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SYSTEMATIC REVIEW

Impact of *Helicobacter pylori* Antibiotic Resistance on Treatment Outcomes in Gastrointestinal Lymphomas: A Meta-Analysis

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Abstract

Aims/Background With the increasing prevalence of antibiotic-resistant strains of *Helicobacter pylori* (*H. pylori*), especially in the context of its association with gastrointestinal (GI) lymphomas, understanding the current patterns of resistance and their implications for treatment strategies is crucial. Our study aims to investigate the antibiotic resistance patterns of *H. pylori* in patients with GI lymphoma.

Methods A comprehensive literature search was conducted using major electronic databases up to August 2023. The primary focus was on the antibiotic resistance patterns of *H. pylori* in GI lymphoma. The data included study characteristics, patient demographics, details of *H. pylori* antibiotic resistance, and outcomes such as all-cause mortality (AM), tumor progression rate (TPR), clinical cure rate (CCR), and long-term recurrence rate (LRR) following initial cure in patients with GI lymphoma.

Results From 2325 identified articles, 9 were included, representing 934 patients with GI lymphoma. Significant differences in AM were observed in patients who were resistant to clarithromycin (standard mean difference, SMD: 2.27, 95% confidence intervals, CIs: 0.63 to 3.91, $p = 0.007$) and there were no differences in AM between amoxicillin-resistant patients and controls (SMD: 1.35, 95% CIs: –0.54 to 3.25, $p = 0.16$). Patients who were resistant to both clarithromycin and amoxicillin showed a pronounced difference in AM (SMD: 5.13, 95% CIs: 1.78 to 8.48, $p = 0.003$). Clarithromycin resistance significantly affected CCR after *H. pylori* eradication therapy (SMD: –4.12, 95% CIs: –5.42 to –2.82, $p < 0.00001$). Elevated TPR was observed in patients who were resistant to clarithromycin (SMD: 7.09, 95% CIs: 4.57 to 9.61, $p < 0.00001$) and amoxicillin (SMD: 11.03, 95% CIs: 5.81 to 16.25, $p < 0.0001$). LRR also exhibited significant differences in patients who were resistant to clarithromycin (SMD: 9.31, 95% CIs: 6.16 to 12.47, $p < 0.00001$) and amoxicillin (SMD: 13.81, 95% CIs: 2.78 to 24.85, $p = 0.01$).

Conclusion Increasing antibiotic resistance in *H. pylori* strains poses a significant challenge for the treatment of GI lymphomas. Tailored treatment strategies in which resistance patterns are imperative for effective management and improved patient outcomes.

Key words: *H. pylori*; antibiotic resistance; gastrointestinal (GI); lymphomas; clarithromycin; amoxicillin

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Introduction

Helicobacter pylori (*H. pylori*), a gram-negative bacterium, is a significant pathogen that infects approximately half of the world's population (White et al,

2021). *H. pylori* is recognized as one of the most prevalent human infections, with its presence being linked to chronic active gastritis, which can further lead to peptic ulcer, atrophic gastritis, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT)-lymphoma (Lee et al, 2016; Savoldi et al, 2018; Thung et al, 2016). The global prevalence of *H. pylori* infection varies, with some regions reporting rates as high as 80% (Lee et al, 2016). Such high prevalence rates underscore the importance of effective treatment strategies, especially in the context of antibiotic resistance.

Gastrointestinal (GI) lymphomas encompass a heterogeneous spectrum of malignancies originating from lymphoid tissue within the gastrointestinal tract. The most common primary lymphoma of the gastrointestinal tract is B-cell lymphoma arising from MALT (Caletti et al, 2003; Watanabe et al, 2020). The stomach is the predominant site affected, but MALT lymphomas can also manifest in other parts of the gastrointestinal tract, such as the rectum and duodenum (Watanabe et al, 2020). A significant association has been established between *H. pylori* infection and the development of gastric MALT lymphoma (Caletti et al, 2003). Eradication of *H. pylori* has been shown to lead to regression of MALT lymphoma in various cases, emphasizing the bacterium's influence on the pathogenesis and progression of MALT lymphomas (Caletti et al, 2003).

To address *H. pylori* infections, various antibiotics have been utilized. The primary antibiotics for *H. pylori* eradication include amoxicillin, clarithromycin, and metronidazole (Subsomwong et al, 2022; Zeng et al, 2022). Tetracycline and levofloxacin are also used as alternative treatments, especially in cases of resistance or intolerance to the primary antibiotics (Huang et al, 2021). These antibiotics are often combined with proton pump inhibitors (PPIs) to enhance treatment efficacy (Jiang et al, 2022).

