: PPIamoxicillinlevofloxacin – metronidazole)

Author, year	Study design	Country	Patient number	Mean age(years)	Follow-up(weeks)	Diagnostics/Eradication detection tool	H. pylori eradication regimen	Regimens	Dose of folic acid
Hu X 2024	RCT	China	50	48.12±3.28 48.27±3.46	2	Gastric biopsy, tissue culture, 14 C- UBT and/or the 13 C-UBT	PBQT	PBQT+ Folic acid	10 mg qd
Zhang X X 2023	RCT	China	82	43.26±4.27 44.15±3.96	12	Gastric biopsy, tissue culture, 14 C- UBT and/or the 13 C-UBT	PAC	PAC+ Folic acid	10 mg tid
Zhang J J 2022	RCT	China	102	49.67±5.68 50.3±5.77	2	Gastric biopsy, 14 C- UBT and/or the 13 C-UBT	PBQT	PBQT+ Folic acid+VB12	0.4 mg tid
Wang S Q 2022	RCT	China	120	50.12±4.11 50.23±4.20	2	Gastric biopsy, 13 C-UBT	PBQT	PBQT+ Folic acid+VB12	0.4 mg tid
Liu X X 2022	RCT	China	62	71.93±4.55 74.29±2.93	2	Gastric biopsy, tissue culture, 14 C- UBT and/or the 13 C-UBT	PBQT	PBQT+ Folic acid+VB12	5 mg tid
Jia Y L 2022	RCT	China	92	45.30±4.72 45.22±4.10	12	Gastric biopsy, tissue culture, 14 C- UBT and/or the 13 C-UBT	PAC	PAC+ Folic acid	10 mg tid
Huang X X 2022	RCT	China	64	66.38±2.13 66.41±2.38	12	Gastric biopsy,14 C- UBT	Sequential therapy	Sequential therapy+Folic acid+Teprenone	10 mg tid
Zhang J C 2021	RCT	China	96	48.21±1.35 48.36±1.27	2	Gastric biopsy, tissue culture	PBQT	PBQT+ Folic acid	10 mg tid
Liu X J 2020	RCT	China	140	67.95 ± 4. 35 65.68 ± 5. 90	12	The rapid urease test, culture, the 13 C-UBT and/or the stool H.pylori antigen test.	Sequential therapy	Sequential therapy+Folic acid+Teprenone	10 mg tid
An Q 2020	RCT	China	60	39.68±6.13 39.49±6.22	2	Gastric biopsy, tissue culture, 14 C- UBT and/or the 13 C-UBT	PALM	PALM+Folic acid+Bismuth	10 mg tid
Yang Z L 2020	RCT	China	78	41.67±4.79 39.27±5.17	12	Gastric biopsy, tissue culture, 14 C- UBT and/or the 13 C-UBT	PBQT	PBQT+ Folic acid	10 mg tid
Sun H L 2019	RCT	China	78	42.63±4.82 43.75±7.21	1	Gastric biopsy	PAL	PAL+Folic acid	10 mg tid
Meng Y 2019	RCT	China	80	46.24±0.16 47.12±0.21	1	Gastric biopsy, tissue culture, 14 C- UBT and/or the 13 C-UBT	PAL	PAL+Folic acid	10 mg tid
Yang C J 2019	RCT	China	62	45.19±3.66 45.02±3.75	1	Gastric biopsy, tissueculture, 14 C- UBT and/or the 13 C-UBT	PAL	PAL+Folic acid	10 mg tid
Wang L L 2019	RCT	China	102	48.3±5.3 48.4±5.3	12	Gastroscopy and pathological examination	PAL	PAL+Folic acid+VB12	10 mg tid
Qin Y 2018	RCT	China	96	50.18±3.37 50.30±3.22	12	Gastric biopsy	PAL	PAL+Folic acid	10 mg tid

was unclear. The remaining 1 study was single-blind, and the selection bias was high.

Attrition bias: incomplete outcome data

All studies mentioned the complete outcome data, so all studies had a low risk of bias in this field.

Reporting bias: selective reporting

All studies reported all the research results mentioned in the article, so they all have a low risk of bias.

Other bias

Since no other latent sources of bias were found, the 16 studies all had a low risk of bias in this field.

