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Effectiveness of *Helicobacter pylori* eradication in the treatment of early-stage gastric mucosa-associated lymphoid tissue lymphoma: An up-to-date meta-analysis

Lemos FFB *et al*. *H. pylori* eradication in early-stage DML

Abstract

BACKGROUND

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (GML) is usually a low-grade, B-cell neoplasia strongly associated with *Helicobacter pylori* (*H. pylori*)-induced chronic gastritis. Clinical practice guidelines currently recommend *H. pylori* eradication as the preferred initial treatment for early-stage GML. Despite the advances in determining the practical effect of bacterial eradication as the sole initial therapy for early-stage GML, an updated powerful statistical combination of the available evidence is an imperative requirement.

AIM

To perform a meta-analysis to assess the complete remission rate (CR) of *H. pylori*-positive early-stage GML after bacterial eradication.

METHODS

Literature search: We performed independent computer-assisted searches of PubMed/MEDLINE, Embase and Cochrane Central databases until September 2022. Study selection: Prospective and retrospective observational studies evaluating the CR of early-stage GML after bacterial eradication therapy in *H. pylori*-positive patients. The risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools. Statistical analysis: The pooled estimate of the complete histopathological remission rate (CR) and respective confidence intervals (95%CI) were calculated following the random-effects model. The heterogeneity and inconsistency were assessed using Cochran's Q test and I^2 statistic, and heterogeneity was defined as P-value < 0.01 and I^2 > 50%, respectively. Subgroup and meta-regression analyses were conducted to explore potential sources of heterogeneity.

RESULTS

The title and abstract of 1576 studies were screened and 96 articles were retrieved and elected for full-text reading. Finally, 61 studies were included in the proportional meta-analysis (P-MA). Forty-six were prospective and fifteen were retrospective uncontrolled, single-arm, observational studies. The overall risk of bias was low to moderate in all but one report, with an average critical appraisal score across all studies of 79.02%. A total of 2936 *H. pylori*-positive early-stage GML patients, in whom *H. pylori* were successfully eradicated, were included in the analysis The pooled CR of *H. pylori*-positive early-stage GML after bacterial eradication was 75.18% (95%CI: 79.45%-79.91%). P-MA indicated the substantial heterogeneity in CR reported across studies (I^2 = 92%; P < 0.01). Meta-regression analysis identified statistically significant effect modifiers: the proportion of patients with t(11;18)(q21;q21)-positive GML and studies' risk of bias.

CONCLUSION

Comprehensive evidence synthesis suggests the effectiveness of *H. pylori* eradication as the sole initial therapy for early-stage GML. Although the substantial heterogeneity observed across studies limits the interpretation of the pooled overall CR, the present study is a relevant alternative for informing clinical practice.

Key Words: Lymphoma; B-cell; Marginal zone; Gastric mucosa-associated lymphoid tissue lymphoma; Stomach lymphoma; *Helicobacter pylori*; Therapeutics; Eradication therapy

Lemos FFB, Castro CT, Calmon MS, Silva Luz M, Pinheiro SLR, Faria Souza Mendes dos Santos C, Correa Santos GL, Marques HS, Delgado HA, Teixeira KN, Souza CL, Oliveira MV, Freire de Melo F. Effectiveness of *Helicobacter pylori* eradication in the treatment of early-stage gastric mucosa-associated lymphoid tissue lymphoma: An up-to-date meta-analysis. *World J Gastroenterol* 2023; In press

Core Tip: Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (GML) is usually a low-grade, B-cell neoplasia strongly associated with *Helicobacter pylori* (*H. pylori*)-induced chronic gastritis. Clinical practice guidelines currently recommend *H. pylori* eradication as the preferred initial treatment for early-stage gastric MALT lymphoma. Despite the advances in determining the practical effect of bacterial eradication as sole initial therapy for early-stage GML, an updated powerful statistical combination of the available evidence is an imperative requirement. Hence, we aim to perform a systematic review with proportional meta-analysis to assess the complete remission rate of *H. pylori*-positive early-stage GML after eradication therapy.

INTRODUCTION

Marginal zone lymphomas (MZLs) are the third most common type of B-cell non-Hodgkin's lymphoma, after diffuse large B-cell lymphoma and follicular lymphoma[1]. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours - Lymphoid Neoplasms subdivides MZLs into four subtypes: Extranodal MZL of mucosa-associated lymphoid tissue (MALT), primary cutaneous MZL, nodal MZL and paediatric MZL[2].

