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REVIEW

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Efficacy of *Helicobater pylori* eradication in patients with diffuse large B-cell lymphoma of the stomach: A systematic review

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Abstract

Objectives: The role of *Helicobater pylori* eradication in the treatment of high-grade diffuse large B-cell lymphoma (DLBCL) of the stomach is unclear.

Methods: We performed a systematic review and meta-analysis of currently available data. DLBCL-remission rate after eradication therapy, post-remission maintenance, and response rate in the case of additional oncological therapy were extracted.

Results: By considering data of seven studies, the DLBCL remission was achieved in 81 (53.3%; 95% CI = 45.3–61.2) out of 152 *H. pylori* eradicated patients. The regression rate did not differ between pure DLCBL and DLCBL with MALT component, between stage I and stage II disease, and between Caucasians and Asians. Disease regression was maintained in all patients after at a median of 63 months (range: 46–29) follow-up. In those non-responders, DLBLC remission after additional chemo-immunotherapy was achieved in 63 (98.4%; 95% CI = 95.4–100) out of 64 patients.

Conclusions: Data this systematic review suggest considering *H. pylori* eradication as first-line therapy to treat infected patients with early-stage, high-grade gastric lymphoma.

KEYWORDS

chemo-immunotherapy, *Helicobacter pylori*, high-grade lymphoma, stomach

1 | INTRODUCTION

The stomach is the most frequent site of extra-nodal lymphomas, which represent 2–8% of all gastric tumours.[1] Primary gastric lymphomas mainly include low-grade B-cell MALT-lymphoma and diffuse large B-cell lymphoma (DLBCL) that account for approximately one third of cases.[2] The latter is classified as pure (*de novo*) DLBC-lymphoma and MALT-transformed DLBC-lymphoma (DLBCL-MALT). In the last three decades, the role of *H. pylori* in inducing low-grade, B-cell MALT-lymphoma in genetically susceptible subjects has been largely demonstrated, and current guidelines recommend bacterial eradication as first-line therapy when the disease is diagnosed in early stages.[3,4] On the other hand, the pathogenic role of *H. pylori* in DLBCL has been scarcely addressed, although the first two cases of lymphoma remission achieved exclusively with bacterial eradication were reported on 1997.[5,6] The possibility of inducing remission of DLBLC—whose clinical behaviour is distinctly more aggressive than that of MALT-lymphoma—with a simple antibiotic therapy and without chemo-immunotherapy is a definite advantage for both patients and health resources utilisation.

Therefore, we designed a systematic review to answer to the following clinically relevant questions: (1) What is the remission rate of gastric high-grade lymphoma in infected patients following only *H. pylori* eradication? Is the initial lymphoma remission maintained at

long-term follow-up? In those non-responders, is the eradication therapy detrimental in terms of disease progression or response to the additional oncological therapy?

2 | METHODS

2.1 | Literature review

Computer-assisted search was performed on PubMed for studies published from January 01, 2000, through May 31, 2022, by using the exploded medical subject heading terms '*Helicobacter pylori* AND gastric diffuse large B-cell lymphoma OR gastric high-grade lymphoma'. The search was limited to studies published in English and reporting data on remission of primary DLBCL with solely *H. pylori* eradication therapy. Following abstract evaluation, the full text of all relevant studies was retrieved, and manual searches of reference lists from identified relevant articles were performed to identify any additional studies that might have been missed. When more than one publication from the same investigator or group was available, only the most updated or the larger series including the entire sample size was considered. Case reports and studies that included case series with less than five patients were excluded. Two investigators extracted data according to a specifically designed database and conflicting data were resolved by discussion. Whenever possible, data were extrapolated and analysed according to the disease stage, splitting patients with lymphoma confined to the gastric wall (stage I or I_{E1}-I_{E2}) from those with perigastric lymph nodes involvement (stage II1 or II_{E1}) according to either Lugano or Ann Arbor classification as modified by Musshof.[7,8] In addition, data were compared by sub-grouping patients based on DLBCL or DLCBL-MALT. Only cases with histological confirmed remission of lymphoma at 2–6 months following exclusively *H. pylori* eradication therapy were considered.

2.2 | Statistical analysis

Lymphoma remission rates and their 95% confidence intervals (CI) were computed, and comparisons were performed by using Chi-square test or Fisher's exact test, as appropriate. Differences were considered significant at 5% probability level. Data from eligible studies were extracted and summarised in a specific excel database. For the outcome, effect size and standard errors with 95% CI were calculated. To incorporate the influence of study size on the outcome, adjusted proportions and standard errors were calculated prior to analyse, by using a logistic transformation. The effect measure was computed using the Metaprop routine command for the meta-analysis of proportions in Stata. This provides procedures for pooling the proportion in a meta-analysis of multiple studies, and supplies the results in a forest plot. The CIs were based on the exact binomial. Meta-analysis was performed for studies with more than five patients by using a random-effects model and the DerSimonian and Laird method to derive the summary estimate. Data were analysed with Stata V.15.1 (StataCorp).