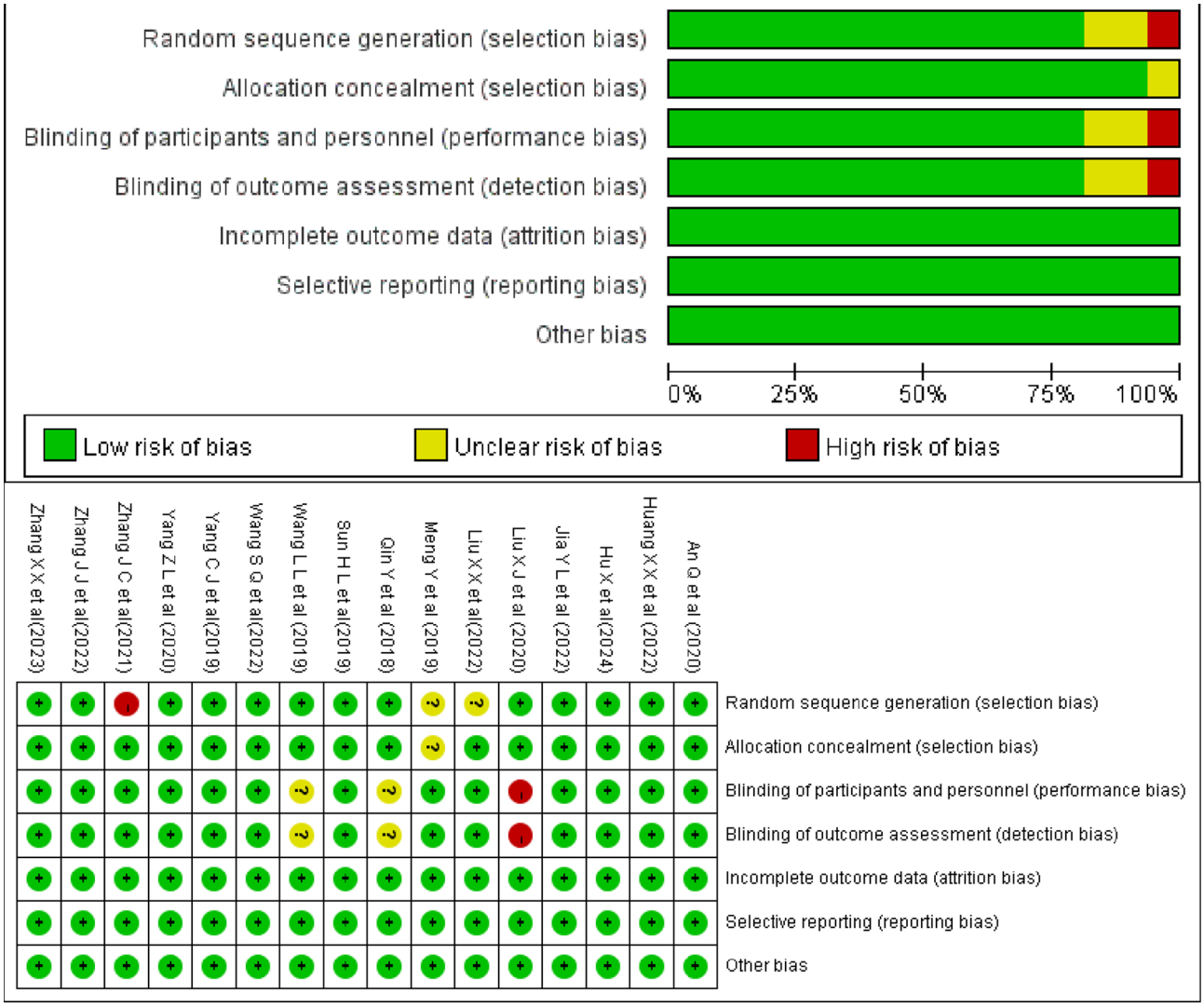

Fig. 2 Risk of bias summary

Primary outcome: efficacy of the use of folic acid

Total effective rate

13 studies reported the total effective rate, which reached the clinical efficacy evaluation criteria [9, 10, 43, 44]. Low-moderate heterogeneity was observed ($I^2 = 36\%$, $p = 0.10$) and the random effects model was used. Figure 3 showed that a significant difference was observed in the total effective rate between the folic acid therapy group and the lack folic acid group (95.09% vs.79.06%, pooled RR = 1.19, 95% CI: 1.12–1.26, $p < 0.00001$). The treatment of folic acid therapy had a higher total effective rate, which is better than conventional therapies. (Figure.3: Forest plot of the effect of folic acid therapy versus conventional therapy on the total effective rate of CAG)

Heterogeneity analyses

For the primary outcome (Total effective rate), We further discuss the sources of heterogeneity. Sensitivity analyses were executed by omitting one study at a time to evaluate whether the exclusion of any single study drastically altered the results of the remaining studies. All the sensitivity analyses conducted with ITT data yielded similar results to ensure the results of our meta-analysis were robust (Fig. 4). Then, by utilizing data from ITT analysis, we conducted subgroup analyses to examine any factors that could affect the overall results and any sources of heterogeneity. In a subgroup analysis based on age, significant difference in total effective rate was observed between the folic acid therapy group and the conventional therapy group when age < 65 years old ($n = 11$ RCTs, 95.0% vs. 79.7%, pooled RR = 1.18, 95% CI: 1.11–1.26, $p < 0.0001$) or > 65 years old ($n = 2$ RCTs, 95.2% vs. 74.6%, pooled RR = 1.28, 95% CI: 1.10–1.49, $p = 0.002$) was administered. However, there was no significant heterogeneity between the two subgroups ($I^2 = 0$, $P = 0.36$). When the subgroup analyses were stratified according to the regime of Anti-H. In Pylori, the regime of folic acid, and the duration

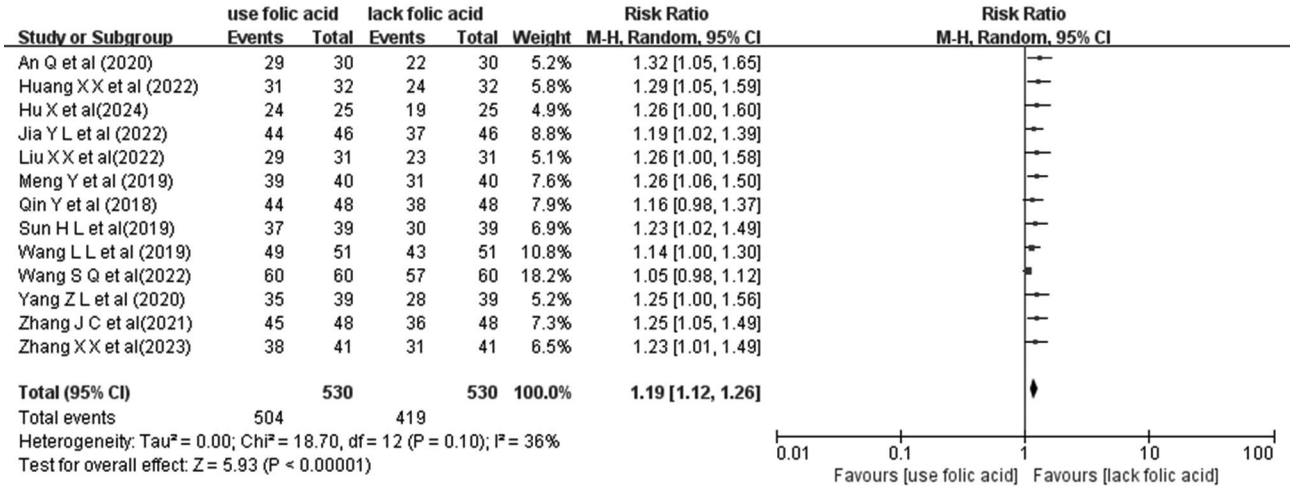

Fig. 3 Forest plot of the effect of folic acid therapy versus conventional therapy on the total effective rate of CAG