Gastric MALT lymphoma (GML) is usually a low-grade, B-cell neoplasia strongly associated with *Helicobacter pylori* (*H. pylori*)-induced chronic gastritis[3]. GML provides the best-characterized model of the antigen-induced transition from normal to malignant marginal-zone B-cells[4]. Despite the lack of lymphoid follicles in the normal gastric mucosa, MALT may appear as a result of inflammatory processes. *H. pylori*-related chronic gastritis microenvironment provides support of *H. pylori*-specific T helper cells for the expansion of polyclonal B cells, which undergo malignant transformation[4,5]. Similar to gastric cancer development, in advanced-stage GML, inflammatory signalling pathway lesions and pro-oncogenic genetic changes allow a microenvironment-independent lymphoma progression, characterizing a "hit-and-run" mechanism[5,6]. The overwhelming evidence of the biological plausibility of a causal

relationship between *H. pylori* infection and GML, is also ratified by epidemiological data[7].

In this sense, even though robust comparative studies such as randomized clinical trials have not been carried out, clinical practice guidelines currently recommend *H. pylori* eradication as the sole initial treatment for early-stage GML[8]. Triple-therapy regimens combining a proton pump inhibitor (PPI) for 4 wk, and clarithromycin with either amoxicillin or metronidazole, for 10-14 d remain the standard therapeutic approach to eradicating the bacterium. However, given the increasing rates of clarithromycin resistance in many countries, international guidelines also recommend bismuth quadruple therapy (BQT) or concomitant non-BQT as possible alternatives[9-11]. Accordingly, a previous systematic review with pooled data analyses highlighted that, after a long-term follow-up period, lymphoma disappeared in more than 75% of low-grade gastric lymphoma patients with stage I and II_1 disease treated by bacterial eradication[12]. The previous study also identified that its findings are even more significant when the neoplastic lesion is confined within the submucosa, the main lesion is localized in the distal stomach, and t(11;18)(q21;q21) translocation is absent.

However, despite advances in proposing standard interventions, given the rare nature of the neoplasm and the small sample size and heterogeneity of the available studies[12], we recognise the need for an updated powerful statistical synthesis of the available evidence about the practical effect of *H. pylori* eradication as sole initial therapy for early-stage GML. Thus, in the present study, we aim to perform an up-to-date systematic review with meta-analysis to assess the complete histopathologic remission rate (CR) *of H. pylori*-positive early-stage GML after bacterial eradication therapy.

MATERIALS AND METHODS

The present report strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline, which consists of a 27-item checklist and a three-phase flow chart. The checklist includes items considered critical to the

transparent reporting of a systematic review[13]. The statistical analysis was performed by the second author - Castro CT - who has extensive experience in biostatistics.

Literature search

The search strategy was designed following the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis (https://synthesismanual.jbi.global) guideline. We performed independent computer-assisted searches of PubMed/MEDLINE, Embase and Cochrane Central databases until September 2022. Medical Subject Headings and Embase Subject Headings (Emtree) index terms and free-text words were combined for search strategy development. Search terms included 'Lymphoma, B-Cell, Marginal Zone', 'Mucosa-Associated Lymphoid Tissue Lymphoma', 'Marginal Zone B-Cell Lymphoma', 'MALT lymphoma', 'Stomach lymphoma', 'Helicobacter pylori', 'Therapeutics' and 'Eradication therapy'. Boolean operators (AND, OR) were also used to narrow or broaden the search as required. All citations were exported to the Rayyan (https://www.rayyan.ai/) tool and all duplicates were removed.

Study selection

Two researchers independently assessed the articles (Lemos FFB and Calmon MS) according to predefined eligibility criteria. In case of disagreement, a third researcher (Silva Luz M) was consulted. The titles and abstracts of the articles were analyzed and studies that did not fit the inclusion criteria were excluded. The full texts were then revised to select eligible studies for meta-analysis.

Studies that met the following criteria were included: (1) Prospective and retrospective observational studies (cohort, case-control, and case series) evaluating the complete remission rate (CR) of early-stage GML after bacterial eradication therapy in *H. pylori*-positive patients; and (2) Only studies including *H. pylori*-positive patients exclusively treated with antibiotic eradication therapy. Only trials enrolling patients with either stage I or II_1, according to Lugano classification, were eligible for meta-analysis[14].

