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SYSTEMATIC REVIEWS

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

Fabian Fellipe Bueno Lemos, Caroline Tianeze de Castro, Mariana Santos Calmon, Marcel Silva Luz, Samuel Luca Rocha Pinheiro, Clara Faria Souza Mendes dos Santos, Gabriel Lima Correa Santos, Hanna Santos Marques, Henrique Affonso Delgado, Kádima Nayara Teixeira, Cláudio Lima Souza, Márcio Vasconcelos Oliveira, Fabrício Freire de Melo

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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 $I^2 > 50\%$, 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 bacterial eradication was 75.18% (95%CI: 70.45%-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, 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

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.

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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 II_1 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 II_1 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 I^2 statistic[16]; heterogeneity was defined as $P < 0.01$ 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 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).

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*	Germany	Prospective	NR	50	50	24	50	HE

[73], 1997								
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.

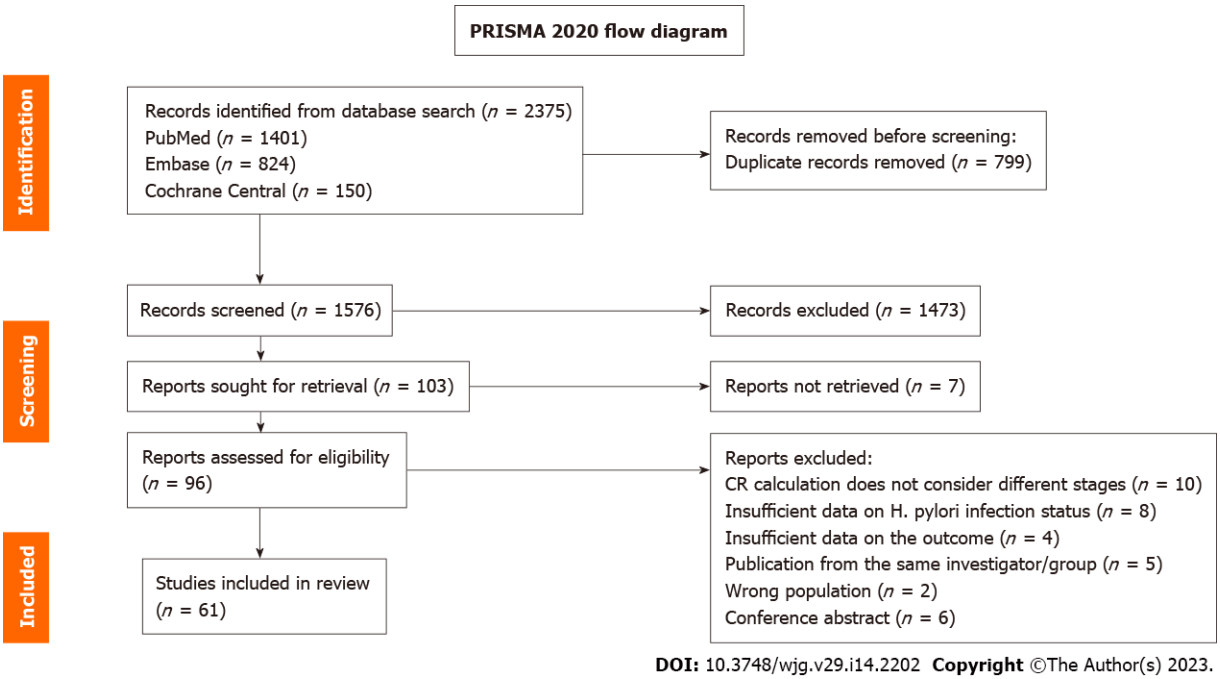

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 flow diagram. The flow chart describes the flow of information through the different stages of the systematic review and maps the number of records identified, included, and excluded, and the reasons for study exclusion.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

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 2B shows the discriminated assessments for each question across all studies.

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.