However, the increasing prevalence of antibiotic-resistant strains of *H. pylori*, especially in the context of their association with GI lymphomas, has become a significant concern in medical research and practice. Clarithromycin and metronidazole, the primary antibiotics used for *H. pylori* eradication, are experiencing increasing resistance levels. For instance, in South Asia, resistance rates have surged to 27% for clarithromycin, 69% for metronidazole, and 16% for tetracycline (Shrestha et al, 2023; Suzuki et al, 2022). Similarly, in North Wales, 24% of strains showed resistance to metronidazole, while 7% resisted clarithromycin (Awad et al, 2020; Shrestha et al, 2023). Due to this escalating resistance, there's a growing recommendation to adopt quadruple regimens as the first-line therapy for *H. pylori* eradication (Kim and Chung, 2020).

Given the complexities surrounding *H. pylori* treatment, the implications of antibiotic resistance, and the profound association with GI lymphomas, there is a pressing need to understand the current patterns of resistance and their implications for treatment strategies (Kim and Chung, 2020). This meta-analysis aims to shed light on the antibiotic resistance patterns of *H. pylori* in GI lymphoma and discuss the potential implications for future treatment strategies.

Methods

Search Strategy

This manuscript was written to comply with PRISMA guidelines (please see **Supplementary material** for details). Adhering to the PICOS (population, intervention, comparison, outcome, study type) framework, a comprehensive literature search was conducted using major electronic databases, including Google Scholar, Embase, Cochrane Library, PubMed, and Ovid, up to August 2023. The search strategy was designed to identify all relevant studies investigating the antibiotic resistance patterns of *H. pylori* in GI lymphoma. The following keywords and their combinations were used: "*Helicobacter pylori*", "Antibiotic resistance", "Gastrointestinal lymphoma", "Clarithromycin", "Amoxicillin", "Tetracycline", "Levofloxacin", and "Metronidazole".

Inclusion and Exclusion Criteria

For this meta-analysis, the studies were carefully chosen based on specific criteria to ensure both relevance and reliability. We included studies that investigated the antibiotic resistance patterns of *H. pylori* in patients with gastrointestinal lymphoma. These studies should have provided data on antibiotic resistance rates, notably amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin resistance. Furthermore, we preferred research that reported outcomes such as all-cause mortality (AM), tumor progression rate (TPR), clinical cure rate (CCR), or the long-term recurrence rate (LRR) following initial cure in patients with GI lymphoma, whether they exhibited resistance to one or several of the aforementioned antibiotics. Studies that utilized culture-based methods or advanced molecular techniques for determining antibiotic resistance were particularly valued, as were those that transparently outlined methodologies for antibiotic susceptibility testing. Both prospective and retrospective observational studies, which encompassed a range of designs from cohort and case-control to cross-sectional study, were considered. However, the scope was limited to the studies published either in English or those accompanied by an available English translation.

On the flip side, we excluded studies that did not specifically focus on the antibiotic resistance patterns of *H. pylori* in GI lymphoma patients or those that failed to provide explicit resistance rates for the antibiotics under consideration. Types of publications, such as case reports, review articles, editorials, and expert opinions, were deemed outside our purview. Additionally, any studies marred by unclear methodologies, incomplete datasets, or those that manifested as duplicates or had overlapping datasets were also systematically omitted from our analysis.

Data Extraction

For each eligible study, the data were meticulously extracted by two independent reviewers to ensure accuracy and consistency. Discrepancies between the reviewers were resolved through discussion or, if necessary, consultation with a third reviewer. The extracted data included study characteristics (e.g., author, publication year, study design, and country of origin), patient demographics (e.g., age,

gender, and number of participants), details of *H. pylori* antibiotic resistance, and AM, TPR, CCR, and LRR following initial cure in patients with GI lymphoma.

Bias Assessment of Selected Literatures

To guarantee the validity and reliability of the findings from our meta-analysis, a rigorous assessment of potential biases in the selected studies was undertaken. We utilized the Cochrane Collaboration, which is the tool renowned for its comprehensive evaluation of the risk of bias in randomized trials. This tool assesses various domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was critically appraised and categorized as 'low risk', 'high risk', or 'unclear risk' of bias.

To offer a visual representation of our bias assessment, we employed the "robvis" R package, generating a traffic light plot that provided a succinct overview of the risk of bias across the selected studies. This comprehensive assessment was conducted collaboratively with two independent reviewers who led the evaluation. In cases of disagreement or ambiguity, discussions were held to reach a consensus. If mutual agreement remained elusive, a third reviewer was consulted to provide authoritative resolution, ensuring the integrity and thoroughness of our bias assessment process.

