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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 GML

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**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. To determine the practical effect of bacterial eradication as the sole initial therapy for early-stage GML, an updated analysis and review of available evidence is imperative.

AIM

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

METHODS

We performed independent, computer-assisted literature searches using the PubMed/MEDLINE, Embase, and Cochrane Central databases through September 2022. Prospective and retrospective observational studies evaluating the CR of early-stage GML following bacterial eradication in *H. pylori*-positive patients. The risk of bias was assessed using Joanna Briggs Institute (JBI) Critical Appraisal Tools. The pooled estimate of the complete histopathological remission rate and respective confidence intervals (95%CI) were calculated following the random-effects model. Heterogeneity and inconsistency were assessed using Cochran’s *Q* test and *I2* statistic, and heterogeneity was defined as *P* < 0.01 and *I²* > 50%, respectively. Subgroup and meta-regression analyses were conducted to explore potential sources of heterogeneity.

RESULTS

The titles and abstracts of 1576 studies were screened; 96 articles were retrieved and selected 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 a single 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* was successfully eradicated, were included in the analysis. The pooled CR of *H. pylori*-positive early-stage GML after bacterialeradication was 75.18% (95%CI: 70.45%-79.91%). P-MA indicated the substantial heterogeneity in CR reported across studies (*I2* = 92%; *P* < 0.01). Meta-regression analysis identified statistically significant effect modifiers, including the proportion of patients with t(11;18)(q21;q21)-positive GML and the risk of bias in each study.

CONCLUSION

Comprehensive synthesis of available evidence suggests that *H. pylori* eradication is effective 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 to informing clinical practice.

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

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**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 GML. Despite advances in determining the practical effect of bacterial eradication as sole initial therapy for early-stage GML, an updated meta-analysis of available evidence is imperative. We performed 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 non-Hodgkin B-cell lymphoma following diffuse large B-cell lymphoma and follicular lymphoma[1]. The 5th edition of the World Health Organization Classification of Hematolymphoid Tumors - Lymphoid Neoplasms subdivides MZL into 4 subtypes: Extranodal MZL of mucosa-associated lymphoid tissue (MALT), primary cutaneous MZL, nodal MZL, and pediatric MZL[2].

Gastric MALT lymphoma (GML) is a low-grade B-cell neoplasia commonly 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 inflammation. *H. pylori* chronic gastritis induces specific T helper cells and the subsequent expansion of polyclonal B cells, which can undergo malignant transformation[4,5]. Similar to that of gastric cancer, in advanced-stage GML, inflammatory signaling pathway and pro-oncogenic genetic changes allow a microenvironment-independent progression of the tumor, characterizing a “hit-and-run” mechanism[5,6]. The overwhelming evidence suggesting a causal relationship between *H. pylori* infection and GML is also supported by epidemiological data[7].

Although 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, which comprises a proton pump inhibitor (PPI) for 4 wk and clarithromycin with either amoxicillin or metronidazole for 10-14 d, remains standard. However, given the increasing rate of bacterial 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, stage I or II1 gastric lymphoma patients treated with bacterial eradication[12]. This study also identified that when the neoplastic lesion is confined to the submucosa, the main lesion is localized in the distal stomach, and t(11;18)(q21;q21) translocation is absent, the effectiveness of *H. pylori* eradication is even greater.

Given the low incidence of GML and the small sample sizes and heterogeneity of available studies[12], there is a need for an updated statistical analysis of the current evidence regarding *H. pylori* eradication as the sole initial therapy. Here, we performed a systematic literature review with meta-analysis to assess the complete histopathologic remission rate of *H. pylori*-positive early-stage GML after bacterial eradication therapy.

**MATERIALS AND METHODS**

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline, which consists of a 27-item checklist and a 3-phase flowchart. The checklist includes items considered critical to the transparent reporting of a systematic review[13].

***Literature search***

The search strategy was designed following the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis (https://synthesismanual.jbi.global). We performed independent, computer-assisted searches of the PubMed/MEDLINE, Embase, and Cochrane Central databases for studies published before September 2022. Medical Subject Headings and Embase Subject Headings (Emtree) index terms and free-text words were combined. 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 according to predefined eligibility criteria. In the case of disagreement, a 3rd researcher 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 (CR) rate of early-stage GML after bacterial eradication therapy in *H. pylori*-positive patients; and (2) Studies including *H. pylori*-positive patients exclusively treated with antibiotic eradication therapy. Also, only trials enrolling patients with either stage I or II1 GML according to Lugano classification were included[14].