Exclusion criteria were as follows: (1) Studies that did not report the CRs of *H. pylori*-positive early-stage GML after bacterial eradication; (2) Studies investigating high-grade or diffuse large B cell lymphomas, except for those where it is possible to extrapolate data from a subgroup with early-stage GML; (3) Studies that included patients with non-gastric sites of MALT lymphoma or ineligible study subjects, such as animals or children; (4) Full-text article is not available and/or abstract, and article is not available in English; (5) Case reports, reviews, meta-analyses, systematic reviews, editorials, conference abstracts; and (6) Studies with insufficient data regarding treatment outcome.

Risk of bias assessment

Two researchers (Correa Santos GL and Faria Souza Mendes dos Santos C) assessed the risk of bias in the included studies using the JBI checklists for (cohort, case-control, and case series)[15]. In cases of disagreement, a third researcher (Delgado HA) was consulted. These tools include multiple questions that aim to assess the methodological quality of a study and determine the extent to which a study has addressed the possibility of bias in its design, conduct, and analysis. The percentage of risk of bias was calculated by the number of "yes" (Y) answers selected in the checklist. Questions with "not applicable" (N/A) answers were not considered in the calculation. The risk of bias was classified using the following categories: high (scores up to 49.0%), moderate (scores between 50.0 and 70.0%), and low (scores above 70.0%).

Data extraction

Two investigators (Silva Luz M and Pinheiro SLR) extracted data from the selected studies using a predefined data extraction worksheet. Subsequently, any discrepancies were resolved by a third reviewer (Lemos FFB). The primary outcome was the complete histopathologic remission of the lymphoma after bacterial eradication in *H. pylori*-positive early-stage GML patients. Data was extracted concerning the following: (1) Included study-related information (first author, year of publication, country of origin,

study design, and study size); (2) Clinical characteristics of the study population (disease stage, diagnostic methods for *H. pylori* infection, and eradication schemes); (3) Number of *H. pylori*-positive early-stage GML patients treated only with bacterial eradication; (4) Number of patients in whom *H. pylori* was successfully eradicated (either directly provided or calculated); and (5) Number of patients who finally achieved complete remission of the lymphoma (either directly provided or calculated). The stage of the lymphoma was assessed using the Lugano classification system[13].

Statistical analysis

The pooled estimate of the complete histopathological remission rate (CR) and respective confidence intervals (95%CI) were calculated following the random-effects model. Forest plots were used to summarize the results. The heterogeneity and inconsistency were assessed using Cochran's Q test and I^2 statistic[16] and heterogeneity was defined as P-value < 0.01 and I^2 > 50%, respectively. A subgroup analysis by study design (prospective; retrospective) was conducted to create more homogenous groups. Furthermore, a meta-regression analysis was conducted to explore potential sources of heterogeneity, such as publication year (≤ 2015; > 2015), geographic region of the study (Asian; Western), the prevalence of the translocation t (11;18) (q21; q21) and studies' risk of bias (Low; moderate; high). Publication bias analysis was not performed once this measure is inappropriate for proportional meta-analysis (P-MA)[17]. All analyses were performed in the R software, version 4.2.1 (R: A Language and Environment for Statistical Computing, Vienna, Austria), using the 'Meta' package, version 5.2-0.

RESULTS

Literature search and study selection

Figure 1 depicts the flow of information through the different phases of the systematic review. Database searches identified 2375 reports, and duplicates were removed. The title and abstract of 1576 studies were screened and 96 articles were retrieved and elected for full-text reading. Finally, 61 studies were included in the meta-analysis.

Reasons for exclusion were as follows: (1) Ten reports did not consider different stages in CR calculation; (2) Eight had insufficient data on *H. pylori* infection status; (3) Six were conference abstracts; (4) Five were publications of the same investigator or group; (5) Four had insufficient data on the outcome; and (6) Two reports included ineligible study subjects.

Study characteristics

Table 1 summarizes the characteristics of the studies included in the P-MA. The included reports were prospective and retrospective observational studies, published between 1993 and 2021. A sample of 3315 patients with early-stage GML was obtained, of which 3003 were *H. pylori*-positive. A total of 2936 patients in whom *H. pylori* was successfully eradicated were included in the analysis. Twenty-nine of the included studies were conducted in Asian countries and thirty-two were in Western countries. Concerning study design, forty-six were prospective and fifteen were retrospective uncontrolled, single-arm, observational studies. The median number of *H. pylori*-eradicated early-stage GML patients was 38 (ranging from 6-193). Multiple diagnostic tests for *H. pylori* infection and eradication were used, including histologic examination, *H. pylori* culture, rapid urease test, 13C- or 14C-urea breath test, serology and *H. pylori* stool antigen. In most studies, two diagnostic tools were associated to determine *H. pylori* infection status. Finally, in most studies, eradication therapy consisted of a combination of two antibiotics, such as amoxicillin and clarithromycin, with a PPI. However, dual, and quadruple therapies (two antibiotics + PPI + bismuth or three antibiotics + PPI) have also been used. Treatment duration ranged from 7 to 21 d (Table 2).