P-MA of the CR

The overall CR of *H. pylori*-positive early-stage GML after bacterial eradication was 75.18% (95%CI: 70.45%-79.91%). P-MA highlighted substantial heterogeneity in CR rate reported across studies (I^2 = 92%; P < 0.01) (Figure 3A).

Exploring heterogeneity - subgroup and meta-regression analysis

Considering the high heterogeneity across 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 rate 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 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.

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.

P-MA highlighted that the overall CR rate of *H. pylori*-positive early-stage GML after bacterial eradication 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 (I^2 = 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%; 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 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

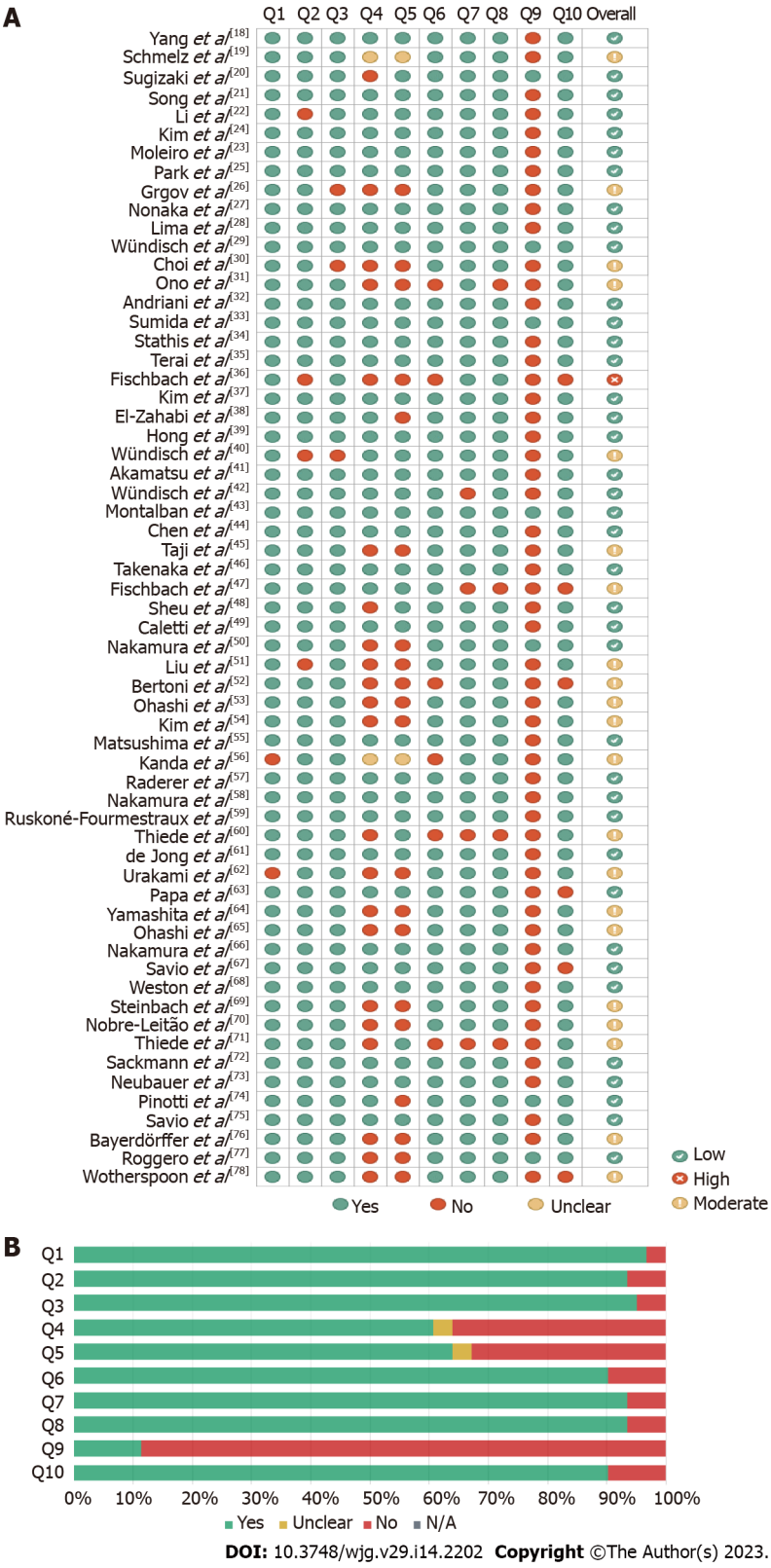