Exclusion criteria were as follows: (1) Studies that did not report the CR rate 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 not available or article 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 independently assessed the risk of bias using the JBI checklists for cohort, case-control, and case series studies[15]. In cases of disagreement, a 3rd researcher was consulted. These tools include multiple questions 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 bias percentage risk 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 extracted data from the selected studies using a predefined data extraction worksheet. Any discrepancies were resolved by a 3rd reviewer. The primary outcome was the complete histopathologic remission of the lymphoma after bacterial eradication in *H. pylori*-positive early-stage GML patients. Data were extracted with respect to the following: (1) Included study-related information (1st 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 provided or calculated); and (5) Number of patients who finally achieved complete remission of the lymphoma (either 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 and respective confidence intervals (95%CI) were calculated following the random-effects model. Forest plots were used to summarize the results. Heterogeneity and inconsistency were assessed using Cochran’s *Q* test and *I2* statistic[16]; heterogeneity was defined as *P* < 0.01 and *I²* > 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 risk of bias (low; moderate; high). Analysis of publication bias was not performed as this measure is inappropriate for proportional meta-analysis (P-MA)[17]. All analyses were performed using 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 titles and abstracts of 1576 studies were screened and 96 articles were retrieved and selected for full-text reading. Finally, 61 studies were included in the meta-analysis. Reasons for exclusion were as follows: (1) 10 reports did not consider different stages in CR calculation; (2) 8 had insufficient data on *H. pylori* infection status; (3) 6 were conference abstracts; (4) 5 were publications of the same investigator or group; (5) 4 had insufficient data on the outcome; and (6) 2 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 32 in Western countries. Concerning study design, 46 were prospective and 15 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 testing, 13C- or 14C-urea breath testing, serology, and *H. pylori* antigen stool testing. In most studies, at least 2 diagnostic tools were used to determine *H. pylori* infection status. Also in most studies eradication therapy consisted of a combination of 2 antibiotics, such as amoxicillin and clarithromycin, with a PPI. However, dual and quadruple therapies (2 antibiotics + PPI + bismuth or 3 antibiotics + PPI, respectively) were also used. Treatment duration ranged from 7 d to 21 d (Table 2).

***Risk of bias in studies***

Risk of bias was assessed using JBI checklists (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 1 study[36], with an average critical appraisal score across all studies of 79.02% (Figure 2A).

An increased risk of bias was due to “No” or “Unclear” answers to the following questions: (1) Was there clear reporting of the presenting site(s)/clinic(s) demographic information? (54/61 studies); (2) Did the case series have consecutive inclusion of participants (24/61 studies); (3) Did the case series have complete inclusion of participants? (22/61 studies); (4) Was there clear reporting of the demographics of the participants in the study? (6/61 studies); (5) Was statistical analysis appropriate? (6/61 studies); (6) Was the condition measured in a standard, reliable way for all participants included in the case series? (4/61 studies); (7) Was there clear reporting of clinical information of the participants? (4/61 studies); (8) Was there clear reporting of clinical information of the participants? (3/61 studies); (9) Were the outcomes or follow-up results of cases clearly reported? (8/61 studies); and (10) Were there clear criteria for inclusion in the case series? (2/61 studies). Figure 2Bshows 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 bacterialeradication was 75.18% (95%CI: 70.45%-79.91%). P-MA highlighted substantial heterogeneity in CR rate reported across studies (*I2* = 92%; *P* < 0.01) (Figure 3A).

***Exploring heterogeneity - subgroup and meta-regression analysis***

Considering the high heterogeneity across studies (*I2* = 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 rate after eradication therapy: 75.51% (95%CI: 64.96%-86.07%; *I2* = 96%; *P* < 0.01) and 75.08% (95%CI: 69.80-80.36; *I2* = 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 study risk of bias were sources of heterogeneity. More precisely, studies with greater than 30% of patients with t(11;18)(q21;q21)-positive GML and high risk of bias showed the pooled estimate of the CR rate decreased to 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), respectively. There was no significant difference in outcomes with respect to geographic region (Table 3).

**DISCUSSION**

GML is rare and typically comprises a low-grade neoplasm[18]. *H. pylori* infection is predominant pathogenic mechanism underlying the development of GML[19], and international guidelines strongly recommend *H. pylori* eradication therapy for all patients 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 synthesis of evidence regarding *H. pylori* eradication as the sole initial therapy for early-stage GML. We identified prospective and retrospective uncontrolled, single-arm observational studies with a total of 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 robust comparative studies (*e.g.,* prospective cohort studies) precluded pairwise meta-analysis (PW-MA); instead, a P-MA was conducted. In contrast to comparative PW-MA, which calculates a pooled estimate of effect over 2 groups, P-MA enables the calculation of a grouped overall proportion[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 given condition in the absence of higher-quality evidence. This represents an alternative for informed decision making, especially in our field where robust comparative studies are scarce.

P-MA highlighted that the overall CR rate of *H. pylori*-positive early-stage GML after bacterialeradication was 75.18% (95%CI: 70.45%-79.91%), suggesting that *H. pylori* eradication as the sole initial therapy for early-stage GML is effective. 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%)]. On the other hand, the substantial heterogeneity observed across studies (*I2* = 92%; *P* < 0.01) limits, though does not preclude, the interpretation of the pooled overall CR rate. Subgroup analysis revealed that retrospective and prospective studies estimated similar overall CR rates after eradication therapy [75.51% (95%CI: 64.96%-86.07%; *I2*= 96%; *P* < 0.01) and 75.08% (95%CI: 69.80%-80.36%; *I2* = 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 greater than 30% of patients with t(11;18)(q21;q21)-positive GML or 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, respectively. In this sense, we reiterate the results of Zullo *et al*[12] which highlight the presence of 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 localized low-grade GML[8]. The anti-*H. pylori* regimen should be chosen based on regional microbial susceptibility; in many regions, BQT or high-dose PPI clarithromycin-containing triple therapy may be recommended as first-line empirical treatment[83]. In case of eradication failure, second-line treatment should be attempted following the currently recommended algorithm for empirical *H. pylori* eradication or as guided by 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 localized GML. Chemotherapy, immunotherapy, or combination chemoimmunotherapy are mainly considered if RT is not feasible or otherwise not indicated[84,85].