Statistical Analysis

The primary aim of this meta-analysis was to discern the relationship between the antibiotic resistance patterns of *H. pylori* and various outcomes in patients with GI lymphoma. Specifically, we focused on AM, TPR, CCR, and LRR observed after the initial cure in patients with GI lymphoma. To synthesize the data quantitatively, a random-effects model was utilized, considering both intra-study and inter-study variations. We gauged the heterogeneity of the incorporated studies using the I^2 statistic, with values surpassing 50% indicative of considerable heterogeneity. When faced with pronounced heterogeneity, we performed subgroup analyses to pinpoint potential sources, which could range from variances in study design and patient demographics to the methodologies adopted for gauging antibiotic resistance. Our results were expressed in terms of odds ratios (ORs) for dichotomous outcomes and standard mean differences (SMDs) for continuous outcomes, each with a 95% confidence interval (CI). We set a threshold *p*-value of less than 0.05 to demarcate statistical significance in all our analyses, and all computations were performed using the RevMan 5.4 software (Cochrane Collaboration, London, UK).

Results

In our comprehensive search, 2325 articles were identified. Following a rigorous screening process that included evaluations for duplicates, full-text accessibility, and alignment with our inclusion criteria, we shortlisted 9 pertinent studies (Bilgilier et al, 2016; Chen et al, 2005; Kim et al, 2016; Kuo et al, 2012; Li et al, 2016; Nakamura et al, 2005; Nakamura et al, 2012; Wündisch et al, 2005; Wündisch et al, 2012) for inclusion in our meta-analysis, as illustrated in Fig. 1. These studies

Table 1. Characteristics of the selected studies.

Reference	Year	Age (years)	n	Types of GI lymphoma (n)	Resistant drug (n)	Outcomes
Bilgilier et al (2016)	2016	72 ± 9	17	MALT	Clarithromycin (7)	AM, CCR, TPR
Chen et al (2005)	2005	MALT: 60 (30−84); DLBCL: 56 (21−83)	58	MALT (34); DLBCL (24)	clarithromycin (MALT: 11, DLBCL: 8), metronidazole (MALT: 8)	AM, LRR
Kim et al (2016)	2016	58.8 ± 9.8	54	MALT	clarithromycin (10), amoxicillin (5)	AM, CCR, TPR
Li et al (2016)	2016	53 ± 4	103	MALT	clarithromycin (35), clarithromycin + amoxicillin (15), amoxicillin (7), clarithromycin + metronidazole (8)	AM, CCR, TPR
Nakamura et al (2005)	2005	61.7 (16–84)	113	MALT (96); DLBCL (17)	clarithromycin (MALT: 40, DLBCL: 2), metronidazole (11), tetracycline (MALT: 6, DLBCL: 4)	AM, LRR
Nakamura et al (2012)	2012	61 (16–87)	323	MALT	clarithromycin (45), clarithromycin + levofloxacin (16), amoxicillin resistance (12), clarithromycin + metronidazole (8)	AM, LRR
Wündisch et al (2012)	2012	62 (29–88)	120	MALT	clarithromycin (27), amoxicillin (12), clarithromycin + amoxicillin (13)	AM, TPR, LRR
Wündisch et al (2005)	2005	60 (18–76)	96	MALT	clarithromycin (10), amoxicillin (4), clarithromycin + amoxicillin (3)	AM, LRR
Kuo et al (2012)	2012	MALT: 63 (34–88); DLBCL: 55 (35–83)	50	MALT (16); DLBCL (34)	clarithromycin (MALT: 4, DLBCL: 2), amoxicillin (MALT: 4), clarithromycin + amoxicillin (DLBCL: 3)	AM, TPR, CCR

Abbreviations: GI, gastrointestinal; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; AM, all-cause mortality; CCR, clinical cure rate; TPR, tumor progression rate; LRR, long-term recurrence rate.

collectively included 934 patients diagnosed with GI lymphoma. Some of these patients underwent first-line antibiotic therapy aimed at *H. pylori* eradication, whereas others had *H. pylori* samples extracted for laboratory-based antibiotic resistance profiling. All studies provided detailed records on the progression, outcomes, and associated parameters of gastrointestinal lymphoma. The characteristics of these studies, including their unique features and the nature of the recorded data, are presented in Table 1. Our risk-of-bias assessment showed that, among the 9 studies, 1 study displayed a marginal, non-significant bias. In contrast, the remaining 8 studies were evaluated as having a low risk of bias, as illustrated in Figs. 2,3. All included studies reported AM rates among patients with GI lymphoma. Notably, 9 studies documented AM data for patients exhibiting resistance to clarithromycin. Our analysis revealed a statistically significant difference in AM between patients resistant to clarithromycin and the control group, which comprised patients without resistance to the standard antibiotics used for *H. pylori* eradication ($I^2 = 98\%$, $p < 0.00001$; Random: standard mean difference, SMD: 2.27, 95% CIs: 0.63 to 3.91, $p = 0.007$), as depicted in Fig. 4.

