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Original Article

Association between *TLR10* rs10004195 Gene Polymorphism and Risk of *Helicobacter pylori* Infection: A Meta-analysis

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Abstract

Background and objectives: *Helicobacter pylori* (*H. pylori*) infection can cause multiple secondary digestive disorders. Some studies have found that polymorphisms in Toll-like receptor (*TLR*) genes, including *TLR*10 rs10004195, may be associated with increased susceptibility to *H. pylori* infection. Despite conflicting reports, we conducted a meta-analysis to clarify the relationship between these factors.

Methods: We conducted an exhaustive review, encompassing all relevant literature up to February 2024, using databases such as PubMed, Embase, Web of Science, and the China National Knowledge Infrastructure. We screened studies based on specific criteria and evaluated their quality using the Newcastle-Ottawa scale. Heterogeneity testing and meta-analysis were performed using Stata 17.0 software, and SPSSAU was used for publication bias evaluation and sensitivity analysis.

Results: Eight of the 487 identified studies met the inclusion criteria, comprising 3,004 and 2,140 individuals in the *H. pylori*-positive and negative control groups, respectively. Our results demonstrated that individuals carrying the AA genotype at the *TLR10* rs10004195 locus had a significantly increased likelihood of *H. pylori* infection when analyzed using the recessive genetic model (OR: 1.64, CI: 1.04–2.58, $p = 0.034$). No statistically significant associations were found in the other four genetic models.

Conclusions: Our findings suggest that carrying the *TLR10* rs10004195 AA genotype is associated with a significantly elevated risk of *H. pylori* infection. This information could be used to assess future risk of *H. pylori* infection in healthy individuals and provide personalized health guidance based on individual genetic polymorphisms.

Introduction

Helicobacter pylori (*H. pylori*), a prevalent gastric pathogen, affects over fifty percent of the global population, with more than 10 million individuals newly infected.[1] The occurrence and progression of stomach pathologies, such as peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue lymphoma, have been linked to this infection.[2,3] Interestingly, some individuals have never been infected with *H. pylori* during their lifetime.[4] Studies have shown that susceptibility to infection depends on a combination of *H. pylori* virulence factors, environmental factors, genetic susceptibility of the host, and the effectiveness of the host immune system.[5,6]

Toll-like receptors (TLRs) belong to the pathogen-associated molecular pattern family, which specifically recognizes various pathogenic microorganisms, including *H. pylori*, and activates both specific and non-specific immune responses.[7] TLRs' specific recognition of ligands triggers NF-κB activation, which subsequently promotes the production of inflammation-related cytokines and chemokines.[8,9] TLRs play an essential role in the recognition of *H. pylori* and the subsequent innate and adaptive immune responses.[10,11] *H. pylori* expresses various pathogen-related molecular pattern antigens, including lipopolysaccharide (LPS) and flagellin.[12] TLR10, as a functional receptor, is involved in the innate immune response to *H. pylori* infection. TLR10 can form a heterodimer with TLR2, called the TLR2/TLR10 heterodimer, which functions

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in *H. pylori* LPS recognition.[13–15] A study that employed real-time quantitative polymerase chain reaction and immunohistochemical examination on gastric biopsy specimens from both *H. pylori*-infected patients and uninfected individuals revealed a significant increase in the expression of *TLR10* mRNA and TLR10 in the gastric epithelial cells of infected patients. Upon exposure to heat-killed *H. pylori* or its lipopolysaccharide, the TLR2/TLR10 heterodimer, among the TLR2 subfamily heterodimers, elicited the strongest NF-κB activation. These observations underscore the pivotal role of TLR10 in the immunological defense against *H. pylori* infection.[16]

The presence of genetic variants in TLRs is hypothesized to significantly influence an individual's predisposition to *H. pylori* infection.[17] Accumulating evidence indicates that genetic polymorphisms and expression levels of *TLR2*, *TLR4*, *TLR5*, and *TLR9* can modulate susceptibility to *H. pylori* infection.[18] *TLR10* rs10004195 is a polymorphic site located within the promoter region of the *TLR10* gene, where the nucleotide changes from T to A.[19] Recently, numerous case-control studies have found a correlation between the *TLR10* rs10004195 gene polymorphism and susceptibility to *H. pylori* infection. However, due to limited statistical certainty in studies with small sample sizes, results have indicated that certain *TLR10* rs10004195 genotypes may increase, decrease, or have no effect on susceptibility to *H. pylori* infection. To further explore the role of *TLR10* rs10004195 in the risk of *H. pylori* infection, we conducted a quantitative analysis of high-quality research findings from these studies, aiming to eliminate the impact of factors such as insufficient sample sizes.[20]

Materials and methods

Literature search

Our meta-analysis adhered to the guidelines in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Checklist (File S1).[21–24] The databases, containing PubMed, EMBASE, Web of Science, and China National Knowledge Infrastructure, were independently searched by two authors, including literature from database establishment to February 2024. The search keywords were: "Polymorphism" or "Polymorphisms" or "Variant", "*Helicobacter pylori* infection" and "Toll-like receptor". No restrictions were placed on publication dates or language.