To our knowledge, our study is the first systematic review with meta-analysis to assess the CR rate of *H. pylori*-positive early-stage GML after *H. pylori* eradication. Our work has 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. 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 the interpretation of 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 rate, our study is a relevant alternative for informing clinical practice. 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. As such, 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 recognized the need for an updated powerful statistical synthesis of the available evidence regarding 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) to assess the complete remission (CR) rate of *H. pylori*-positive early-stage GML after bacterial eradication therapy.

***Research methods***

We performed independent computer-assisted searches of PubMed/MEDLINE, Embase and Cochrane Central databases culling reports published before September 2022. Prospective and retrospective observational studies evaluating the CR rate of early-stage GML after bacterial eradication therapy in *H. pylori*-positive patients were eligible for inclusion. The risk of bias was assessed using the JBI Critical Appraisal Tools. We followed the random-effects model to calculate the pooled estimate of the complete histopathological remission rate and respective confidence intervals (95%CI). We used Cochran’s *Q* test and *I2* statistic to assess the heterogeneity and inconsistency, and we set the threshold for heterogeneity as *P* < 0.01 and *I²* > 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 bacterialeradication was 75.18% (95%CI: 70.45%-79.91%). On the other hand, the substantial heterogeneity observed across studies (*I2* = 92%; *P* < 0.01) limits, but does not preclude, the interpretation of the pooled overall CR rate. Subgroup analysis revealed that retrospective and prospective studies presented similar overall CR rate estimates after eradication therapy: 75.51% (95%CI: 64.96%-86.07%; *I2*= 96%; *P* < 0.01) and 75.08% (95%CI: 69.80%-80.36%; *I2* = 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 greater 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, respectively.

