ISSN 1519-6984 (Print)
ISSN 1678-4375 (Online)

Original Article

Association between genetic polymorphisms and host susceptibility to *Helicobacter pylori* infection: a systematic review and meta-analysis

Associação entre polimorfismos genéticos e suscetibilidade do hospedeiro à infecção por *Helicobacter pylori*: uma revisão sistemática e meta-análise

H. C. O. Santos-Dutra[a,b], C. C. P. Costa[b], D. N. Maciel[a], A. F. P. L. Ramos[a], R. S. Santos[b*] and M. S. Barbosa[a*]

[a]Universidade Federal de Goiás – UFG, Instituto de Patologia Tropical e Saúde Pública – IPTSP, Núcleo de Estudo em *Helicobacter pylori* – NEHP, Goiânia, GO, Brasil

[b]Universidade Federal de Goiás – UFG, Instituto de Ciências Biológicas – ICB, Núcleo de Pesquisas em Neurogenética – NEUROGENE, Goiânia, GO, Brasil

Abstract

Host genetic polymorphisms are predictive markers of susceptibility to infections. The gram-negative bacterium *Helicobacter pylori* can cause inflammation and molecular changes with various clinical outcomes. This study aimed to characterize host molecular biomarkers associated with susceptibility to *H. pylori* infection through a systematic review using PRISMA guidelines. The research was conducted across five databases, selecting observational studies without time or language restrictions and excluding animal studies. The protocol was registered in PROSPERO (CRD42023409085). Out of 4.683 articles, 35 were included, identifying 43 polymorphisms in 30 genes. 06 polymorphisms were analyzed in the meta-analysis: *IL1B*-C31T (rs1143627), *IL1B*-C511T (rs16944), *TLR1* C>T (rs4833095), *TLR4* A>G (rs4986790), *TLR10* A>T (rs10004195), and *TNF308* G>A (rs1800629). *IL1B*-C511T and *TLR4* A>G increased susceptibility, while *TLR1* C>T and *TLR10* A>T offered protection. Host genetic determinants are strongly related to infection susceptibility. This study identified genomic variants and characterized the host genetic risk profile, contributing to targeted approaches for the target population and personalized medicine in the prevention, diagnosis, and treatment of *H. pylori* infection.

Keywords: bacteria, precision medicine, systematic review, meta-analysis.

Resumo

Os polimorfismos genéticos no hospedeiro são marcadores preditivos de suscetibilidade a infecções. A bactéria gram-negativa *Helicobacter pylori*, pode causar inflamação e alterações moleculares com diversos desfechos clínicos. Este estudo teve como objetivo caracterizar biomarcadores moleculares do hospedeiro associados à suscetibilidade à infecção por *H. pylori*, através de uma revisão sistemática usando as diretrizes PRISMA. A pesquisa foi realizada em cinco bases de dados, selecionando estudos observacionais sem restrições de tempo ou idioma e excluindo estudos com animais. O protocolo foi registrado na PROSPERO (CRD42023409085). De 4.683 artigos, 35 foram incluídos, identificando 43 polimorfismos em 30 genes. 06 polimorfismos foram analisados na meta-análise: *IL1B*-C31T (rs1143627), *IL1B*-C511T (rs16944), *TLR1* C>T (rs4833095), *TLR4* A>G (rs4986790), *TLR10* A>T (rs10004195) e *TNF308* G>A (rs1800629). *IL1B*-C511T e *TLR4* A>G aumentaram a suscetibilidade, enquanto *TLR1* C>T e *TLR10* A>T ofereceram proteção. Os determinantes genéticos do hospedeiro estão fortemente relacionados à suscetibilidade à infecção. Este estudo identificou variantes genômicas e caracterizou o perfil de risco genético do hospedeiro, contribuindo para abordagens específicas para população-alvo e medicina personalizada na prevenção, diagnóstico e tratamento da infecção por *H. pylori.*

Palavras-chave: bactéria, medicina de precisão, revisão sistemática, meta-análise.

1. Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative bacillus, microaerophilic, which colonizes the stomach of more than 40% of the population (Li et al., 2023). Its incidence rate can reach up to 90% in developing countries, such as Brazil (Bassagh et al., 2019). Transmission can occur through oral-oral, fecal-oral, iatrogenic, and zoonotic routes, with person-to-person transmission being crucial for the bacteria's spread (Atapoor et al., 2014).

*e-mail: rdssantos@ufg.br; santiago@ufg.br
Received: October 3, 2024 – Accepted: January 5, 2025
Editor: Marcelo A. M. Esquisatto

This is an Open Access article distributed under the terms of the Creative Commons Attribution license (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Since 1994, *Helicobacter pylori* has been classified as a Group I carcinogen by the International Agency for Research on Cancer (IARC), being recognized as the primary risk factor for gastric cancer (IARC, 2014). Chronic infection with this oncobacterium is considered the main cause of non-cardia gastric cancer, accounting for almost all cases of this disease. Globally, gastric cancer is one of the leading causes of cancer-related mortality, resulting in over 700,000 deaths annually (Sung et al., 2021).

Although most carriers of the bacterium do not present clinical symptoms, infection by this microorganism can result in a range of pathological conditions, such as gastritis, peptic ulcer, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphomas (MALT lymphomas) (Fischbach and Malfertheiner, 2018). These outcomes result from the interaction of various factors, including environmental aspects, social factors, characteristics of the gastric environment, bacterial virulence, and host genetics (Amieva and Peek Junior, 2016). Additionally, the treatment of *Helicobacter pylori* infection faces increasingly significant challenges due to the growing prevalence of multi-antibiotic-resistant strains. The World Health Organization has classified this antimicrobial resistance as a global priority (Savoldi et al., 2018), highlighting the urgency of developing more effective therapeutic strategies.