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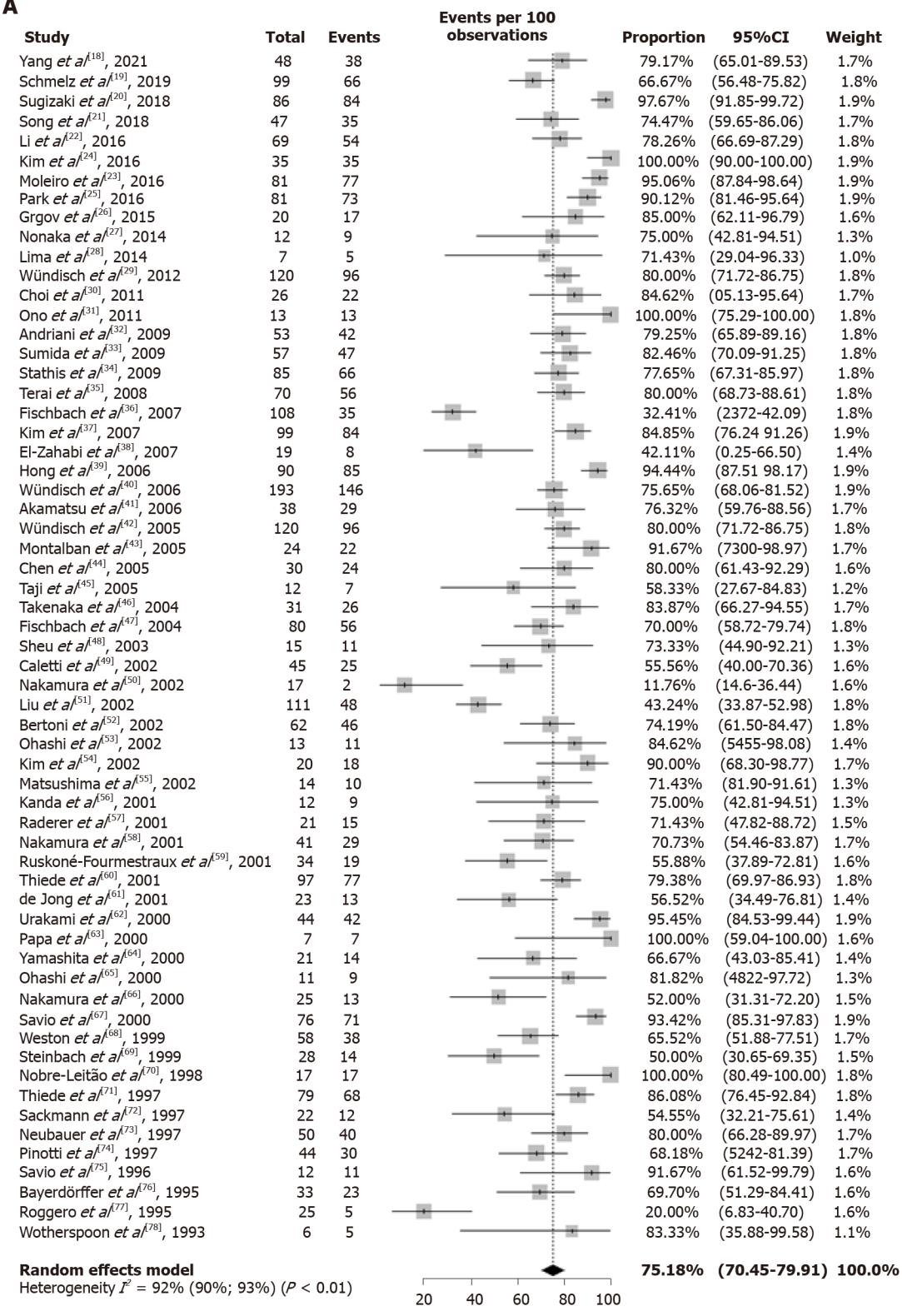
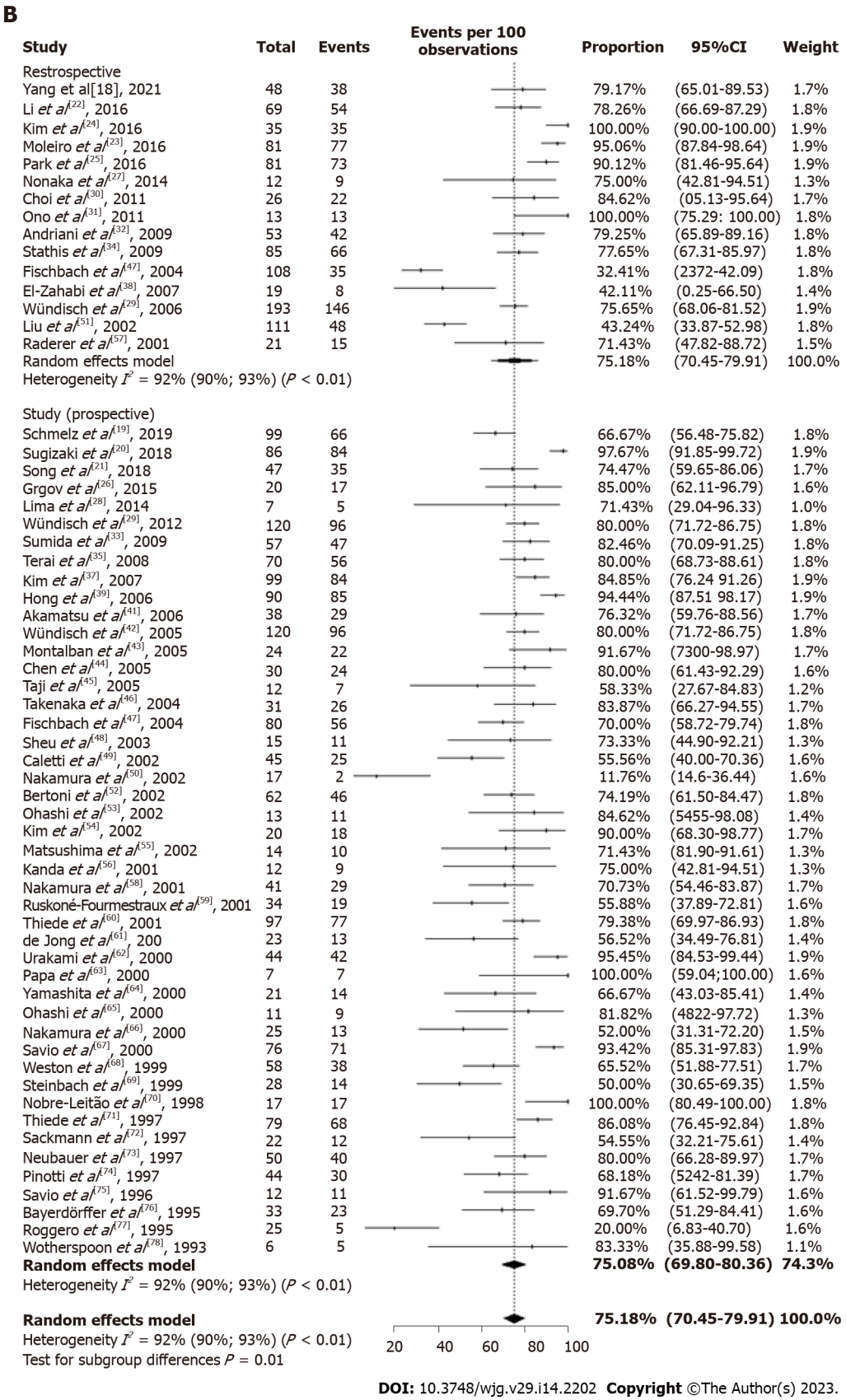
Figure 2 Risk of bias assessment by the Joanna Briggs Institute Critical Appraisal Tool. The critical appraisal checklist for case series consists of 10 questions: Q1: Were there clear criteria for inclusion in the case series? Q2: Was the condition measured in a standard, reliable way for all participants 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.