Criteria for inclusion and exclusion

The inclusion criteria were as follows: (a) A case-control study that assesses the relationship between *TLR10* rs10004195 polymorphism and the risk of *H. pylori* infection; (b) Availability of exact genotype frequencies, either directly obtained or indirectly calculated from the literature; and (c) Genetic loci in the control group assessed for Hardy-Weinberg equilibrium conformity. The exclusion criteria were: (a) Studies that did not adhere to a case-control design; (b) Literature with missing or duplicate data; and (c) Among similar studies published by the same author, the research with the largest sample size was selected.

Data extraction and research quality evaluation

Two researchers independently retrieved and input information based on the predefined inclusion and exclusion criteria, followed by data comparison. In cases of disputed literature data, discussions were held with the corresponding author to reach a consensus. Extracted data included the first author, publication year, continent (country), age, gender, sample size, Hardy-Weinberg equilibrium conformity, and genotype distribution. The quality assessment of the articles was conducted utilizing the Newcastle-Ottawa scale.[25] The criteria encompassed three key dimensions: the method of selecting cases and controls (0–4); the degree of comparability between groups (0–2); and the assessment of exposure outcomes and relevant factors (0–3).

Statistical analysis

Based on the genotype distribution information extracted from each included study, SPSSAU was used to calculate the OR and 95% CI for each genetic model. Heterogeneity testing and meta-analysis were performed using Stata 17.0 software. To account for heterogeneity, a random effects model was initially applied to aggregate and contrast outcomes. When $p < 0.10$ or $I^2 > 50\%$, heterogeneity was indicated, and the random effects model was used for analysis. Otherwise, a fixed effects model was applied. Publication bias evaluation and sensitivity analysis were conducted using SPSSAU.

Results

Literature retrieval and evaluation results

Figure 1 illustrates the flowchart of the search process for the current meta-analysis. In total, eight studies investigating *TLR10* rs10004195 were included, most of which were conducted in Asia. The total number of subjects was 5,144, including 3,004 individuals in the *H. pylori*-positive group and 2,140 in the negative control group. Table 1 presents a comprehensive overview of the fundamental details and genotype distribution in the literature (Table S1).[10,26–32] The Newcastle-Ottawa scale assessment revealed consistently high quality across all studies, with an average score of 8.00, as shown in Table 2.[10,26–32]

Allele and genotype-wide meta-analysis

After conducting a meta-analysis on each of the five genetic models from the eight investigations included in this meta-analysis, the results revealed the following: The overall detection rate of the recessive homozygote AA genotype was 28.5%. In the *H. pylori*-positive group, the detection rate of the recessive homozygote AA genotype was 31.8%, while in the negative control group, this proportion was only 23.9%. Using the recessive genetic model (AA vs. AT+TT), individuals with the *TLR10* rs10004195 AA genotype were found to have a significantly elevated risk of contracting *H. pylori* infection compared to those with the other two genotypes (OR = 1.64, 95% CI: 1.04–2.58, $p = 0.034$), as shown in Table 3 and Figure 2. No statistically significant relationships were found in any of the other genetic models (Figs. S1–S4).

Between-study publication bias and sensitivity analysis

We conducted a publication bias analysis on the literature included in this study regarding the TLR10 rs10004195. The Egger's test results showed no statistically significant asymmetry (p: 0.308–0.883), indicating no significant publication bias (Figs. S5–S9). Sensitivity analysis results indicated that the current results were stable; regardless of which study was excluded, no significant change was observed in the combined effect size.