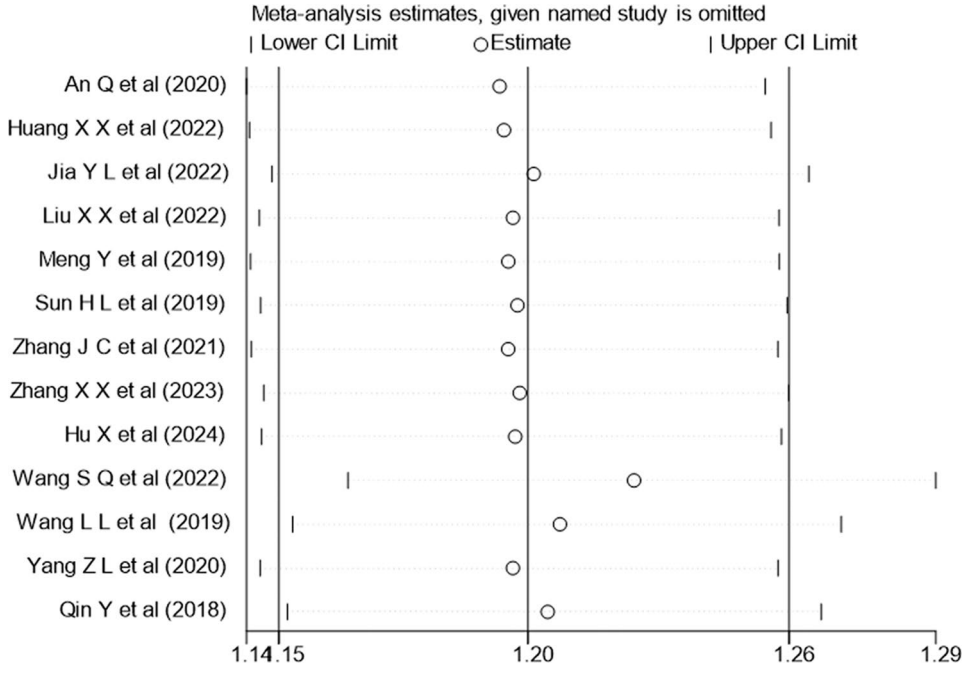

Fig. 4 The result of the sensitivity analyses in total effective rate

of treatment, similar results were seen. Figure 5 presents the results of subgroup analyses. (Figure.5 The subgroups result of folic acid therapy versus conventional therapy on total effective rate). Then, we conducted meta-regression. The results indicated that heterogeneity was not associated with the above 4 factors ($P > 0.05$). Figure 6 presents the results of Meta-regression. (Fig. 6 The results of Meta-regression). Therefore, for the emergence of heterogeneity, we considered sources from the literature itself. Combined with the sensitivity analysis results, we excluded one study (Wang S Q et al.). The results suggested a decrease in heterogeneity ($I^2 = 0$). (Fig. 7 Forest plot of the effect of folic acid therapy versus conventional therapy on the total effective rate of CAG after excluding one study).

Gastric function: PGI、PGR

The change in PGI、PGR

5 studies reported the change in PGI. High heterogeneity was observed ($I^2 = 94\%$, $p < 0.00001$) and the random effects model was used. Figure 8 showed that a significant difference was observed in the change of PGI between the folic acid therapy group and the lack folic acid group (MD = 27.20, 95%CI:23.84–30.56, $p < 0.00001$). (Figure.8 Forest plot of the effect of folic acid therapy versus conventional therapy on PGI of CAG). Moreover, 2 studies reported the

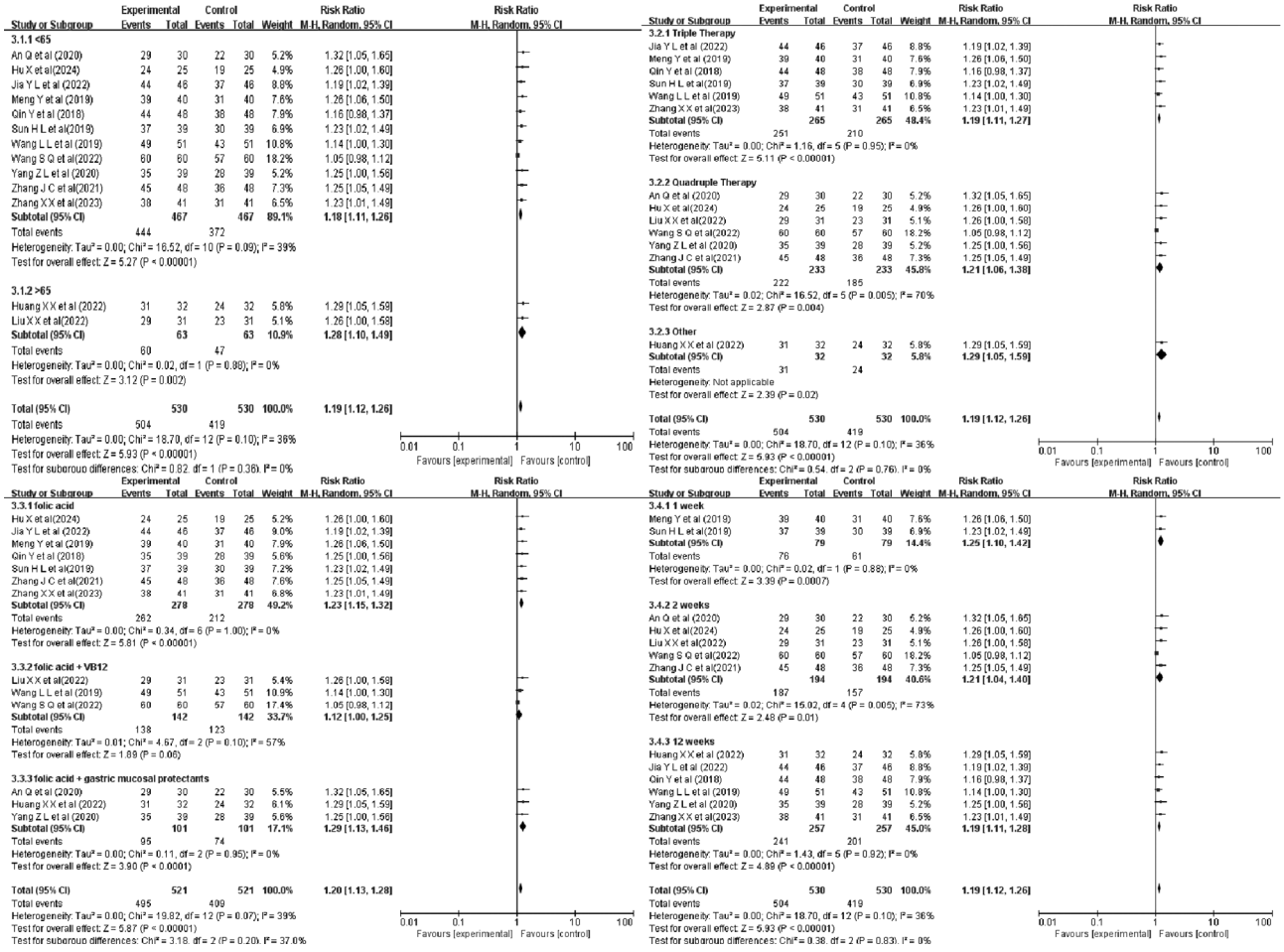

Fig. 5 The subgroups result of folic acid therapy versus conventional therapy on total effective rate

```
Meta-regression                                  Number of obs  =        13
REML estimate of between-study variance          tau2           =  .005222
% residual variation due to heterogeneity        I-squared_res  =    40.75%
Proportion of between-study variance explained   Adj R-squared  =   -27.65%
Joint test for all covariates                    Model F(4,8)   =      0.25
With Knapp-Hartung modification                  Prob > F       =    0.9041
```