A


Study
Total
Events
Events per 100 observations
Proportion
95%CI
Weight
Yang et al[18], 2021 48 38 79.17% (65.01-89.53) 1.7%
Schmelz et al[19], 2019 99 66 66.67% (56.48-75.82) 1.8%
Sugizaki et al[20], 2018 86 84 97.67% (91.85-99.72) 1.9%
Song et al[21], 2018 47 35 74.47% (59.65-86.06) 1.7%
Li et al[22], 2016 69 54 78.26% (66.69-87.29) 1.8%
Kim et al[24], 2016 35 35 100.00% (90.00-100.00) 1.9%
Moleiro et al[23], 2016 81 77 95.06% (87.84-98.64) 1.9%
Park et al[25], 2016 81 73 90.12% (81.46-95.64) 1.9%
Grgov et al[26], 2015 20 17 85.00% (62.11-96.79) 1.6%
Nonaka et al[27], 2014 12 9 75.00% (42.81-94.51) 1.3%
Lima et al[28], 2014 7 5 71.43% (29.04-96.33) 1.0%
Wündisch et al[29], 2012 120 96 80.00% (71.72-86.75) 1.8%
Choi et al[30], 2011 26 22 84.62% (05.13-95.64) 1.7%
Ono et al[31], 2011 13 13 100.00% (75.29-100.00) 1.8%
Andriani et al[32], 2009 53 42 79.25% (65.89-89.16) 1.8%
Sumida et al[33], 2009 57 47 82.46% (70.09-91.25) 1.8%
Stathis et al[34], 2009 85 66 77.65% (67.31-85.97) 1.8%
Terai et al[35], 2008 70 56 80.00% (68.73-88.61) 1.8%
Fischbach et al[36], 2007 108 35 32.41% (2372-42.09) 1.8%
Kim et al[37], 2007 99 84 84.85% (76.24 91.26) 1.9%
El-Zahabi et al[38], 2007 19 8 42.11% (0.25-66.50) 1.4%
Hong et al[39], 2006 90 85 94.44% (87.51 98.17) 1.9%
Wündisch et al[40], 2006 193 146 75.65% (68.06-81.52) 1.9%
Akamatsu et al[41], 2006 38 29 76.32% (59.76-88.56) 1.7%
Wündisch et al[42], 2005 120 96 80.00% (71.72-86.75) 1.8%
Montalban et al[43], 2005 24 22 91.67% (7300-98.97) 1.7%
Chen et al[44], 2005 30 24 80.00% (61.43-92.29) 1.6%
Taji et al[45], 2005 12 7 58.33% (27.67-84.83) 1.2%
Takenaka et al[46], 2004 31 26 83.87% (66.27-94.55) 1.7%
Fischbach et al[47], 2004 80 56 70.00% (58.72-79.74) 1.8%
Sheu et al[48], 2003 15 11 73.33% (44.90-92.21) 1.3%
Caletti et al[49], 2002 45 25 55.56% (40.00-70.36) 1.6%
Nakamura et al[50], 2002 17 2 11.76% (14.6-36.44) 1.6%
Liu et al[51], 2002 111 48 43.24% (33.87-52.98) 1.8%
Bertoni et al[52], 2002 62 46 74.19% (61.50-84.47) 1.8%
Ohashi et al[53], 2002 13 11 84.62% (5455-98.08) 1.4%
Kim et al[54], 2002 20 18 90.00% (68.30-98.77) 1.7%
Matsushima et al[55], 2002 14 10 71.43% (81.90-91.61) 1.3%
Kanda et al[56], 2001 12 9 75.00% (42.81-94.51) 1.3%
Raderer et al[57], 2001 21 15 71.43% (47.82-88.72) 1.5%
Nakamura et al[58], 2001 41 29 70.73% (54.46-83.87) 1.7%
Ruskoné-Fourmestraux et al[59], 2001 34 19 55.88% (37.89-72.81) 1.6%
Thiede et al[60], 2001 97 77 79.38% (69.97-86.93) 1.8%
de Jong et al[61], 2001 23 13 56.52% (34.49-76.81) 1.4%
Urakami et al[62], 2000 44 42 95.45% (84.53-99.44) 1.9%
Papa et al[63], 2000 7 7 100.00% (59.04-100.00) 1.6%
Yamashita et al[64], 2000 21 14 66.67% (43.03-85.41) 1.4%
Ohashi et al[65], 2000 11 9 81.82% (4822-97.72) 1.3%
Nakamura et al[66], 2000 25 13 52.00% (31.31-72.20) 1.5%
Savio et al[67], 2000 76 71 93.42% (85.31-97.83) 1.9%
Weston et al[68], 1999 58 38 65.52% (51.88-77.51) 1.7%
Steinbach et al[69], 1999 28 14 50.00% (30.65-69.35) 1.5%
Nobre-Leitão et al[70], 1998 17 17 100.00% (80.49-100.00) 1.8%
Thiede et al[71], 1997 79 68 86.08% (76.45-92.84) 1.8%
Sackmann et al[72], 1997 22 12 54.55% (32.21-75.61) 1.4%
Neubauer et al[73], 1997 50 40 80.00% (66.28-89.97) 1.7%
Pinotti et al[74], 1997 44 30 68.18% (5242-81.39) 1.7%
Savio et al[75], 1996 12 11 91.67% (61.52-99.79) 1.6%
Bayerdörffer et al[76], 1995 33 23 69.70% (51.29-84.41) 1.6%
Roggero et al[77], 1995 25 5 20.00% (6.83-40.70) 1.6%
Wotherspoon et al[78], 1993 6 5 83.33% (35.88-99.58) 1.1%
Random effects model 75.18% (70.45-79.91) 100.0%
Heterogeneity I^2 = 92% (90%; 93%) (P < 0.01)
20
40
60
80
100