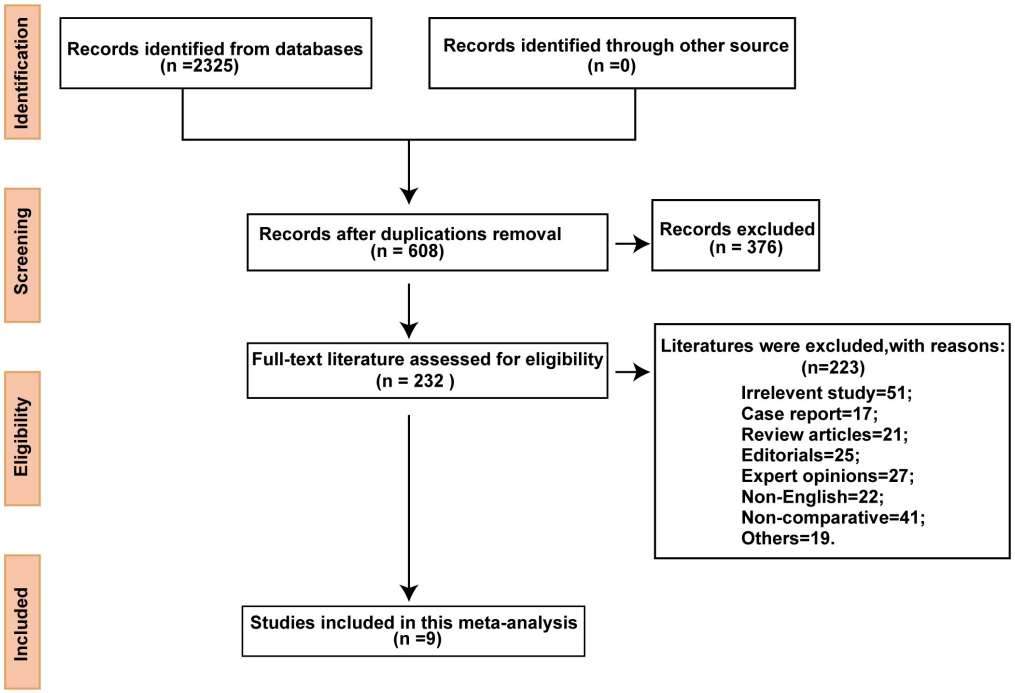

Fig. 1. Flow diagram of the research process.

6 studies provided AM data for patients resistant to amoxicillin, indicating no significant difference in AM between these patients and the control group ($I^2 = 96\%$, $p < 0.00001$; Random: SMD: 1.35, 95% CIs: –0.54 to 3.25, $p = 0.16$), as shown in Fig. 5. Furthermore, 4 studies reported AM data for patients who were resistant to both clarithromycin and amoxicillin, revealing a significant difference between these patients and the control group ($I^2 = 95\%$, $p < 0.00001$; Random: SMD: 5.13, 95% CIs: 1.78 to 8.48, $p = 0.003$), as illustrated in Fig. 6.