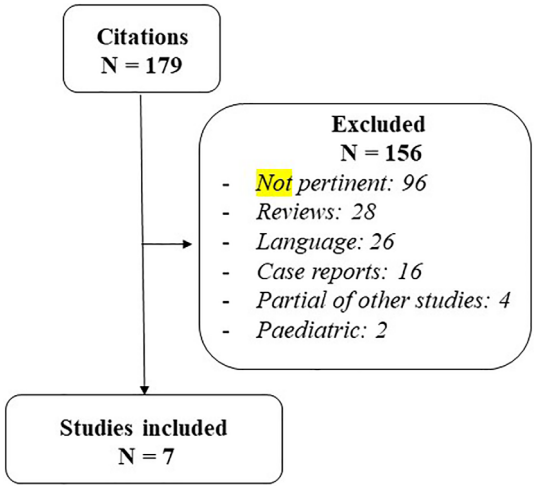

FIGURE 1 Flow-chart of literature searching

2.3 | Quality assessment

The quality of each study included was assessed by two independent reviewers using the Methodological Index for Non-Randomised Studies (MINORS).[9] Disagreements were discussed with a third reviewer. Each item is scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). When conducting sub-analyses, we considered study quality as poor (<5), fair (6–10), or good (>11), as previously reported.[9]

3 | RESULTS

3.1 | Descriptive analysis

A total of 179 citations were found on PubMed. Following title and abstracts review, seven (three retrospective, three prospective, and one combined) studies[10–16] met inclusions criteria, including three studies performed in Japan, two studies in Taiwan, and one each in Italy and in Germany. The others studies were ultimately excluded for different reasons (Figure 1). Overall, data of 154 *H. pylori* positive high-grade gastric lymphoma patients were available, including 92 cases with pure DLBCL and 62 patients with DLCBL-MALT. Lymphoma was diagnosed at stage I in 92 patients, at II stage in 52 patients, whilst the stage was not available for the remaining 10 patients. The location of lymphoma in the stomach was available for 109 cases, and the main lesion involved the antral region in 52 (47.7%) patients, and the gastric body in 57 (52.3%) patients. *Helicobater pylori* eradication and lymphoma remission were assessed at 2–6 months.

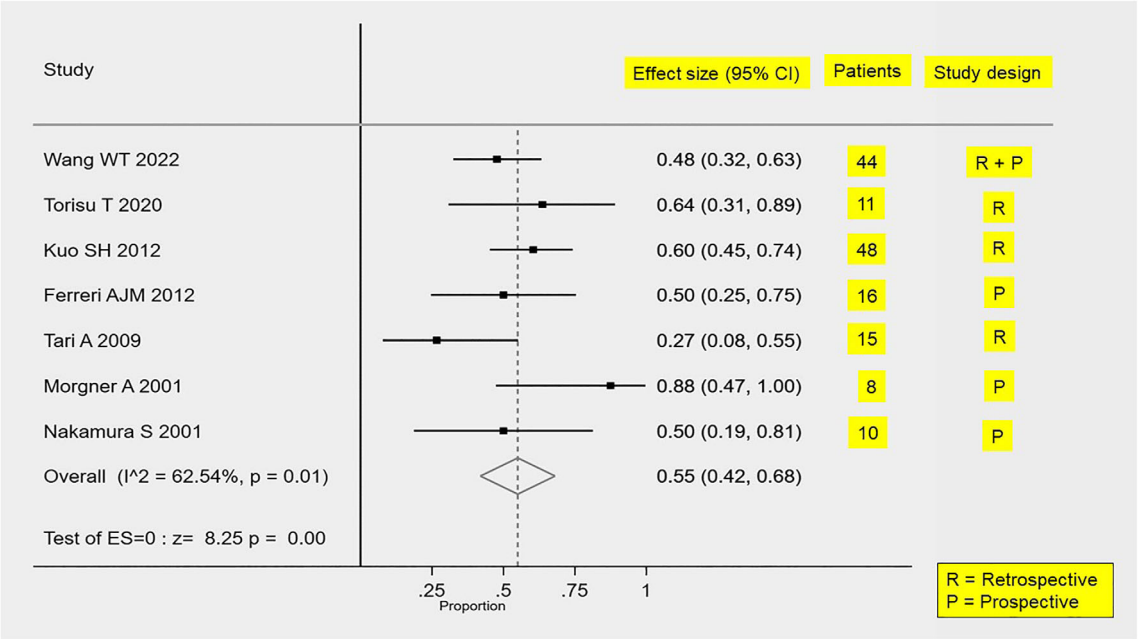

FIGURE 2 Results of meta-analysis

Study included	Quality assessment								Score	Rate
	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size		
Huang WT 2022	2	0	1	2	2	2	2	0	11	Good
Torisu T 2020	2	0	1	1	1	0	2	0	7	Fair
Kuo SH 2012	2	2	0	1	2	2	2	0	11	Good
Ferreri AJM 2012	2	0	2	2	2	2	2	0	12	Good
Tari A 2009	1	0	1	1	2	2	2	0	9	Fair
Morgner A 2001	2	0	0	0	1	2	2	0	7	Fair
Nakamura S 2001	2	0	2	2	2	2	2	0	12	Good