Risk of bias in studies

The risk of bias in studies was assessed using JBI checklists and the results are shown in Figure 2. The included single-arm uncontrolled observational studies were classifiable

and assessed as case series. The overall risk of bias was low to moderate in all but one[x] report, with an average critical appraisal score across all studies of 79.02% (Figure 2A).

The increased risk of bias was due to the number of "No" or "Unclear" answers to the following questions: (1) Was there clear reporting of the presenting site(s)/clinic(s) demographic information? ("No" or "Unclear" in 54/61 studies); (2) Did the case series have consecutive inclusion of participants ("No" or "Unclear" in 24/61 studies); (3) Did the case series have complete inclusion of participants? ("No" or "Unclear" in 22/61 studies); (4) Was there clear reporting of the demographics of the participants in the study? ("No" or "Unclear" in 6/61 studies); (5) Was statistical analysis appropriate? ("No" or "Unclear" in 6/61 studies); (6) Was the condition measured in a standard, reliable way for all participants included in the case series? ("No" or "Unclear" in 4/61 studies); (7) Was there clear reporting of clinical information of the participants? ("No" or "Unclear" in 4/61 studies); (8) Was there clear reporting of clinical information of the participants? ("No" or "Unclear" in 3/61 studies); (9) Were the outcomes or follow-up results of cases clearly reported? ("No" or "Unclear" in 8/61 studies); and (10) Were there clear criteria for inclusion in the case series? ("No" or "Unclear" in 2/61 studies). Figure 2B shows the discriminated assessments for each question across all studies.

P-MA of the CR

The overall CR of *H. pylori*-positive early-stage GML after bacterial eradication was 75.18% (95%CI: 79.45%-79.91%). P-MA highlighted substantial heterogeneity in CR reported across studies (I^2 = 92%; P < 0.01) (Figure 3A).

Exploring heterogeneity - subgroup and meta-regression analysis

Considering the high heterogeneity among the studies (I^2 = 92%; P < 0.01), a subgroup analysis by study design was conducted. The subgroup analysis revealed that retrospective and prospective studies presented similar overall CR after eradication therapy: 75.51% (95%CI: 64.96%-86.07%; I^2 = 96%; P < 0.01) and 75.08% (95%CI: 69.80-80.36; I^2 = 89%; P < 0.01), respectively (Figure 3B). The meta-regression analysis

indicated that the proportion of patients with t(11;18)(q21;q21)-positive GML and the studies' risk of bias were sources of heterogeneity. More precisely, studies with more than 30% of patients with t(11;18)(q21;q21)-positive GML and high risk of bias decreased in 0.40 (95%CI: -0.59 to -0.22; $P < 0.0001$) and 0.43 (95%CI: -0.77 to -0.09; $P = 0.0139$) the pooled estimate of the CR, respectively. There was no statistically significant difference regarding the geographic region of the studies (Asian; Western) for the evaluated outcome (Table 3).

DISCUSSION

GML is a usually low-grade rare neoplasm[18]. *H. pylori* infection is the main pathogenic factor underlying its development[19]. International guidelines strongly recommend *H. pylori* eradication therapy for all patients with GML, irrespective of stage. In localized *H. pylori*-positive GML, bacterial eradication is the preferred initial treatment[79,80].

This study aimed to provide an up-to-date comprehensive evidence synthesis of the real-world effect of *H. pylori* eradication as the sole initial therapy for early-stage GML. We identified prospective and retrospective uncontrolled, single-arm, observational studies, comprising 3315 patients with early-stage GML, of which 3003 were *H. pylori*-positive. A total of 2936 patients in whom *H. pylori* was successfully eradicated were included in the analysis. The unavailability of comparative studies of robust design, such as prospective cohort studies, precluded Pairwise meta-analysis (PW-MA), leading to the conduction of a P-MA. In contrast to comparative PW-MA (that allows the synthesis of data from two unique groups to produce a pooled estimate of effect), P-MA is a method of data synthesis that enables the calculation of a grouped, overall proportion of a certain number of individuals proportions[81,82]. Though single-group analysis may not produce measures of relative association, it can be useful for estimating the impact of a treatment on a certain condition in the absence of higher-quality evidence. Therefore, this type of analysis is an alternative for informed decision-making, especially in our field, in which robust comparative studies are scarce.