_ES	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
age	.1047014	.1224846	0.85	0.418	-.1777487	.3871515
theregimeoffolicacid	-.0039827	.0594307	-0.07	0.948	-.1410302	.1330648
theregimeofantihpylori	-.0078472	.0799338	-0.10	0.924	-.1921748	.1764805
followuptime	-.0183937	.0475422	-0.39	0.709	-.1280263	.0912389
_cons	1.14417	.1511487	7.57	0.000	.79562	1.492719

Fig. 6 The results of Meta-regression

change in PGR, which was defined by the PGI/PGII. Moderate heterogeneity was observed ($I^2 = 64\%$, $p = 0.10$), and the random effects model was used. Figure 9 showed that a significant difference was observed between the folic acid therapy group and the lack folic acid therapy group (pooled MD = 2.22, 95% CI: 1.54–2.91, $p < 0.00001$). (Figure.9: Forest plot of the effect of folic acid therapy versus conventional therapy on PGR of CAG). A comprehensive analysis can be drawn from the presence of folic acid for the treatment of

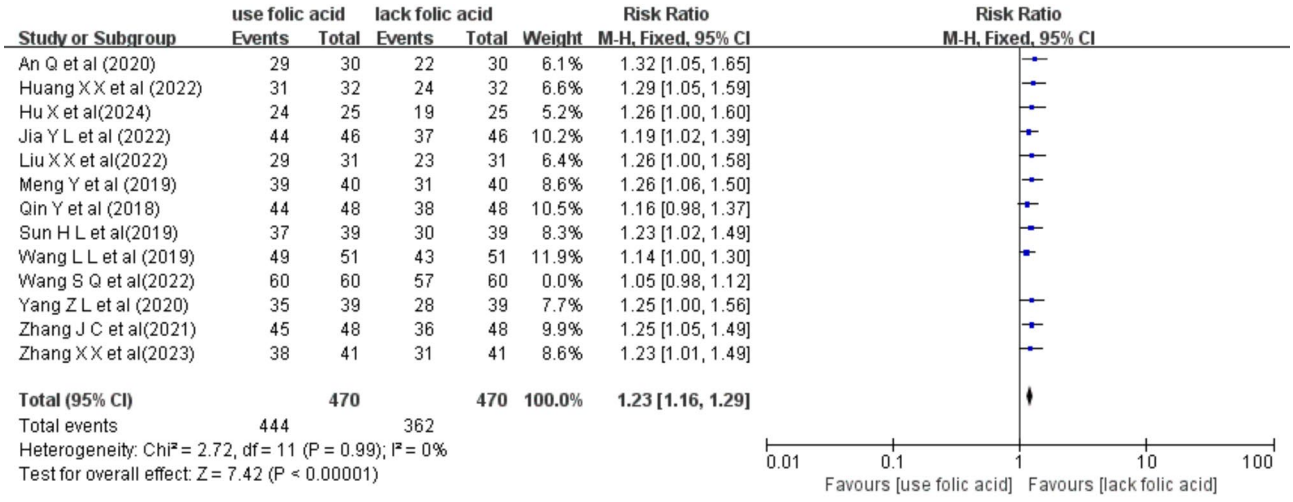

Fig. 7 Forest plot of the effect of folic acid therapy versus conventional therapy on the total effective rate of CAG after excluding one study

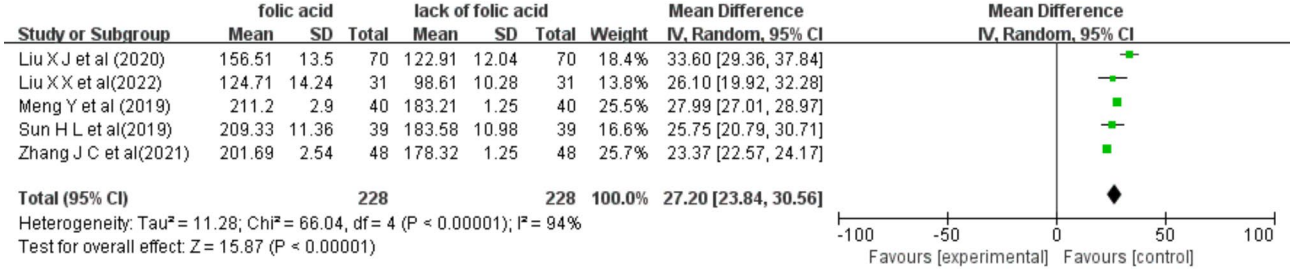

Fig. 8 Forest plot of the effect of folic acid therapy versus conventional therapy on PGI of CAG

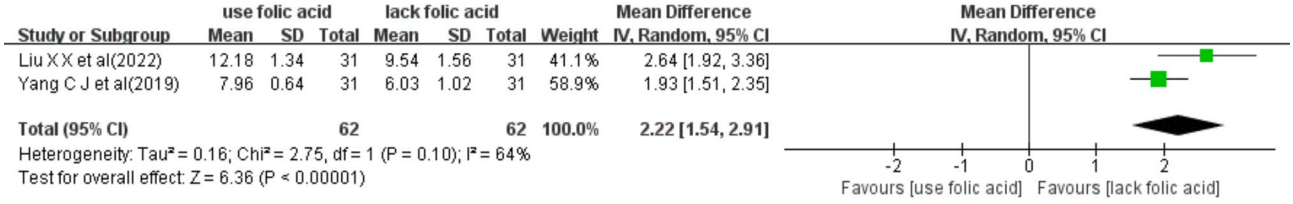

Fig. 9 Forest plot of the effect of folic acid therapy versus conventional therapy on PGR of CAG

CAG can effectively improve serum pepsin and promote the recovery of gastric function.

Heterogeneity analyses

We further discuss the sources of heterogeneity. Sensitivity analyses were executed by omitting one study at a time to evaluate whether the exclusion of any single study drastically altered the results of the remaining studies. We excluded 2 studies (Liu X J et al、Zhang J C et al.). Figure 10 showed the result after excluding studies ($I^2 = 0$). (Fig. 10 Forest plot of the effect of folic acid therapy versus conventional therapy on the change in PGI of CAG after excluding studies).