FIGURE 3 Assessment of studies quality

3.2 | Lymphoma remission rates

Helicobater pylori infection was cured in 152 (98.7%; 95% CI = 96.9–100.4) out of 154 patients following antibiotic therapies. Overall, lymphoma remission was achieved in 81 (53.3%; 95% CI = 45.3–61.2) out of 152 eradicated patients, with rates ranging from 36.3% to 87.5% in different studies. The meta-analysis of data found a 55% (95% CI = 42–68) cumulative probability of inducing tumour remission with solely *H. pylori* eradication with a high degree of heterogeneity (I^2: 62%; Figure 2). According to the lymphoma type, remission

was equally achieved in DLCBL-MALT (33/55, 60%; 95% CI = 47–72.9) and in those with pure DLBCL (40/81, 49.3%; 95% CI = 38.4–60.2) ($p = 0.3$). Similarly, the remission did not differ between patients treated in stage I disease (40/79, 50.7%; 95% CI = 38.4–63.1) and in those in stage II (6/14, 42.8%; 95% CI = 16.9–68.7) ($p = 0.7$), as well as between Asian (66/128, 51.5%; 95% CI = 42.9–60.2) and Caucasian (15/24, 62.5%; 95% CI = 43.1–81.8) patients ($p = 0.4$). The long-term follow-up was available for 61 patients who were cured with only *H. pylori* eradication, and all remained disease-free at median of 63 months (range: 46–29), whilst three patients deceased due to lymphoma-independent causes. Out of 71 patients who failed to achieve remission, data on additional haematological chemo-immunotherapy—mainly doxorubicin, cyclophosphamide, vincristine, and prednisone-based therapy and rituximab (R-CHOP)—were reported for 64 cases and all (98.4%; 95% CI = 95.4–100), but one achieved complete remission.

3.3 | Quality assessment

Overall, the quality of studies was low with four studies of 'good' and three studies of 'fair' quality (Figure 3).

4 | DISCUSSION

By pooling data of more than 150 patients with gastric high-grade B-cell lymphomas to search for and treat *H. pylori* led to complete remission in more than half of the infected patients. Such remission also appeared to be long-lasting at follow-up, and no lymphoma recurrence was reported in all considered studies. Moreover, the time needed to perform and assess the benefit of antibiotic therapy (2–6 months) was associated with neither disease progression nor the reduction of subsequent chemotherapy efficacy. Altogether these observations suggest that the attempt of inducing remission of early-stage, high-grade gastric lymphoma with a simple, inexpensive, and safe eradication therapy for *H. pylori* is worthy and it is advisable as first-line therapy. Although not statistically significant, we observed that remission rate tended to be lower in patients with pure DLBCL, in those with stage II disease, and in Caucasian patients. Therefore, further studies are needed to investigate on potential predictive factors of response. The requirement of other investigations is further strengthened by the observation that the overall quality of available studies is low, even if the realisation of a large, specifically designed, randomised trial probably remains improbable.

The benefit of *H. pylori* eradication in DLBLC was not unexpected. The pathogenic role of *H. pylori* in low-grade B-cell MALT-lymphoma is widely demonstrated and different guidelines suggest bacterial eradication as first-line therapy in these patients.[3,4] Indeed, the cure of infection is associated with a lymphoma remission rate in near 80% and more than 55% in patients with stage I or II_1, respectively.[17] In addition, eradication therapy may induce MALT-lymphoma remission even in some patients in whom *H. pylori* is not evident.[18] Thus, a possible role of *H. pylori* in DLBLC was probable. Lymphomagenesis may be related to the chronic antigenic stimulation of B-cell response by *H. pylori* bacteria, similarly to the HCV infection. Indeed, chronic HCV infection may sustain a multi-step evolution toward low-grade and eventually to high-grade lymphoma.[19–21]

A long-term follow-up is advised following gastric lymphoma remission after *H. pylori* eradication, not only for a potential disease recurrence, but also for the increased risk of gastric cancer development in these patients.[22]

In conclusion, data this systematic review suggest considering *H. pylori* eradication as first-line therapy to treat infected patients with early-stage, high-grade gastric lymphoma.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception of the study design, and contributed to the acquisition, analysis, and interpretation of the study data. All authors participated in the drafting of the manuscript, provided the final approval of the submitted version, and agree to be held accountable for all aspects of the work.

FUNDING INFORMATION

No fund was received for this study.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data were collected in a specific database, and they may be accessible following a reasonable request.

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