***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 rate, 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. 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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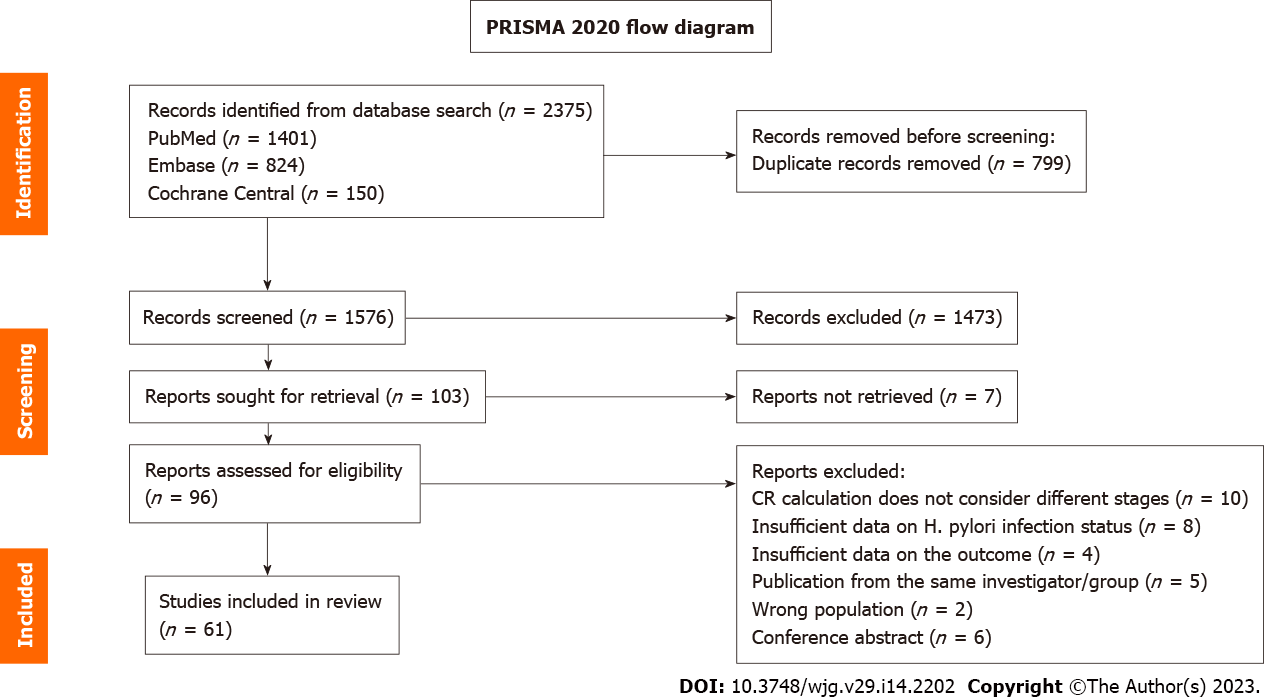
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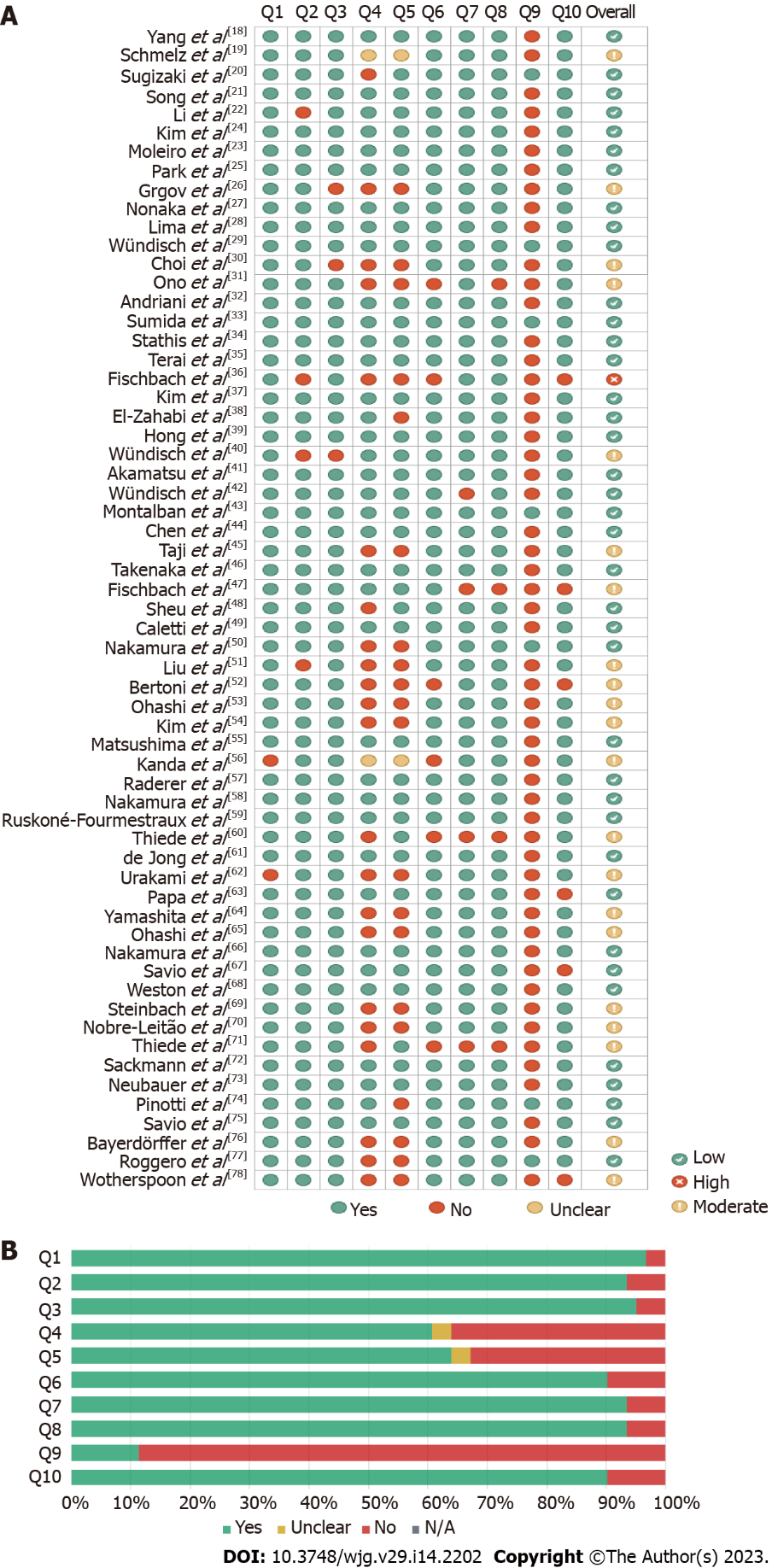
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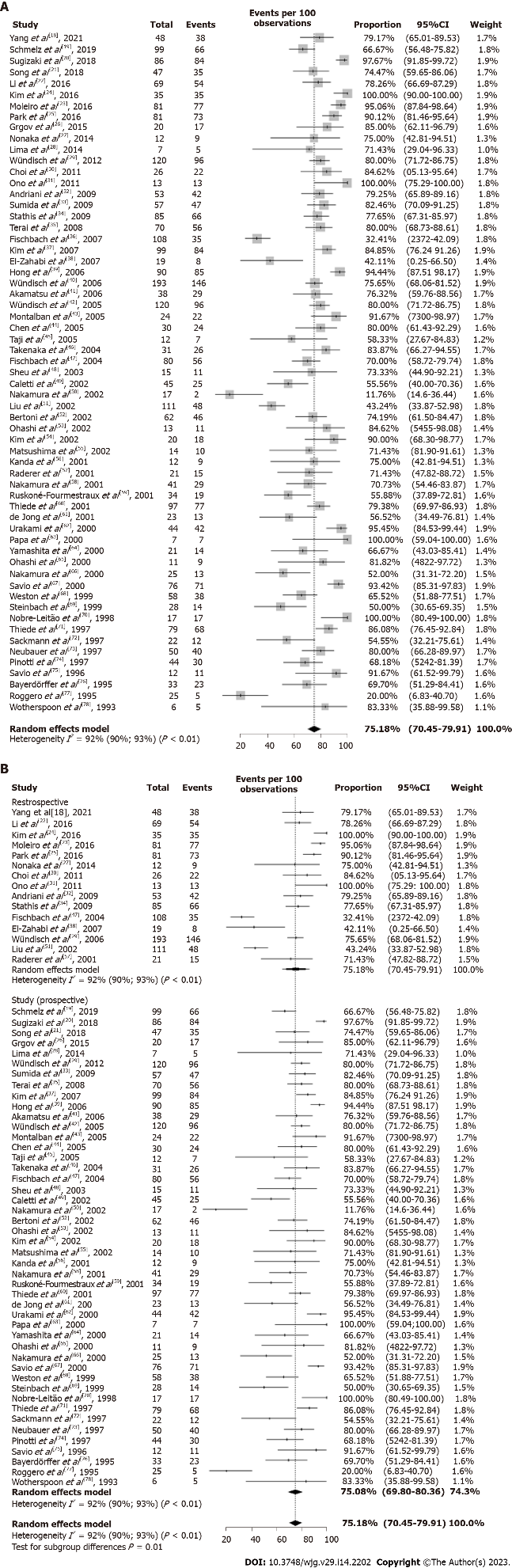
**Figure Legend**



**Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 flow diagram.** The flow chart describes the flow of information through the different stages of the systematic review and maps the number of records identified, included, and excluded, and the reasons for study exclusion. *H. pylori*: *Helicobacter pylori*.