Adverse events

Incidence of adverse reactions

8 RCTs involving 584 patients were conducted to evaluate the incidence of total adverse events. Low-moderate heterogeneity was observed ($I^2 = 39\%$, $p = 0.12$), and the random effects model was used. Our results showed that the folic acid therapy group had a lower-moderate incidence of total adverse events than the lack folic acid therapy group, and the results are not statistically significant (11.64% vs. 14.04%, RR = 0.86, 95% CI: 0.46–1.60, $p = 0.64$). The results showed that the incidence of adverse reactions was low in both treatments, and folic acid supplementation was safe. (Figure.11 Forest plot of the effect of folic acid therapy versus conventional therapy on the incidence of total adverse events of CAG). Concerning specific adverse events, our statistical analysis showed

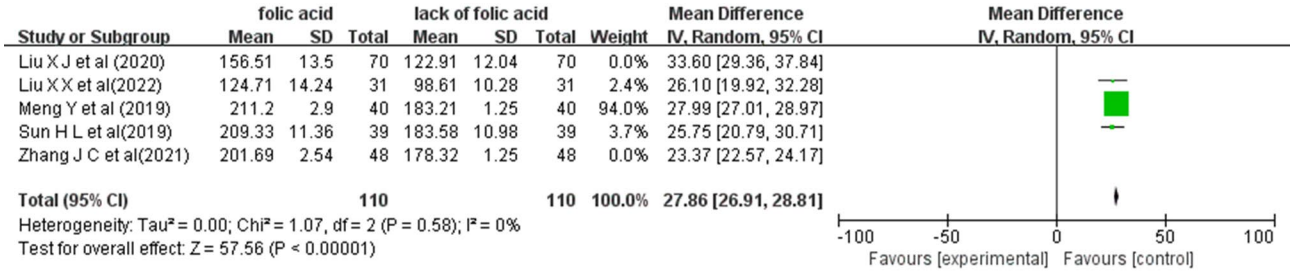

Fig. 10 Forest plot of the effect of folic acid therapy versus conventional therapy on the change in PGI of CAG after excluding studies

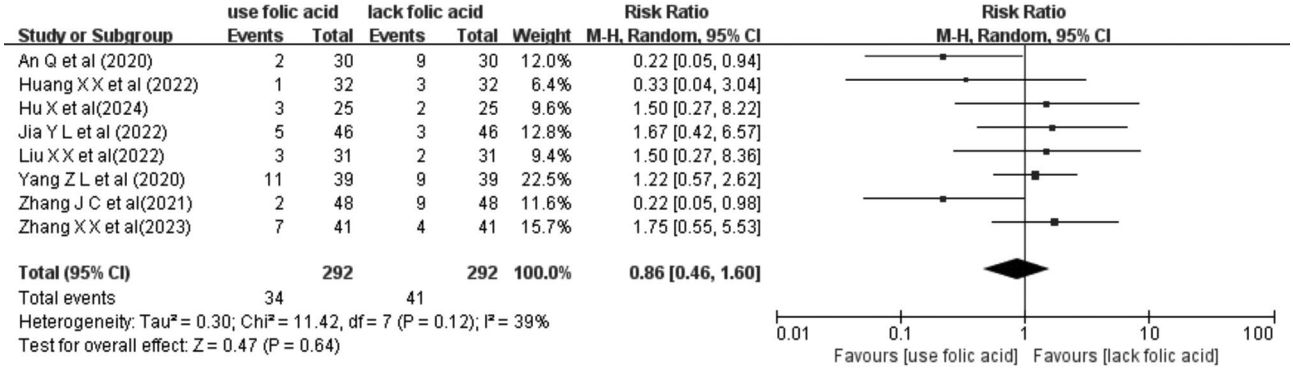

Fig. 11 Forest plot of the effect of folic acid therapy versus conventional therapy on the incidence of total adverse events of CAG

Table 2 Specific details of adverse events

Adverse events	experimental group	control group
diarrhea	6	6
rash	4	6
nausea	5	5
constipation	6	5
melena	-	2
flushed face	-	1
vomit	3	2
abdominal distension	1	-
headache	1	1
pruritus	1	-
swirl	4	2
sitophobia	1	-
insomnia	-	1
drug fever	-	1
anemia	1	4
gastrorrhagia	1	3
gastric ulcer	-	2
total	34	41

that rash, diarrhea, constipation, and nausea occurred frequently with both treatments. Notably, anemia was more common with conventional therapy and dizziness was more common with folic acid therapy. The details can be seen in Table 2.

Heterogeneity analyses

Sensitivity analyses were executed by omitting one study at a time to evaluate whether the exclusion of any single study drastically altered the results of the remaining studies. We excluded one study (An Q et al、Zhang J C et al.). The results suggested a decrease in heterogeneity ($I^2 = 0$). (Fig. 12 Forest plot of the effect of folic acid therapy versus conventional therapy on the incidence of adverse reactions of CAG after excluding studies).

Publication bias test

For the primary outcome (Total effective rate), we utilized Egger's test for quantitative detection of publication bias. Egger's test suggested substantial publication bias. (p Egger = 0.000). (Fig. 13 shows the results of Egger's test). Further investigation using the trim-and-fill test indicated that the publication bias did not affect the estimations. (Fig. 14 show the results of trim-and-fill test)

Discussion

To our knowledge, this is the first meta-analysis to investigate the effects of folic acid in chronic atrophic gastritis with Helicobacter pylori Infection in comparison to the anti-HP therapy without folic acid. In this meta-analysis of 16 RCTs involving 1364 patients, we found that folic acid therapy had a higher total effective rate and lower incidence of adverse events compared to conventional therapy. Besides, compared with conventional therapy,

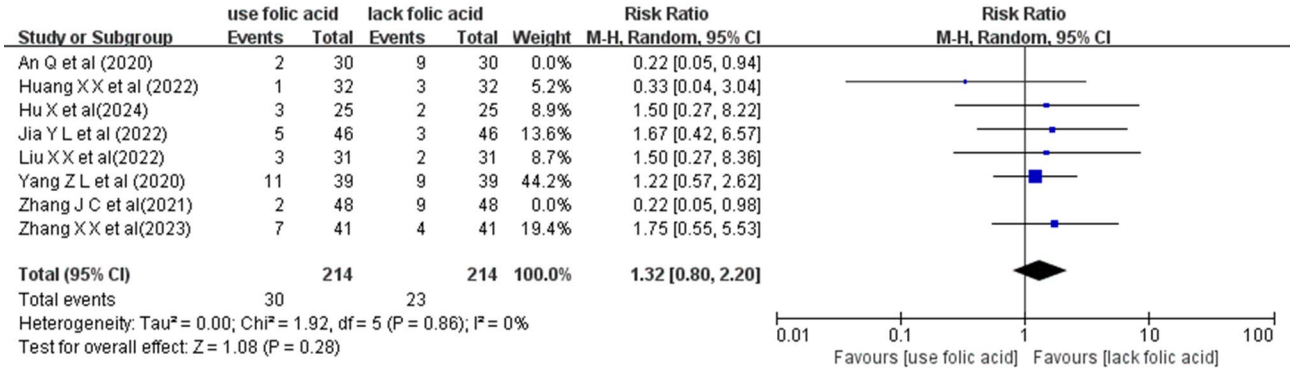

Fig. 12 Forest plot of the effect of folic acid therapy versus conventional therapy on the incidence of adverse reactions of CAG after excluding studies

```
Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  13                                  Root MSE      =   .3155

------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |   .9568224   .016112    59.39   0.000       .92136    .9922847
        bias |   2.853223   .211733    13.48   0.000     2.387202    3.319244
------------------------------------------------------------------------------

Test of H0: no small-study effects          P = 0.000
```