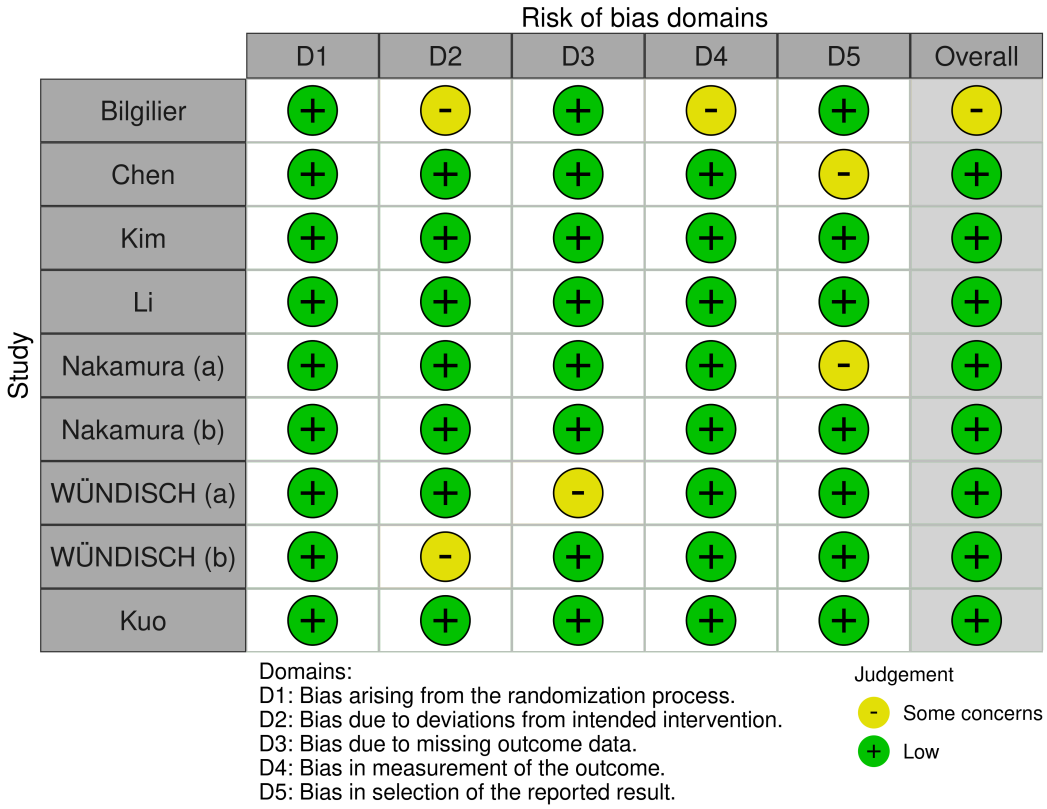

Fig. 2. Traffic light plot of risk of bias item across all reviewed studies.

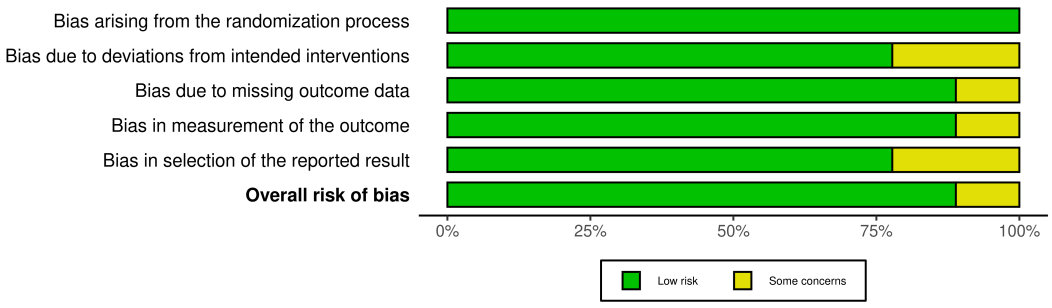

Fig. 3. Distribution of risk of biases in the included studies.

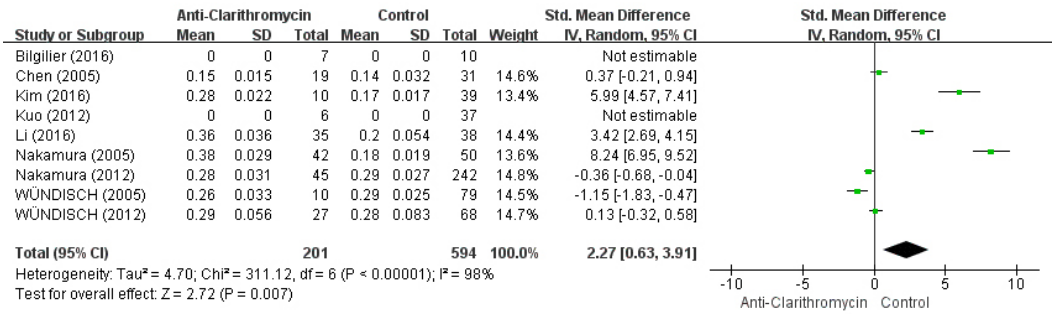

Fig. 4. The effect's forest plot illustrating the effect of clarithromycin resistance on all-cause mortality (AM) in gastrointestinal (GI) lymphoma patients compared to controls.

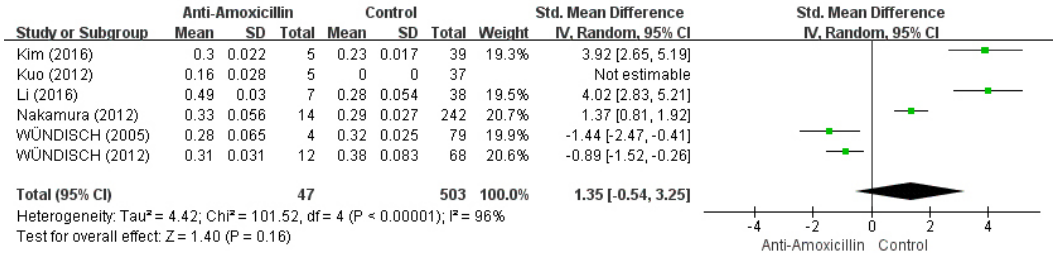

Fig. 5. The effect's forest plot depicting the impact of amoxicillin resistance on AM in GI lymphoma patients, compared to controls.