Discussion

Genetic variations in *TLR10* have been linked to various infectious diseases, such as complex skin and subcutaneous tissue infections, tuberculosis, bacterial meningitis, and Congo hemor-

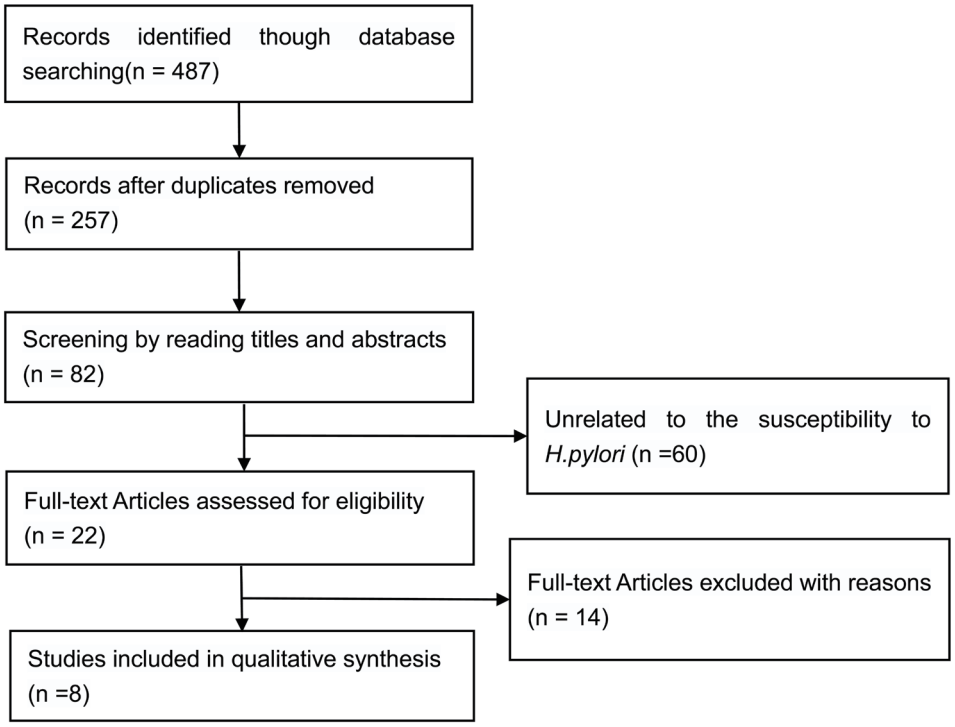

Fig. 1. PRISMA flowchart illustrating the progression of the literature review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

rhagic fever.[33–36] Recent studies have also found that the *TLR10* rs10004195 gene polymorphism may influence the risk of host susceptibility to *H. pylori* infection to a certain extent.[28] However, the conclusions drawn by different studies are not entirely consistent. Our findings reveal a notably elevated detection frequency of the recessive homozygous AA genotype in the *H. pylori*-positive cohort compared to the negative control group. Furthermore, carrying the *TLR10* rs10004195 AA genotype significantly increases

Table 1. Attributes of all case-control investigations included in the meta-analysis

Literature	Year	Continent (Country)	Age	Gender		Size of the sample	HWE	Genotype type frequency (Case)			Genotype type frequency (Control)		
				HP (+)	HP (–)								
			HP (+)/ HP (–)	M/F	M/F	HP (+)/ HP (–)*		AA	AG	GG	AA	AG	GG
Emad M. Eed[10]	2020	Aisa (Arabia)	45±17.7/ 42±22.3	117/93	41/39	210/80	Yes	124	61	25	33	30	17
Fu-bing Tang[26]	2015	Aisa (China)	48.9±6.4/ 49.5±6.8	731/780	473/569	1,486/1,008	Yes	498	712	276	308	493	207
Laith AL-Eitan[27]	2021	Aisa (Jordan)	–	–	–	223/217	Yes	11	8	204	28	7	182
Sevgi Kalkanli Tas[28]	2020	Aisa-Europe (Turkey)	47.7±12/ 51.2±12	83/122	84/111	205/195	Yes	54	37	114	7	38	150
Taweesak Tongtawee[29]	2018	Aisa (Thailand)	46±1.5/ 42±2.5	71/133	65/131	204/196	Yes	59	10	135	22	123	51
Ying Su[30]	2016	Aisa (China)	–	–	–	418/234	Yes	130	190	98	72	125	37
Xin-juan Yu[31]	2014	Aisa (China)	48.7±10.8/ 49.4±12.1	142/59	130/52	201/182	Yes	54	87	60	33	93	56
M. Ravishankar Ram[32]	2015	Asia (Malaysia)	–	–	–	57/28	Yes	24	18	15	9	11	8

*Methods for confirming *H. pylori* infection in the included literature: rapid urease test, serum anti-*H. pylori* antibody detection, C13/14 breath test; F, Female; HP, *H. pylori*; HWE, Hardy-Weinberg Equilibrium; M, Male; –, not extracted.