Fig. 13 The results of Egger's test in total effective rate

```
       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   1.155   1.113   1.196   54.703    0.000      13
Random |   1.196   1.137   1.254   39.876    0.000

Test for heterogeneity: Q= 19.173 on 12 degrees of freedom (p= 0.084)
Moment-based estimate of between studies variance =  0.004

Trimming estimator: Linear
Meta-analysis type: Random-effects model

iteration |  estimate    Tn    # to trim     diff
----------+-----------------------------------------
    1     |    1.196     67         3          91
    2     |    1.175     74         5          14
    3     |    1.159     77         5           6
    4     |    1.159     77         5           0

Filled
Meta-analysis (exponential form)

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   3.115   2.999   3.235   58.804    0.000      18
Random |   3.187   3.033   3.349   45.819    0.000

Test for heterogeneity: Q= 24.078 on 17 degrees of freedom (p= 0.117)
Moment-based estimate of between studies variance =  0.003
```

Fig. 14 The results of the trim-and-fill test in total effective rate

adding folic acid can better promote the recovery of gastric mucosa and gastric function.

CAG is a chronic inflammation mainly caused by inherent fiber atrophy. However, the pathogenesis of this disease is still not well understood. Helicobacter pylori infection, lifestyle, and duodenal reflux are the main causes of this disease, but they are also closely related to genetic and environmental factors. Our meta-analysis indicated that compared with conventional triple or quadruple therapy, supplemented folic acid can increase the total effective rate, and enhance the repair of the gastric mucosa. The current research results show that the etiology of CAG is unclear, and the treatment outcome is also affected by many factors. Our subgroup result showed that the age, follow-up time, and different anti-Helicobacter pylori regimens exerted no influence on the results. Notably, there was low-moderate heterogeneity among different folic acid regimens. Through sensitivity analysis, we found the sources of heterogeneity (Wang S Q et al.). We found that the folic acid group in the study had a particularly high response rate (100%). Further analysis revealed that the therapy they chose was a combination of quadruple therapy and folic acid + VB12. Compared with other studies with the same conditions, the majority of patients had mild disease. We speculate that this is the reason for its better therapeutic effect. Therefore, folic acid combined with VB12 may have a better effect on the treatment of mild patients with H. pylori infection on the basis of effective anti-H. Pylori infection.

H. pylori eradication has the potential to alleviate gastric inflammation, facilitate the mending of the mucosa, cure peptic ulcers, and substantially decrease the risk of gastric cancer. Hence, several international guidelines and consensuses [14, 45, 46] recommend bismuth-containing quadruple therapy (BQT) as a first-line therapy in regions with high clarithromycin resistance. With the emergence of the new acid inhibitor, a potassium-competitive acid blocker (P-CAB), is widely used for acid-related diseases as it has a quicker onset and greater and more enduring acid inhibition than proton pump inhibitors (PPI) [47–48]. More and more studies have shown that based on vonoprazan therapy is superior to PPI. However, more large randomized controlled trials in different countries and regions are still needed to explore its treatment further. Our research group also focuses on the efficacy of vonoprazan on CAG. Studies have shown that vonoprazan can improve the gastrointestinal mucosal function of patients with CAG, enhance the level of gastric motility, and help cure HP infection [49–50]. It has an anti-inflammatory effect and has good clinical efficacy and safety. However, more large-sample, multi-center RCTS are needed. Notably, there is a lack of studies on the efficacy of vonoprazan combined with folic acid for CAG.

PG I, PG II, and gastrin are reliable indicators for evaluating gastrointestinal function. When gastric body atrophy occurs, PG I decreases and PG II increases. The ratio of PG I and PGII, namely PGR, can effectively reflect the degree of gastric atrophy. Gastrin is an important gastrointestinal hormone, that can stimulate the proliferation and differentiation of gastric mucosal cells, and the decrease of gastrin level suggests that gastric body atrophy may occur [51]. In our meta-analysis, we analyzed PG I and PGR. The results show that, compared with conventional therapy, folic acid can better improve gastric function and repair gastric mucosa. However, the heterogeneity of results was high. By item-by-item exclusion, we found two articles (Liu X J et al、Zhang J C et al.) with sources of heterogeneity. In Liu X J et al's research, in addition to folic acid, a gastric mucosal protective agent was added. It undoubtedly promotes the repair of the gastric mucosa. In Zhang J C et al's research, we found that the majority of patients had mild disease. However, due to the small sample size and some bias in the articles, it can also have an impact on the heterogeneity of the results.

Adverse events are a frequent occurrence during the process of treatment, and their presence can greatly reduce patient compliance. This lack of compliance can have a major impact on the success of the eradication. According to our meta-analysis, the incidence of adverse reactions was lower in the folic acid group than in the conventional group, although the difference was not statistically significant. There was low-moderate heterogeneity in our results. The sources of heterogeneity were further analyzed. In An Q's research, we note that in addition to folic acid in the experimental group, their study also used compound aluminum-bismuth. Compound bismuth aluminate belongs to gastric mucosal protective agent, which can promote the regeneration and repair of gastric mucous membranes, improve patients' symptoms, and reduce adverse reactions. Similarly, the incidence of adverse effects was lower in other studies using bismuth.

Folic acid is a water-soluble vitamin. HP eradication can increase folic acid absorption, reduce methylenetetrahydrofolate reductase genotypic variation, provide a guarantee for normal methylation, inhibit the production of the 5-methyltetrahydrofolate acid pathway, promote DNA synthesis and repair, reduce damage, inhibit the process of proliferation, improve symptoms of atrophy and hyperplasia, control the development of disease, and obtain an ideal therapeutic effect. A meta-analysis indicates that folic acid has a beneficial effect in the treatment of pathological changes of GPC when the dose is maintained at 20–30 mg/d and the duration of treatment is maintained at 3–6 months [21]. For CAG, such a long treatment duration may not be necessary. In our meta-analysis, out of the 16 studies we included, 13 RCTs supplemented folic acid 30 mg/d, and the duration of treatment was maintained from 1 week to 12 weeks; 4 RCTs combined with Vitamin B12 and supplemented folic acid with a low dose and the duration of treatment was 2

weeks to 12 weeks. It is worth noting that the results of our subgroup showed that the regimen of folic acid and treatment duration exerted no influence on the results. Although short-term follow-up results suggest a significant treatment effect, there is still a lack of long-term follow-up studies to determine the duration of follow-up.