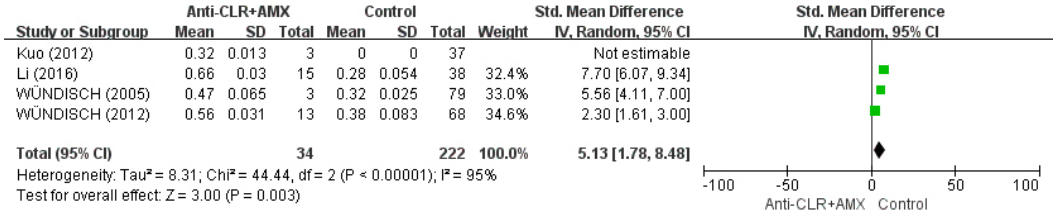

Fig. 6. The effect's forest plot illustrating the impact of combined clarithromycin and amoxicillin resistance on AM in GI lymphoma patients, compared to controls.

4 studies reported CCR after *H. pylori* eradication therapy in patients who were resistant to clarithromycin, indicating a significant impact of clarithromycin resistance on post-eradication CCR (I^2 = 79%, p = 0.003; Random: SMD: –4.12, 95% CIs: –5.42 to –2.82, $p < 0.00001$), as presented in Fig. 7. Additionally, 5 studies documented TPR in patients who were resistant to clarithromycin, revealing a significantly higher TPR in these patients compared to the control group (I^2 = 94%, $p < 0.00001$; Random: SMD: 7.09, 95% CIs: 4.57 to 9.61, $p < 0.00001$), as shown in Fig. 8. Similarly, 4 studies reported TPR for patients who were resistant to amoxicillin, indicating a significantly higher TPR in these patients than in the control group (I^2 = 97%, $p < 0.00001$; Random: SMD: 11.03, 95% CIs: 5.81 to 16.25, $p < 0.0001$), as depicted in Fig. 9.

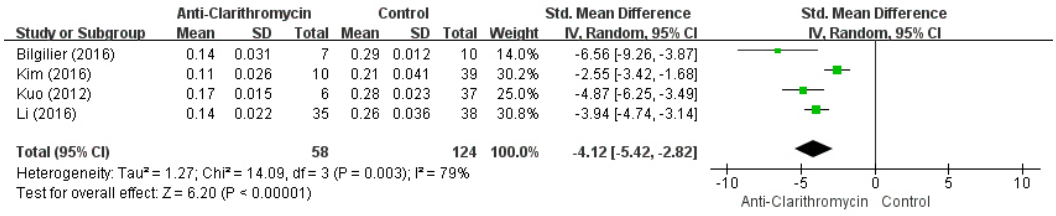

Fig. 7. The effect's forest plot highlighting the influence of clarithromycin resistance on clinical cure rate (CCR) in GI lymphoma patients, compared to controls.

5 studies evaluated LRR in patients with GI lymphoma who were resistant to clarithromycin or not, revealing a significant difference between the two groups (I^2 = 97%, $p < 0.00001$; Random: SMD: 9.31, 95% CIs: 6.16 to 12.47, $p < 0.00001$), as presented in Fig. 10. Among these, 3 studies further reported LRR for patients who were resistant to amoxicillin, indicating a significant statistical difference be-

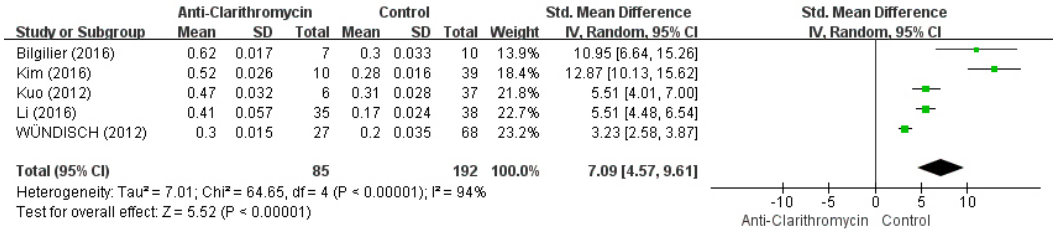

Fig. 8. The effect's forest plot illustrating the impact of clarithromycin resistance on tumor progression rate (TPR) in GI lymphoma patients, relative to controls.

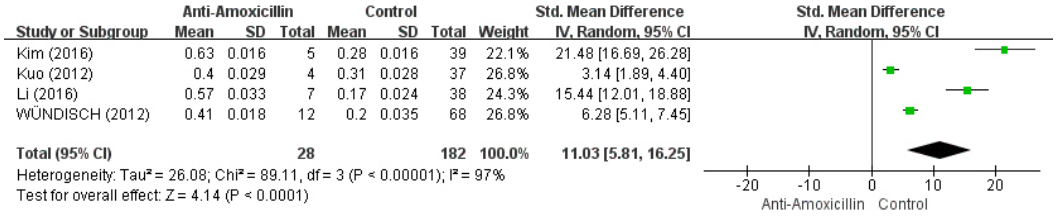

Fig. 9. The effect's forest plot depicting the influence of amoxicillin resistance on TPR in GI lymphoma patients, compared to controls.