Table 2. Evaluation of the quality of eight case-control studies using the Newcastle-Ottawa scale criteria

Literature	Selection of enrolled study subjects	Between-group comparability	Exposure outcomes and factors	Total
Emad M. Eed[10]	3	2	3	8
Fu-bing Tang[26]	3	2	3	8
Laith AL-Eitan[27]	4	2	3	9
Sevgi Kalkanli Tas[28]	4	2	3	9
Taweesak Tongtawee[29]	3	2	2	7
Ying Su[30]	3	2	3	8
Xin-juan Yu[31]	3	2	3	8
M. Ravishankar Ram[32]	3	2	2	7
Average	3.25	2	2.75	8.00

Table 3. Meta-analysis results of the relationship between *TLR10* rs10004195 gene polymorphism and the risk of *H. pylori* infection

Comparison	N	Association analysis			Mode	Heterogeneity analysis	
		OR	95%CI	p		*p*	I ²(%)
A vs. T	8	1.12	(0.79, 1.59)	0.512	Random	<0.001	91.90
AA vs. AT+TT	8	*1.64*	*(1.04, 2.58)*	*0.034*	Random	<0.001	87.20
AA vs. TT	8	1.37	(0.82, 2.29)	0.235	Random	<0.001	85.30
TT vs. AT+AA	8	1.14	(0.65, 2.03)	0.646	Random	<0.001	92.70
TA vs. TT	8	0.64	(0.32, 1.25)	0.191	Random	<0.001	92.50

CI, confidence interval; N, the number of articles; OR, odds ratio; *p*, *p*-value. Results showing a significant correlation ($p < 0.05$) are highlighted in italic for emphasis.

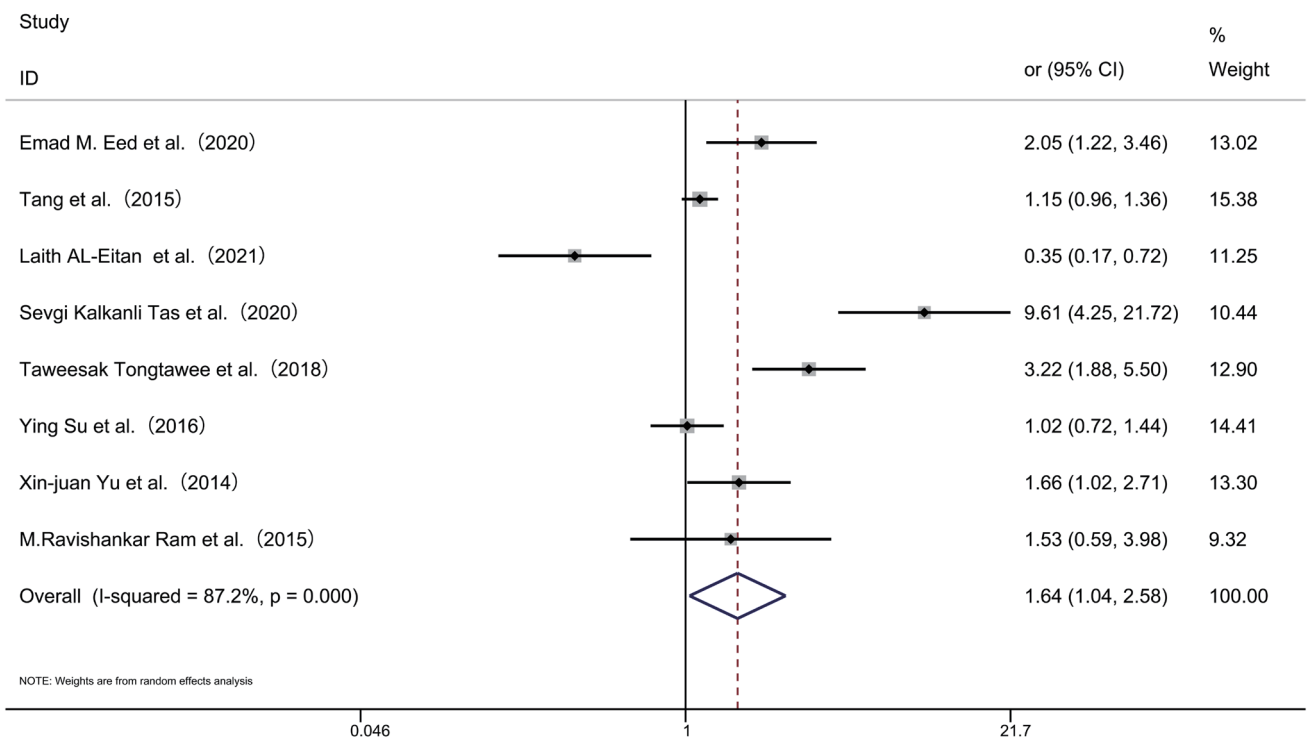

Fig. 2. Forest plot illustrating the associations between *TLR10* rs10004195 polymorphism and the risk of *H. pylori* infection analyzed under the recessive genetic model (AA vs. AT+TT). CI, confidence interval; OR, odds ratio.

the risk of *H. pylori* infection (OR = 1.64) when analyzed using a recessive genetic model.