As mentioned previously, this is the first meta-analysis to analyze the efficacy of folic acid in chronic atrophic gastritis with Helicobacter pylori Infection comprehensively. This study boasts several noteworthy strengths that contributed to its overall robustness. First, we conducted an extensive and exhaustive search across multiple databases, including registered clinical trials, ensuring the inclusion of the most current and relevant research. Moreover, our review is strengthened by its rigorous methodology, which adheres to the PRISMA standards. Furthermore, this study diligently considered key treatment variables, such as the age and the regime of folic acid administered, which are essential as variables that can significantly impact treatment efficacy and safety. We performed subgroup analyses of the primary outcome measures to account for this effect and filled the gap of previous research.

Nevertheless, there were several limitations that need to be taken into account. Firstly, For some indicators with a small number of included articles (< 3), such as inflammation indicators, we did not further analyze them due to too much heterogeneity. Secondly, due to the restricted data included in the study, we did not delve further into antibiotic resistance and its impact on eradicating H. pylori. Thirdly, due to the lack of clear diagnostic criteria, we did not include literature that used traditional Chinese medicine treatment. Finally, since the trials were mainly conducted in China and the sample size was limited, further research is required to determine whether this conclusion can be applied to other countries.

Conclusion

In conclusion, HP-related CAG, as early as possible anti-HP treatment and folic acid supplementation should be taken. Gastric mucosal protective agents can improve the curative effect and can be selected according to the condition of patients with obvious adverse reactions. For patients with obvious adverse reactions, gastric mucosal protective agents can be selected according to their condition. If bismuth is not included in the anti-HP regimen, bismuth is recommended. Our results may provide potential evidence for the clinical application of folate in CAG treatment. Future studies should focus on the efficacy of folic acid therapy for CAG in different regions and optimize the regimens of folic acid therapy continuously.

Abbreviations

CAG	Chronic atrophic gastritis
H. pylori	Helicobacter pylori
RCT	Randomized controlled trials
RR	Risk ratio
CI	Confidence intervals
MD	Mean difference
SMD	Standard mean difference
ITT	Intention-to-treat
PGI	Pepsinogen I
PGR	Pepsinogen I/II Ratio
BQT	Bismuth-containing quadruple therapy
P-CAB	Potassium-competitive acid blocker

Acknowledgements

Not applicable.

Author contributions

Conceptualization: HL; JCL; Methodology: HL; Data curation and Software: JCL; Investigation: HL; JCL; MYL; New software &visualization: HL; Writing—original draft: JCL; Writing—review & editing: HL; MYL; Resources & project administration: JCL; MYL. All authors read and approved the final manuscript.

Funding

None.

Data availability

The data support the findings of this study and are available within the article. The other data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 14 October 2024 / Accepted: 23 January 2025
Published online: 07 February 2025

References

1. Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, Harvey JD, Henrikson HJ, Lu D, Pennini A, Xu R, et al. Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the global burden of disease study 2019. JAMA Oncol. 2022;8:420–44.
2. Li J, Pan J, Xiao D, et al. Chronic atrophic gastritis and risk of incident upper gastrointestinal cancers: a systematic review and meta-analysis. J Transl Med. 2024;22(1):429.
3. Jia J, Zhao H, Li F, et al. Research on drug treatment and the novel signaling pathway of chronic atrophic gastritis. Biomed Pharmacother. 2024;176:116912.
4. Cheng X, Niu MQ, Wang N, et al. Comparative observation of rabeprazole quadruple therapy combined with vitamin B12 folic acid in the treatment of Helicobacter pylori-associated chronic atrophic gastritis. J Clin Psychosom Dis. 2022;28(02):121–3.
5. Stadtlander CT, Waterbor JW. Molecular epidemiology, pathogenesis and prevention of gastric cancer. Carcinogenesis. 1999;20:2195–208.
6. Kapadia CR. Gastric atrophy, metaplasia, and dysplasia: a clinical perspective. J Clin Gastroenterol. 2003;36:S29–36.
7. Laurèn P. The two histological main types of gastric carcinoma: are diffuse and so-called intestinal-type carcinoma. Acta Pathol MicrobiolScand. 1965;64:31–49.
8. Fukao A, Hisamichi S, Ohsato N, et al. Correlation between the prevalence of gastritis and gastric cancer in Japan. Cancer Causes Control. 1993;4:1720.
9. Genta RM. Gastric atrophy and atrophic gastritis – nebulous concepts in search of a definition. Aliment Pharmacol Ther. 1998;12:17–23.