DOI: 10.3748/wjg.v29.i14.2202

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.

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 I^2 statistic to assess the heterogeneity and inconsistency, and we set the threshold for heterogeneity as $P < 0.01$ 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: 70.45%-79.91%). On the other hand, the substantial heterogeneity observed across studies ($I^2 = 92\%$; $P < 0.01$) 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%; $I^2 = 96\%$; $P < 0.01$) 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 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.

FOOTNOTES

Author contributions: Lemos FFB, Castro CT, Teixeira KN, Souza CL, Oliveira MV, and Freire de Melo F contributed to the conceptualization of the manuscript; Lemos FFB, Castro CT, Teixeira KN, Souza CL, Oliveira MV, and Freire de Melo F designed the study methodology; Lemos FFB, Castro CT, Calmon MS, Silva Luz M, Pinheiro SLR, Faria Souza Mendes dos Santos C, Santos GLC, Marques HS and Delgado HA were responsible for manuscript visualization; Lemos FFB, Calmon MS, Silva Luz M, Pinheiro SLR, Faria Souza Mendes dos Santos C, Santos GLC, Marques HS, Delgado HA, Teixeira KN, Souza CL, Oliveira MV, and Freire de Melo F contributed to the investigation; Lemos FFB, Calmon MS, Silva Luz M, Pinheiro SLR, Faria Souza Mendes dos Santos C, Santos GLC, Marques HS, Delgado HA performed formal analysis; Lemos FFB wrote the original draft; Castro CT and Silva Luz M were responsible for manuscript editing; Castro CT, Silva Luz M, Teixeira KN, Souza CL, and Oliveira MV were responsible for manuscript writing and review; and Freire de Melo F supervised the writing of the original draft.

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