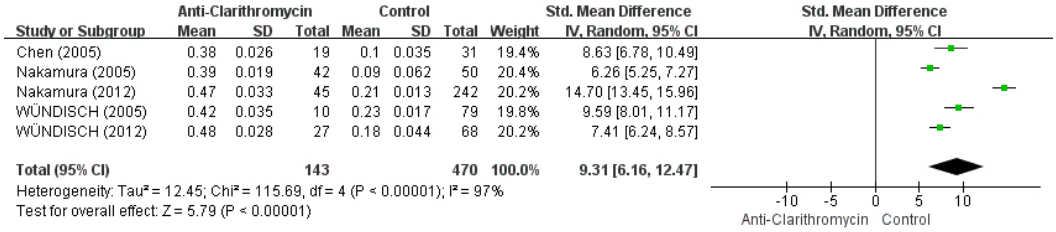

Fig. 10. The effect's forest plot illustrating the impact of clarithromycin resistance on the long-term recurrence rate (LRR) in GI lymphoma patients, relative to controls.

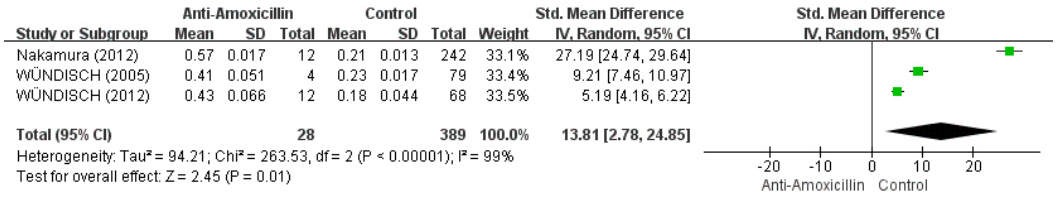

Fig. 11. The effect's forest plot highlighting the influence of amoxicillin resistance on LRR in GI lymphoma patients, compared to controls.

tween these patients and the control group ($I^2 = 99\%$, $p < 0.00001$; Random: SMD: 13.81, 95% CIs: 2.78 to 24.85, $p = 0.01$), as illustrated in Fig. 11.

Lastly, our publication bias assessment, utilizing Egger's quantitative regression analysis and funnel plot visualization (Fig. 12), did not detect any significant bias in the AM data of clarithromycin-resistant patients ($p > 0.05$). However, it's noteworthy that the most of the evaluated outcomes were deemed suboptimal in quality, with no discernible bias in selective reporting.

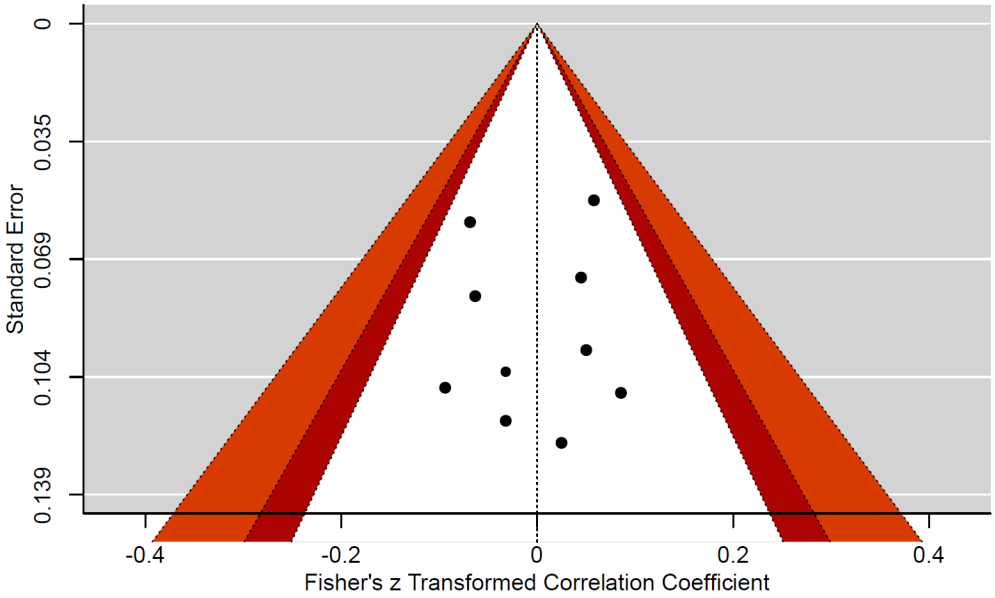

Fig. 12. Funnel plot assessing publication bias for AM in GI lymphoma patients with clarithromycin resistance, compared to controls.