10. Dai YY, Ye ZD, Huang HH. Effect of Helicobacter pylori eradication therapy combined with folic acid on chronic hepatitis B long-term effects in patients with atrophic gastritis. World Chin J Digestion. 2017;25(19):1777–82.
11. Cheng XJ, Lin JC, Tu SP. Etiology and Prevention of Gastric Cancer. Gastrointest Tumors. 2016;3(1):25–36.
12. Usui Y, Matsuo K, Momozawa Y. Helicobacter pylori, homologous-recombination genes, and gastric cancer. Reply N Engl J Med. 2023;389:379–81.
13. Malfertheiner P, Megraud F, Rokkas T, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut. 2022. https://doi.org/10.1136/gutjnl-2022-327745. Epub ahead of print.
14. Zhou L, Lu H, Song Z, et al. 2022 Chinese national clinical practice guideline on Helicobacter pylori eradication treatment. Chin Med J (Engl). 2022;135:2899–910.
15. Liu JD. Effect of Helicobacter pylori eradication on digestive tract symptoms in patients with chronic atrophic gastritis. Chin Med Clin. 2021;21(4):663–5.
16. Eto I, Krumdieck CL. Role of vitamin B12 and folate deficiencies in carcinogenesis. Adv Exp Med Biol. 1986;206:313–30.
17. Choi SW, Mason JB. Folate and carcinogenesis: an integrated scheme. J Nutr. 2000;130:129–32.
18. Cao DZ, Sun WH, Ou XL, et al. Effects of folic acid on epithelial apoptosis and expression of Bcl-2 and p53 in premalignant gastric lesions. World J Gastroenterol WJG. 2005;11(11):1571.
19. Fang JY, Xiao SD. Effect of trans-retinoic acid and folic acid on apoptosis in human gastric cancer cell lines MKN-45 and MKN-28. J Gastroenterol. 1998;33(5):656–61.
20. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing the risk of bias in randomized trials. BMJ. 2011;343:d5928.
21. Lei J, Ren F, Li W, et al. Use of folic acid supplementation to halt and even reverse the progression of gastric precancerous conditions: a meta-analysis. BMC Gastroenterol. 2022;22(1):370.
22. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
23. Berezanskaya J, Cade W, Best TM, et al. ADHD prescription medications and their effect on athletic performance: a systematic review and meta-analysis. Sports Med Open. 2022;8:5. https://doi.org/10.1186/s40798-021-00374-y.
24. Higgins J, Green S. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
26. Chang SC, Goldstein BY, Mu L, et al. Plasma folate, vitamin B12, and homocysteine and cancers of the esophagus, stomach, and liver in a Chinese population. Nutr Cancer. 2015;67(2):212–23.
27. Huang XX. Clinical efficacy of rabeprazole combined with folic acid and teprenone in the treatment of elderly patients with Helicobacter pylori positive chronic atrophic gastritis. J Ration Use Drugs Clin Pract. 2022;15(1):93–5.
28. Liu XX. Effect of folic acid combined with VB12 and quadruple therapy in the treatment of elderly patients with hp positive chronic atrophic gastritis. Practical Integr Traditional Chin Western Med Clin Pract. 2022;22(17):56–8.
29. Zhang JJ, Li HP, Wu XR. Effect of folic acid combined with VB12 in the treatment of patients with HP-associated chronic atrophic gastritis. Heilongjiang Med Sci. 2022;45(3):45–6.
30. Wang SQ. Efficacy of vitamin B12 and folic acid combined with quadruple therapy in the treatment of HP-related CAG and its effect on E-Cad and MMP-9. J Practical Rural Doctors China. 2022;29(3):55–9.
31. Zhang JC, Guo SJ, Long S. Application significance of folic acid combined with quadruple therapy in patients with hp positive chronic atrophic gastritis. Chin Foreign Med Res. 2021;19(10):4–6.
32. Liu XJ, Gao WT. Clinical study of sequential therapy combined with folic acid and teprenone in the treatment of elderly patients with Helicobacter pylori positive chronic atrophic gastritis. Chin J Clin Pharmacol. 2020;36(13):1794–6.
33. Sun HL. Effect of folic acid combined with Helicobacter pylori eradication in the treatment of patients with chronic atrophic gastritis. Chin Med Guidelines. 2019;17(16):150.
34. Meng Y. Efficacy of folic acid combined with Helicobacter pylori eradication in the treatment of patients with chronic atrophic gastritis. Abstract Latest Med Inform World. 2019;19(29):105–6.
35. Hu X. Clinical value of folic acid combined with Helicobacter pylori eradication in the treatment of chronic atrophic gastritis. Chin Sci Technol J Database Med. 2024;2:0092–5.
36. Yang CJ, Zhang H, Yao JF, et al. Clinical efficacy of folic acid and Helicobacter pylori in the treatment of chronic atrophic gastritis. Mod Dig Interventional Diagnosis Treat. 2019;24(A02):1668–9.
37. Zhang XX. Clinical efficacy of folic acid combined with Helicobacter pylori eradication in the treatment of chronic atrophic gastritis. Kang Yi. 2023;(10):194–6.
38. An Q. Characteristics of Helicobacter pylori infection in patients with chronic atrophic gastritis and prognosis evaluation of eradication therapy. Electron J Gen Dentistry. 2020;7(35):68–7098.
39. Ja YL, Chen J, Feng HX. Clinical efficacy of folic acid combined with Helicobacter pylori eradication in the treatment of chronic atrophic gastritis. Reflexology Rehabilitation Med. 2022;3(8):101–3.
40. Yang ZL. Clinical analysis of folic acid combined with rebamipide in the treatment of Hp-positive chronic atrophic gastritis. Fujian Med J. 2020;42(1):111–3.
41. Wang LL. Clinical efficacy of folic acid combined with Helicobacter pylori eradication in the treatment of chronic atrophic gastritis. J Ration Use Drugs Clin Pract. 2019;12(27):66–7.
42. Qin Y. Effect of folic acid combined with Helicobacter pylori eradication on patients with chronic atrophic gastritis. Famous Doctors. 2018; (12):206–7.
43. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, Garrido M, Kikuchi I, Megraud F, Matysiak-Budnik T, Annibale B, Dumonceau JM, Barros R, Fléjou JF, Carneiro F, van Hooft JE, Kuipers EJ, Dinis-Ribeiro M. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa De Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019;51(4):365–88. https://doi.org/10.1055/a-0859-1883.
44. Lahner E, Zagari RM, Zullo A, Di Sabatino A, Meggio A, Cesaro P, Lenti MV, Annibale B, Corazza GR. Chronic atrophic gastritis: natural history, diagnosis, and therapeutic management. A position paper by the Italian Society of Hospital Gastroenterologists and Digestive endoscopists [AIGO], the Italian Society of Digestive Endoscopy [SIED], the Italian Society of Gastroenterology [SIGE], and the Italian Society of Internal Medicine [SIMI]. Dig Liver Dis. 2019;51(12):1621–32.
45. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112:212–39.
46. Fallone CA, Chiba N, van Zanten SV, et al. The Toronto consensus for the treatment of Helicobacter pylori infection in adults. Gastroenterology. 2016;151:51–69. e14.
47. Laine L, Sharma P, Mulford DJ, et al. Pharmacodynamics and pharmacokinetics of the potassium-competitive acid blocker vonoprazan and the proton pump inhibitor lansoprazole in US subjects.Am. J Gastroenterol. 2022;117:1158–61.
48. Abdel-Aziz Y, Metz DC, Howden CW. Review article: potassium-competitive acid blockers for the treatment of acid-related disorders. Aliment Pharmacol Ther. 2021;53:794–809.
49. Li HT, Zhang X, Ji YX. Clinical efficacy of vonoprazan fumarate in the treatment of chronic atrophic gastritis. Drug use Monit China. 2024;21(3):234–8.
50. Hu YM, Jiang YG, Zhang SJ, et al. Effect of vonoprazan combined with quadruple therapy in the treatment of Helicobacter pylori positive patients with chronic atrophic gastritis and its influence on gastrointestinal hormones. Med Innov China. 2023;20(30):10–5.
51. Sun LH, Kong FF, Zhao Q, et al. Efficacy of vonolaxan fumarate combined with targeted health education intervention in the treatment of Hp-positive chronic atrophic gastritis. Gen Pract China. 2023;21(3):458–62.

Publisher's note