**Figure 2 Risk of bias assessment by the Joanna Briggs Institute Critical Appraisal Tool.** The critical appraisal checklist for case series consists of 10 questions: Q1: Were there clear criteria for inclusion in the case series? Q2: Was the condition measured in a standard, reliable way for all participants included in the case series? Q3: Were valid methods used for identification of the condition for all participants included in the case series? Q4: Did the case series have consecutive inclusion of participants? Q5: Did the case series have complete inclusion of participants? Q6: Was there clear reporting of the demographics of the participants in the study? Q7: Was there clear reporting of clinical information of the participants? Q8: Were the outcomes or follow-up results of cases clearly reported? Q9: Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Q10: Was statistical analysis appropriate? The percentage of risk of bias was calculated by the number of “yes” answers selected in the checklist. Questions with “not applicable” 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%). A: Overall risk of bias; B: Risk of bias summary: Discriminated assessments for each question across all studies. N/A: Not applicable.



**Figure 3 Overall complete remission rate of *Helicobacter pylori*-positive early-stage** **gastric mucosa-associated lymphoid tissue lymphoma.** A: After eradication therapy; B: After eradication therapy by study design. CI: Confidence interval.

**Table 1 Characteristics of the included studies**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **Design** | **Study period** | **Study population** | | | | |
| **Early-stage gastric MALT lymphoma, *n*** | **Lugano stage** | **Median follow-up in mo** | ***H. pylori-*positive early-stage GML, *n*** | **Diagnosis of *H. pylori* infection** |
| Yang *et al*[18], 2021 | China | Retrospective | 2003-2015 | 70 | 70 | 30 | 52 | UBT; HE |
| Schmelz *et al*[19], 2019 | Germany | Prospective | 2001-2010 | 109 | 109 | 12 | 99 | HE |
| Sugizaki *et al*[20], 2018 | Japan | Prospective | 2010-2016 | 97 | 97 | 37.4 | 97 | HE; HpC; RUT; UBT; HpSA; S |
| Song *et al*[21], 2018 | China | Prospective | 2000-2013 | 122 | 122 | 38 | 47 | RUT; HE; UBT |
| Li *et al*[22], 2016 | China | Retrospective | 2001-2013 | 75 | 75 | 62.9 | 69 | HE; UBT |
| Kim *et al*[24], 2016 | Korea | Retrospective | 2001-2014 | 49 | 49 | 51 | 40 | HE; UBT; RUT |
| Moleiro *et al*[23]*, 2016* | Korea | Retrospective | 2005-2014 | 103 | 103 | 50.5 | 82 | RUT; UBT; HE |
| Park *et al*[25], 2016 | Portugal | Retrospective | 1993-2013 | 103 | 103 | 105 | 87 | HE; HpC; S; UBT |
| Grgov *et al*[26], 2015 | Serbia | Prospective | 2002-2012 | 20 | 20 | NR | 20 | RUT; HE |
| Nonaka *et al*[27], 2014 | Japan | Retrospective | 2007-2012 | 16 | 16 | NR | 12 | HE; S; UBT |
| Lima *et al*[28], 2014 | Brazil | Prospective | 2009-2010 | 8 | 8 | 24 | 7 | RUT; HE; UBT |
| Wündisch *et al*[29], 2012 | Germany | Prospective | 1993-1999 | 120 | 120 | 122 | 120 | HE |
| Choi *et al*[30], 2011 | Korea | Retrospective | 2003-2010 | 35 | 35 | 21.5 | 26 | HE; RUT; UBT |
| Ono *et al*[31], 2011 | Japan | Retrospective | 2003-2009 | 21 | 21 | 1 | 13 | RUT; UBT; HpC; HE; S |
| Andriani *et al*[32], 2009 | Italy | Retrospective | 1993-2006 | 60 | 60 | 65 | 60 | HE |
| Sumida *et al*[33], 2009 | Japan | Prospective | 1997-2007 | 66 | 66 | 40 | 57 | HE; S; UBT |
| Stathis *et al*[34], 2009 | Switzerland | Retrospective | 1990-2006 | 105 | 105 | 75.6 | 85 | HE; S; UBT |
| Terai *et al*[35], 2008 | Japan | Prospective | 1995-2006 | 74 | 74 | 46 | 70 | RUT; HE; S; UBT |
| Fischbach *et al*[36], 2007 | Germany | Retrospective | NR | 108 | 108 | 42.2 | 108 | HE; UBT |
| Kim *et al*[37], 2007 | Korea | Prospective | 1996-2006 | 99 | 99 | 41 | 99 | HE; RUT |