Previous studies conducted by Taweesak Tongtawee and Xinjuan Yu also support our conclusion. Interestingly, research by M. Ravishankar Ram indicated no correlation between *TLR10* rs10004195 polymorphism and *H. pylori* infection among Malaysian individuals.[29,31,32] We attribute this discrepancy to the relatively small sample size in their study and to Malaysia's status as a country of multi-ethnic immigrants. Our research, which integrates all currently published high-quality studies, establishes a substantial association between *TLR10* rs10004195 polymorphism and the susceptibility to *H. pylori* infection in human hosts, with stable results and no evident publication bias. However, the study participants were predominantly from Asian populations, and thus no stratified analysis by ethnicity was conducted. If further research provides sufficient data, meta-analyses with ethnic stratification could yield more valuable results.

TLR10 has been suggested to be a primary receptor involved in the innate immune response elicited by *H. pylori* infection.[16] Previous studies have shown that the expression of TLR10 and its heterodimer on gastric mucosal epithelium can contribute to the immune reaction following *H. pylori* infection by augmenting NF-κB activation and promoting interleukin-1β production.[37,38] *TLR10* gene polymorphisms can modulate the balance between pro-inflammatory and anti-inflammatory reactions, thereby regulating susceptibility to infections and autoimmune diseases.[39] The rs10004195 SNP in *TLR10*'s promoter may affect TLR2/10 heterodimer-mediated immune responses.[40] This variant in *TLR10* could impair the ability of the TLR2/10 heterodimer on the gastric mucus layer to recognize *H. pylori* LPS. Another study found that, compared to other genotypes at the *TLR10* rs10004195 locus, the AA homozygous genotype is associated with a heightened degree of inflammation in Thai patients with *H. pylori*-related gastritis.[15] Therefore, the evidence suggests that *TLR10* rs10004195 can influence the host's ability to recognize *H. pylori* and modulate the functionality of the TLR2/10 heterodimer, thereby affecting the immune response to *H. pylori* infection.

Limitations and future directions

Our meta-analysis did not conduct a stratified analysis based on geographic regions, which is a major limitation since the study populations we included were primarily from Asian regions. Additionally, all the studies in the meta-analysis were case-control studies. Although we retrieved a population-based study conducted by Julia Mayerle,[41] we were unable to extract the genotype frequencies necessary for our analysis from their article.

Our current analysis suggests that the *TLR10* rs10004195 gene polymorphism can serve as an important reference indicator for predicting the risk of *H. pylori* infection in healthy individuals. In the future, it is anticipated that a polygenic risk score model for *H. pylori* infection prediction will be developed, incorporating information from multiple loci, including this one. Of course, establishing such a prediction model will require a large amount of high-quality data for support. Therefore, future research efforts are essential to explore the polymorphism of this gene locus and the risk of *H. pylori* infection in non-Asian populations. Additionally, cohort studies need to be conducted in multiple regions.

Conclusions

By conducting a meta-analysis of high-quality studies on this relevant topic, our research has unified the previous discrepancies in studies examining the relationship between *TLR10* rs10004195 gene polymorphism and susceptibility to *H. pylori* infection, arriving at a conclusion that is more reliable than those drawn from individual studies. Individuals carrying the *TLR10* rs10004195 AA genotype have a significantly higher risk of *H. pylori* infection. Therefore, in clinical applications, patients can be classified based on their genetic characteristics, including the findings from this study, to assess their genetic susceptibility to *H. pylori* infection. Incorporating individual gene polymorphisms enhances the precision of *H. pylori* infection risk assessment, allowing for more personalized health recommendations for patients.

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Conflict of interest

QJD has been an editorial board member of *Exploratory Research and Hypothesis in Medicine* since December 2018. The authors have no other conflicts of interest regarding the publication of this article.

Author contributions

Design of the study (QJD, LLW), selection and data collection process (ZJX, WL, WLL), evaluation of methodological criteria (ZJX, DLJ), disagreement consultation (QJD), and corrections on formulations and illustrations (QJD, LLW). All authors approved the final manuscript.

Data sharing statement

No additional data are available.

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