P-MA highlighted that the overall CR of *H. pylori*-positive early-stage GML after bacterial eradication was 75.18% (95%CI: 79.45%-79.91%). These results are similar to those found in a pooled data analysis published in 2010 by Zullo *et al*[12] [77.5% (95%CI: 75.3-79.7)]. Thereby, our comprehensive evidence synthesis suggests the real-world effectiveness of *H. pylori* eradication as the sole initial therapy for early-stage GML. On the other hand, the substantial heterogeneity observed across studies (I^2 = 92%; P < 0.01) limits, though not precludes, the interpretation of the pooled overall CR. Subgroup analysis revealed that retrospective and prospective studies presented similar overall CR after eradication therapy: 75.51% (95%CI: 64.96%-86.07%; I^2 = 96%; P < 0.01) and 75.08% (95%CI: 69.80-80.36; I^2 = 89%; P < 0.01), respectively. Nevertheless, meta-regression analysis indicated that the proportion of patients with t(11;18)(q21;q21)-positive GML and the studies' risk of bias were sources of heterogeneity. More precisely, studies with more than 30% of patients with t(11;18)(q21;q21)-positive GML and high risk of bias decrease in 0.40 (95%CI: -0.59 to -0.22; P < 0.0001) and 0.43 (95%CI: -0.77 to -0.09; P = 0.0139) the pooled estimate of the CR rate. In this sense, we reiterate the results of Zullo *et al*[12] that point out the t(11;18)(q21; q21) translocation as a predictor of lymphoma remission after bacterial eradication. In contrast to the previous pooled analysis[12], our study did not observe significant differences in lymphoma remission between Western and Asian countries.

Hence, our results reaffirm that *H. pylori* eradication should be given as the first-line treatment for localised low-grade GML[8]. Anti-*H. pylori* regimen should be chosen based on the regional microbial susceptibility; currently, BQT or high-dose PPI clarithromycin-containing triple therapy may be recommended as first-line empirical treatment if proven effective locally[83]. In case of eradication failure, second-line treatment should be attempted following the currently recommended algorithm for empirical *H. pylori* eradication or through individual antibiotic susceptibility testing. For patients with GML refractory to *H. pylori* eradication, irradiation and systemic oncological therapies should be used, depending on the stage of the disease. Radiotherapy (RT) is the first-line choice for the treatment of localised GML.

Chemotherapy, immunotherapy, or combination chemoimmunotherapy are mainly considered if RT is not feasible or not indicated[84,85].

To our knowledge, our study is the first systematic review with meta-analysis that assessed the CR of *H. pylori*-positive early-stage GML after *H. pylori* eradication. Our work has important strengths in its design and execution, such as the use of random-effects meta-analysis to address heterogeneity between included studies, subgroup analyses by study design and meta-regression to explore possible sources of heterogeneity.

Nonetheless, the present analysis has several limitations inherent to the included studies and study design. Due to the unavailability of language resources (*e.g.*, professional translators), we could not include studies in languages other than English (LOTE) in our comprehensive evidence synthesis. Although limiting study inclusion based on the language of publication is a common practice in systematic reviews, it introduces the risk of ignoring key data, referred to as language bias, which may limit our findings[86].

Moreover, discriminated assessments for each JBI Critical Appraisal Tool question across all reports showed that the included series had serious gaps in clinical and demographic information reporting. Thus, exploring possible sources of heterogeneity and identifying predictors of lymphoma remission was difficult. Furthermore, incomplete and non-consecutive inclusion of patients in several studies compromises the reliability of their results and increases the risk of bias. Another limitation was the failure to report the confirmation method for *H. pylori* eradication, which could be a covariate explaining the heterogeneity between studies. Inadequate reporting was an important reason for the exclusion of studies during screening and a complicating factor for data extraction. Observational studies evaluating the CR of GML after bacterial eradication should stratify the observed outcome according to *H. pylori* infection status. Furthermore, it is necessary to discriminate the lymphoma stage in *H. pylori*-positive patients undergoing treatment. In fields in which reliable and robust studies are scarce, proper reporting of the available evidence is vital to inform clinical

practice. Therefore, this meta-analysis should be interpreted in the context of these limitations.