| El-Zahabi *et al*[38], 2007 | Lebanon | Retrospective | 1999-2005 | 22 | 22 | 12 | 19 | HE; S |
| Hong *et al*[39], 2006 | Korea | Prospective | 1996-2003 | 90 | 90 | 45 | 90 | HE; RUT; UBT |
| Wündisch *et al*[40], 2006 | Germany | Retrospective | 1993-2003 | 196 | 196 | 27 | 196 | HE |
| Akamatsu *et al*[41], 2006 | Japan | Prospective | 1993-2006 | 55 | 55 | 37.3 | 38 | HpC; HE |
| Wündisch *et al*[42], 2005 | Germany | Prospective | NR | 120 | 120 | 75 | 120 | HE |
| Montalban *et al*[43], 2005 | Spain | Prospective | 1993-2002 | 24 | 24 | 64 | 24 | HE; UBT |
| Chen *et al*[44], 2005 | Taiwan | Prospective | 1996-1999 | 34 | 34 | 70 | 31 | HE; RUT; S |
| Taji *et al*[45], 2005 | Japan | Prospective | 1995-2001 | 13 | 13 | 32.5 | 12 | HE; HpC; S; UBT; RUT |
| Takenaka *et al*[46], 2004 | Japan | Prospective | 1995-2002 | 33 | 33 | 5 | 33 | HpC; RUT |
| Fischbach *et al*[47], 2004 | Germany | Prospective | NR | 90 | 90 | 44.6 | 80 | RUT; HE; UBT |
| Sheu *et al*[48], 2003 | Taiwan | Prospective | NR | 15 | 15 | NR | 15 | RUT; HE |
| Caletti *et al*[49], 2002 | Italy | Prospective | 1997-1999 | 51 | 51 | 24 | 51 | HE; RUT; S |
| Nakamura *et al*[50], 2002 | Japan | Prospective | 1994-2001 | 21 | 21 | 14.5 | 17 | HpC; S |
| Liu *et al*[51], 2002 | France; Netherlands; Italy; Germany; England | Retrospective | NR | 111 | 111 | NR | 111 | HE; HpC |
| Bertoni *et al*[52], 2002 | England; Italy; Switzerland | Prospective | NR | 62 | 62 | 24 | 62 | HE; S |
| Ohashi *et al*[53], 2002 | Japan | Prospective | NR | 13 | 13 | NR | 13 | RUT; HE; HpC |
| Kim *et al*[54], 2002 | Korea | Prospective | NR | 20 | 20 | 18.3 | 20 | RUT; HE |
| Matsushima *et al*[55], 2002 | Japan | Prospective | 1995-1997 | 14 | 14 | 27.5 | 14 | RUT; HE; HpC; UBT |
| Kanda *et al*[56], 2001 | Japan | Prospective | 1994-1999 | 13 | 13 | 7 | 13 | HE |
| Raderer *et al*[57], 2001 | Austria | Retrospective | 1997-1999 | 22 | 22 | 25 | 22 | HE |
| Nakamura *et al*[58], 2001 | Japan | Prospective | 1994-1998 | 41 | 41 | 20.5 | 41 | HpC; S; HE |
| Ruskoné-Fourmestraux *et al*[59], 2001 | France | Prospective | 1995-1998 | 44 | 44 | 35 | 34 | HE; HpC; S; PCR |
| Thiede *et al*[60], 2001 | Germany | Prospective | NR | 97 | 97 | 20.8 | 97 | NR |
| de Jong *et al*[61], 2001 | Netherlands | Prospective | NR | 23 | 23 | 37 | 23 | HE; HpC |
| Urakami *et al*[62], 2000 | Japan | Prospective | NR | 47 | 47 | 20 | 47 | RUT; HE; HpC |
| Papa *et al*[63], 2000 | Italy | Prospective | 1995-1999 | 7 | 7 | 48 | 7 | HE; UBT |
| Yamashita *et al*[64], 2000 | Japan | Prospective | NR | 21 | 21 | NR | 21 | HE; RUT; HpC |
| Ohashi *et al*[65], 2000 | Japan | Prospective | NR | 11 | 11 | NR | 11 | RUT; HE; HpC |
| Nakamura *et al*[66], 2000 | Japan | Prospective | 1993-1998 | 30 | 30 | NR | 26 | HpC |
| Savio *et al*[67], 2000 | Italy | Prospective | 1991-1997 | 76 | 76 | NR | 76 | HE |
| Weston *et al*[68], 1999 | United States | Prospective | NR | 68 | 68 | NR | 65 | HE |
| Steinbach *et al*[69], 1999 | United States | Prospective | NR | 34 | 34 | NR | 28 | HE; RUT; S |
| Nobre-Leitão *et al*[70], 1998 | Portugal | Prospective | NR | 17 | 17 | 12 | 17 | HE; HpC |
| Thiede *et al*[71], 1997 | Germany | Prospective | NR | 84 | 84 | NR | 84 | NR |
| Sackmann *et al*[72], 1997 | Germany | Prospective | NR | 22 | 22 | 10 | 22 | HE; HpC |
| Neubauer *et al*[73], 1997 | Germany | Prospective | NR | 50 | 50 | 24 | 50 | HE |
| Pinotti *et al*[74], 1997 | Italy; Switzerland | Prospective | 1986-1995 | 86 | 86 | 23.3 | 45 | HE; S |
| Savio *et al*[75], 1996 | Italy; England | Prospective | 1991-1993 | 13 | 13 | NR | 13 | HE |
| Bayerdörffer *et al*[76], 1995 | Germany | Prospective | NR | 33 | 33 | 12.5 | 33 | HE |
| Roggero *et al*[77], 1995 | Switzerland; Italy | Prospective | NR | 26 | 26 | 12 | 26 | HE |
| Wotherspoon *et al*[78], 1993 | England; Italy | Prospective | NR | 6 | 6 | NR | 6 | HE |