Discussion

The association between *H. pylori* infection and gastrointestinal lymphomas, particularly MALT lymphomas, is well-established (Kim and Chung, 2020; Sena Teixeira Mendes et al, 2014; Montalban and Norman, 2006; Park and Koo, 2014). This meta-analysis aimed to elucidate the antibiotic resistance patterns of *H. pylori* in GI lymphoma and discussed the potential implications for future treatment strategies.

Our analysis revealed a statistically significant difference in AM rates among patients with GI lymphoma who were resistance to clarithromycin compared to those without such resistance. This finding underscores the clinical implications of antibiotic resistance for *H. pylori* eradication. The higher TPR observed in patients who were resistant to clarithromycin and amoxicillin further accentuates the challenges posed by antibiotic resistance in managing these patients.

Furthermore, our findings indicate a significant impact of clarithromycin resistance on post-eradication CCR. This suggests that resistance to clarithromycin may compromise the therapeutic efficacy of eradication regimens, leading to suboptimal clinical outcomes. The TPR in patients who resistant to clarithromycin and amoxicillin was also notably higher, emphasizing the potential adverse clinical trajectory that these patients might experience.

Moreover, LRR in patients with GI lymphoma who were resistant to clarithromycin or not, revealed a significant difference, highlighting the potential long-term implications of antibiotic resistance on disease recurrence and patient prognosis. The observed LRR in patients who were resistant to amoxicillin further supports the notion that antibiotic resistance can have profound implications on the clinical course of GI lymphomas.

Our findings resonate with the recent Maastricht VI Consensus, which proposed two strategies for selecting eradication therapy: individualized, based on antibacterial susceptibility, and empirical, taking into account local resistance data (Malfertheiner et al, 2017). The consensus emphasizes the importance of determining *H. pylori* resistance to antibiotics, especially clarithromycin, before choosing therapeutic strategies. This is particularly pertinent given the decreasing efficacy of therapy regimens owing to rising antibiotic resistance in *H. pylori* strains. The prevalence of this type of resistance varies across countries and is influenced by the overall frequency of antibiotic use.

In light of our findings and insights from the literature, it becomes evident that while *H. pylori* eradication remains a cornerstone in the management of GI lymphomas, the rising tide of antibiotic resistance poses significant challenges. Addressing these challenges requires a multifaceted approach encompassing rigorous resistance monitoring, understanding the underlying molecular mechanisms, and continuous refinement of treatment strategies based on emerging data.

Our meta-analysis, though insightful, is subject to several limitations. The heterogeneity among the included studies, evident in the varied study designs and methodologies, might have influenced our pooled estimates. Although we didn't detect a significant publication bias for AM data in patients resistant to clarithromycin, undetected biases for other outcomes remain a concern. The geographical concentration of our study may have limited the broader applicability of our findings. Relying solely on published data could introduce extraction biases, and the depth of such data may not capture the nuances of individual patient-level information. Our primary focus on clinical outcomes meant sidelining the exploration of molecular mechanisms underlying antibiotic resistance. The evolving nature of the treatment regimens and resistance patterns over the years covered by our study adds another layer of complexity. Additionally, potential unmeasured or unreported confounders inherent in observational study-based meta-analyses could have influence the observed associations. Given these constraints, we recommend a cautious interpretation of our findings, anticipating that future research will provide a more comprehensive perspective.

Conclusion

In conclusion, the landscape of *H. pylori* treatment in the context of GI lymphoma is evolving rapidly. As antibiotic resistance continues to increase, there is an urgent need for innovative strategies that can ensure effective eradication of the bacterium while minimizing the risk of treatment failure. Collaborative efforts between researchers, clinicians, and policymakers are crucial in navigating this complex terrain and ensuring optimal patient outcomes.

Key Points

- Out of 2325 articles reviewed, 9 were selected to examine antibiotic resistance patterns in *H. pylori*, encompassing data from 934 patients with GI lymphoma.
- Resistance to clarithromycin and amoxicillin significantly correlated with increased all-cause mortality in patients with GI lymphoma.
- Clarithromycin resistance negatively affected clinical cure rates after *H. pylori* eradication therapy in patients with GI lymphoma.
- Resistance to clarithromycin and amoxicillin significantly increased tumor progression and cancer recurrence rates in patients with GI lymphoma.

Availability of Data and Materials

All data generated or analyzed in this study are included in the present manuscript.

Author Contributions

PJW: data analysis and drafting the manuscript. NW, JH: data collection and investigation; HM: study design and revision of the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

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This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0103.

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