CONCLUSION

This comprehensive evidence synthesis suggests the effectiveness of *H. pylori* eradication as the sole initial therapy for early-stage GML. Although the substantial heterogeneity observed across studies limits the interpretation of the pooled overall CR, our study is a relevant alternative for informing clinical practice. Moreover, we ratify that further robust comparative observational studies are needed to identify predictive factors for GML remission following *H. pylori* eradication and to provide more reliable evidence in our field.

ARTICLE HIGHLIGHTS

Research background

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (GML) is usually a low-grade, B-cell neoplasia strongly associated with *Helicobacter pylori* (*H. pylori*)-induced chronic gastritis. Hence, clinical practice guidelines currently recommend *H. pylori* eradication as the preferred initial treatment for early-stage GML.

Research motivation

Studies that aim to evaluate the effects of *H. pylori* eradication on early-stage GML are generally small and heterogenous single-arm uncontrolled observational studies. Hence, we recognise the need for an updated powerful statistical synthesis of the available evidence about the practical effect of *H. pylori* eradication as sole initial therapy for early-stage GML.

Research objectives

We aimed to perform a systematic review with an up-to-date proportional meta-analysis (P-MA) in order to assess the complete remission rate (CR) of *H. pylori*-positive early-stage GML after bacterial eradication therapy

Research methods

The present report strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. We performed independent computer-assisted searches of PubMed/MEDLINE, Embase and Cochrane Central databases until September 2022. Prospective and retrospective observational studies evaluating the CR of early-stage GML after bacterial eradication therapy in *H. pylori*-positive patients. The risk of bias was assessed using the JBI Critical Appraisal Tools. The unavailability of comparative studies of robust design precluded Pairwise meta-analysis (PW-MA), leading to the conduction of a P-MA. In contrast to comparative PW-MA, P-MA is a method of data synthesis that enables the calculation of a grouped, overall proportion of a certain number of individuals proportions. Though single-group analysis may not produce measures of relative association, it can be useful as an alternative for informed decision-making, especially in our field, in which robust comparative studies are scarce. In this sense, the pooled estimate of the complete histopathological remission rate (CR) and respective confidence intervals (95%CI) were calculated following the random-effects model. The heterogeneity and inconsistency were assessed using Cochran's *Q* test and I^2 statistic, and heterogeneity was defined as *P*-value < 0.01 and I^2 > 50%, respectively. Subgroup and meta-regression analyses were conducted to explore potential sources of heterogeneity.

Research results

P-MA highlighted that the overall CR of *H. pylori*-positive early-stage GML after bacterial eradication was 75.18% (95%CI: 79.45%-79.91%). On the other hand, the substantial heterogeneity observed across studies (I^2 = 92%; *P* < 0.01) limits, though not precludes, the interpretation of the pooled overall CR. Subgroup analysis revealed that

retrospective and prospective studies presented similar overall CR after eradication therapy: 75.51% (95%CI: 64.96%-86.07%; I^2 = 96%; P < 0.01) and 75.08% (95%CI: 69.80-80.36; I^2 = 89%; P < 0.01), respectively. Nevertheless, meta-regression analysis indicated that the proportion of patients with t(11;18)(q21;q21)-positive GML and the studies' risk of bias were sources of heterogeneity. More precisely, studies with more than 30% of patients with t(11;18)(q21;q21)-positive GML and high risk of bias decrease in 0.40 (95%CI: -0.59 to -0.22; P < 0.0001) and 0.43 (95%CI: -0.77 to -0.09; P = 0.0139) the pooled estimate of the CR rate.

Research conclusions

Comprehensive evidence synthesis suggests the effectiveness of *H. pylori* eradication as the sole initial therapy for early-stage GML. Although the substantial heterogeneity observed across studies limits the interpretation of the pooled overall CR, the present study is a relevant alternative for informing clinical practice.

Research perspectives

Inadequate reporting was an important reason for the exclusion of studies during screening and a complicating factor for data extraction. As reliable and robust studies are scarce in our field, we emphasize that proper reporting of the available evidence is vital to inform clinical practice. Lastly, we ratify that further robust comparative observational studies are needed to identify predictive factors for GML remission following *H. pylori* eradication and to provide more reliable evidence in our field.

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