CR: Complete remission rate; GML: Gastric mucosa-associated lymphoid tissue lymphoma; *H.* *pylori*: *Helicobacter pylori*; HE: Histologic examination; HpC: *Helicobacter pylori* culture; HpSA: *Helicobacter pylori* stool antigen; MALT: Mucosa-associated lymphoid tissue; NR: Not reported; PPI: Proton pump inhibitor; RUT: Rapid urease test; S: Serology; UBT: 13C- or 14C-urea breath test.

**Table 2 Characteristics of studies reporting the complete remission rate of *Helicobacter pylori*-positive early-stage gastric mucosa-associated lymphoid tissue lymphoma after bacterial eradication**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Region** | ***H. pylori*-positive early-stage gastric MALT lymphoma, *n*** | ***H. pylori*-eradicated gastric MALT lymphoma patients, *n*** | **CR, *n*** | **t(11;18)(q21;q21)-investigated gastric MALT lymphoma, *n*** | **t(11;18)(q21;q21)-positive gastric MALT lymphoma, *n*** | **Eradication regimen** |
| Yang *et al*[18] | Asian | 52 | 48 | 38 | NR | NR | 7-d-14-d triple therapy or 10-d quadruple therapy |
| Schmelz *et al*[19] | Western | 99 | 99 | 66 | 69 | 7 | 7-d triple therapy |
| Sugizaki *et al*[20] | Asian | 97 | 86 | 84 | 73 | 1 | 7-d triple therapy |
| Song *et al*[21] | Asian | 47 | 47 | 35 | NR | NR | 14-d triple therapy |
| Li *et al*[22] | Asian | 69 | 69 | 54 | NR | NR | ND-day quadruple therapy |
| Kim *et al*[24] | Asian | 40 | 35 | 35 | NR | NR | 7-d-14-d triple therapy or 7-d-14-d bismuth quadruple therapy |
| Moleiro *et al*[23] | Western | 82 | 81 | 77 | NR | NR | 7-d triple therapy or 7-d bismuth quadruple therapy |
| Park *et al*[25] | Asian | 87 | 81 | 73 | NR | NR | 7-d-14-d triple therapy |
| Grgov *et al*[26] | Western | 20 | 20 | 17 | NR | NR | 10-d triple therapy |
| Nonaka *et al*[27] | Asian | 12 | 12 | 9 | NR | NR | 7-d triple therapy |
| Lima *et al*[28] | Western | 7 | 7 | 5 | 8 | 4 | 7-d triple therapy or 10-d triple therapy |
| Wündisch *et al*[29] | Western | 120 | 120 | 96 | 66 | 10 | 14-d dual therapy or 10-d triple therapy |
| Choi *et al*[30] | Asian | 26 | 26 | 22 | NR | NR | ND-day triple therapy or ND-day bismuth quadruple therapy |
| Ono *et al*[31] | Asian | 13 | 13 | 13 | NR | NR | 7-d-triple therapy |
| Andriani *et al*[32] | Western | 60 | 53 | 42 | NR | NR | 7-d-14-d triple therapy or 10-d bismuth quadruple therapy |
| Sumida *et al*[33] | Asian | 57 | 57 | 47 | 66 | 7 | 7-d triple therapy |
| Stathis *et al*[34] | Western | 85 | 85 | 66 | NR | NR | ND-day triple therapy |
| Terai *et al*[35] | Asian | 70 | 70 | 56 | 22 | 0 | 7-d triple therapy |
| Fischbach *et al*[36] | Western | 108 | 108 | 35 | NR | NR | NR |
| Kim *et al*[37] | Asian | 99 | 99 | 84 | NR | NR | 7-d triple therapy or 7-d bismuth quadruple therapy |
| El-Zahabi *et al*[38] | Asian | 19 | 19 | 8 | NR | NR | ND-day quadruple therapy |
| Hong *et al*[39] | Asian | 90 | 90 | 85 | NR | NR | 14-d triple therapy or 14-d bismuth quadruple therapy |
| Wündisch *et al*[40] | Western | 196 | 193 | 146 | NR | NR | NR |
| Akamatsu *et al*[41] | Asian | 38 | 38 | 29 | 8 | 6 | 7-d triple therapy or ND-day quadruple therapy |
| Wündisch *et al*[42] | Western | 120 | 120 | 96 | 65 | 10 | 14-d dual therapy or 10-d triple therapy |
| Montalban *et al*[43] | Western | 24 | 24 | 22 | NR | NR | 14-d triple therapy |
| Chen *et al*[44] | Asian | 31 | 30 | 24 | NR | NR | 14-d triple therapy |
| Taji *et al*[45] | Asian | 12 | 12 | 7 | 13 | 4 | 14-d triple therapy |
| Takenaka *et al*[46] | Asian | 33 | 31 | 26 | NR | NR | ND-day triple therapy |
| Fischbach *et al*[47] | Western | 80 | 80 | 56 | NR | NR | 7-d triple therapy |
| Sheu *et al*[48] | Asian | 15 | 15 | 11 | NR | NR | 14-d triple therapy |
| Caletti *et al*[49] | Western | 51 | 45 | 25 | NR | NR | 7-d triple therapy |
| Nakamura *et al*[50] | Asian | 17 | 17 | 2 | 23 | 7 | 14-d triple therapy |
| Liu *et al*[51] | Western | 111 | 111 | 48 | 111 | 44 | 14-d dual therapy |
| Bertoni *et al*[52] | Western | 62 | 62 | 46 | NR | NR | 7-d triple therapy; 14-d triple therapy or 14-d bismuth quadruple therapy |
| Ohashi *et al*[53] | Asian | 13 | 13 | 11 | NR | NR | 14-d triple therapy |
| Kim *et al*[54] | Asian | 20 | 20 | 18 | NR | NR | 7-d triple therapy or 7-d bismuth quadruple therapy |
| Matsushima *et al*[55] | Asian | 14 | 14 | 10 | NR | NR | ND-day triple therapy |
| Kanda *et al*[56] | Asian | 13 | 12 | 9 | NR | NR | ND-day dual therapy or ND-day triple therapy |
| Raderer *et al*[57] | Western | 22 | 21 | 15 | NR | NR | ND-day dual therapy or ND-day triple therapy |
| Nakamura *et al*[58] | Asian | 41 | 41 | 29 | NR | NR | ND-day triple or ND-day quadruple therapy |
| Ruskoné-Fourmestraux *et al*[59] | Western | 34 | 34 | 19 | NR | NR | 14-d triple therapy |
| Thiede *et al*[60] | Western | 97 | 97 | 77 | NR | NR | 14-d dual therapy or 7-d triple therapy |
| de Jong *et al*[61] | Western | 23 | 23 | 13 | NR | NR | ND-day dual therapy; ND-day triple therapy or ND-day quadruple therapy |
| Urakami *et al*[62] | Asian | 47 | 44 | 42 | NR | NR | 7-d-14-d triple therapy |
| Papa *et al*[63] | Western | 7 | 7 | 7 | NR | NR | 7-d triple therapy |
| Yamashita *et al*[64] | Asian | 21 | 21 | 14 | NR | NR | 14-d triple therapy |
| Ohashi *et al*[65] | Asian | 11 | 11 | 9 | NR | NR | 14-d triple therapy |
| Nakamura *et al*[66] | Asian | 26 | 25 | 13 | NR | NR | 14-d dual therapy; 7-d triple therapy (14-d PPI); 14-d triple therapy |
| Savio *et al*[67] | Western | 76 | 76 | 71 | NR | NR | NR |
| Weston *et al*[68] | Western | 65 | 58 | 38 | NR | NR | ND-day triple or ND-day quadruple therapy |
| Steinbach *et al*[69] | Western | 28 | 28 | 14 | NR | NR | 21-d bismuth quadruple therapy |
| Nobre-Leitão *et al*[70] | Western | 17 | 17 | 17 | NR | NR | 14-d triple therapy |
| Thiede *et al*[71] | Western | 84 | 79 | 68 | NR | NR | NR-day-dual or 7-d-triple therapy |
| Sackmann *et al*[72] | Western | 22 | 22 | 12 | NR | NR | 14-d-dual therapy |
| Neubauer *et al*[73] | Western | 50 | 50 | 40 | NR | NR | 14-d-dual therapy or 7-d-triple therapy |
| Pinotti *et al*[74] | Western | 45 | 44 | 30 | NR | NR | 14-d-triple or quadruple therapy |
| Savio *et al*[75] | Western | 13 | 12 | 11 | NR | NR | NR-day-triple or quadruple therapy |
| Bayerdörffer *et al*[76] | Western | 33 | 33 | 23 | NR | NR | 14-d-dual therapy |
| Roggero *et al*[77] | Western | 26 | 25 | 5 | NR | NR | 14-d-triple therapy |
| Wotherspoon *et al*[78] | Western | 6 | 6 | 5 | NR | NR | NR-day-dual or triple therapy |

CR: Complete remission rate; *H.* *pylori*: *Helicobacter pylori*; MALT: Mucosa-associated lymphoid tissue; NR: Not reported; PPI: Proton pump inhibitor.

**Table 3 Meta-regression according to selected covariates**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Subgroup** | **Studies, *n*** | **Estimate** | **95%CI** | ***P* value** | ***I*2, %** |
| Year | | | | | |
| ≤ 2015 | 54 | - | - | - | 92.5 |
| > 2015 | 7 | 0.11 | -0.03 to 0.25 | 0.1188 |
| Region |  |  |  |  | 92.8 |
| Asian | 29 | - | - | - |
| Western | 32 | -0.06 | -0.15 to 0.03 | 0.2145 |
| Proportion of patients with t(11;18)(q21;q21)-positive gastric MALT lymphoma |  |  |  |  |  |
| ≤ 30% | 7 |  |  |  |  |
| > 30% | 4 | -0.40 | -0.59 to -0.22 | < 0.0001 | 88.6 |
| Risk of bias |  |  |  |  | 92.3 |
| Low | 39 | - | - | - |
| Moderate | 21 | 0.02 | -0.07 to 0.12 | 0.6190 |
| High | 1 | -0.43 | -0.77 to -0.09 | 0.0139 |

MALT: Mucosa-associated lymphoid tissue.



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