The host's genetic conditions, including polymorphisms, are crucial susceptibility factors that can worsen the clinical presentation of the infection due to an imbalance in the host-parasite relationship. Single Nucleotide Polymorphisms (SNPs) in genes encoding components of the response to bacterial infection may play a significant role in modulating the host immune response and susceptibility to *H. pylori* infection (Ramis et al., 2017; Tas et al., 2020).

The bacterium is highly inducer of immune response in the gastric mucosa, inducing the production of inflammatory cytokines by epithelial cells. The predominant response is from the innate immune system, mediated by pattern recognition receptors (PRRs) (Abdiev et al., 2010; Schmausser et al., 2004).

Despite scientific advancements in researching this interaction, there is a significant gap in understanding the genetic basis that influences individual response to the infection. Therefore, the objective of this systematic review with meta-analysis is to identify potential molecular biomarkers in the host associated with susceptibility to *H. pylori* infection. The construction of a genetic panel will contribute to precision medicine, allowing for a more personalized approach in the diagnosis and treatment of the infection.

2. Materials and Methods

2.1. Registration

This systematic review was structured based on the research question: "Which host genetic polymorphisms are associated with increased susceptibility to *Helicobacter pylori* infection?" The protocol for this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42023409085), in accordance with the guidelines of the Joanna Briggs Institute (JBI) for the Etiology and Risk chapter (Moola et al., 2020). Additionally, the protocol was shaped according to the instructions provided by *Helicobacter pylori* Study Center/Neurogenetics Research Center (Santos et al., 2023).

2.2. Search strategy and criteria for inclusion

We employed the acronym PEO (Population, Exposure, Outcome), where P = Population infected with *H. pylori*, E = Presence of genetic polymorphisms susceptible to *H. pylori* infection, and O = Association with *H. pylori* infection, to formulate the inclusion criteria and establish the search strategy.

Observational articles that aligned with the guiding question and were associated with *H. pylori* infection were included without temporal or linguistic restrictions. Review articles, animal studies, duplicates, or those that did not directly address the guiding question were excluded from the analysis.

The search strategy was executed using MeSH terms and keywords in the following databases: Regional Portal of the BVS, EMBASE, National Center for Biotechnology Information (NCBI)/PubMed, Scopus, and Web of Science (Science and Social Science Citation Index), as illustrated in Table 1.

2.3. Study selection

The study selection was conducted by two independent reviewers (HCOS and DNM), aided by the Rayyan® web application, divided into two phases. In Phase 1, articles were assessed based on their titles and abstracts, while in Phase 2, the articles were reviewed in full. All discrepancies were resolved by a third reviewer (AFPLR).

2.4. Risk of bias

The selected articles underwent a bias analysis using the Joanna Briggs Institute (JBI) Critical Assessment Tool for each study type. The assessment was conducted by two independent reviewers (HCOS and CCPC), with all discrepancies resolved by consensus. Questions were answered according to the options "Yes", "No", "Unclear", or "Not applicable". Articles that had more than 60% of questions answered with "Yes" were considered to have a low risk of bias (Muka et al., 2020).

2.5. Data extraction and synthesis

The data were extracted using Microsoft Excel®, by two independent reviewers (HCOS and CCPC). For compilation and descriptive analysis, the following information was collected: (1) first author and year of publication; (2) study design; (3) population; (4) ethnicity; (5) sample size; (6) sex of the case population; (7) sex of the control population; (8) mean age of the case population; (9) mean age of the control population; (10) gene; (11) gene localization; (12) genotyping methods; (13) polymorphism analyzed; (14) type of polymorphism; (15) rs; (16) genotypic and allele for case and control groups; (17) comparison; (18) chi-square value; (19) odds ratio (OR) - 95% confidence interval (95% CI); and (20) p value.

Table 1. Search strategy for each database.

Databases	Search strategy
BVS	((“Helicobacter pylori”) OR (“H. pylori”) OR (“Campylobacter pylori”) OR (“Campylobacter pyloridis”)) AND ((“Polymorphisms, Genetic”) OR (“Genetic Polymorphism*”) OR (“Genetic susceptibility”)) AND (“Infection”)
EMBASE	((‘Helicobacter pylori’ OR ‘Campylobacter pylori’ OR ‘Campylobacter pyloridis’ OR ‘Campylobacter pyloris’ OR ‘Helicobacter infections’ OR ‘Helicobacter pylori infection’) AND ‘genetic polymorphism’ OR ‘polymorphism (genetics)’ OR ‘polymorphism, genetic’) AND ‘infection’
NCBI / PubMed	((“Helicobacter pylori”) OR (“H. pylori”) OR (“Campylobacter pylori”) OR (“Campylobacter pyloridis”)) AND ((“Polymorphisms, Genetic”) OR (“Genetic Polymorphism*”) OR (“Genetic susceptibility”)) AND (“Infection”)
SCOPUS	TITLE-ABS-KEY (((“Helicobacter pylori”) OR (“H. pylori”) OR (“Campylobacter pylori”) OR (“Campylobacter pyloridis”)) AND ((“Polymorphisms, Genetic”) OR (“Genetic Polymorphism*”) OR (“Genetic susceptibility”)) AND (“Infection”))
WEB OF SCIENCE	((“Helicobacter pylori”) OR (“H. pylori”) OR (“Campylobacter pylori”) OR (“Campylobacter pyloridis”)) AND ((“Polymorphisms, Genetic”) OR (“Genetic Polymorphism*”) OR (“Genetic susceptibility”)) AND (“Infection”)

2.6. Statistical analysis

The association between SNPs and susceptibility to *H. pylori* infection was assessed using odds ratio (OR) calculations and 95% confidence intervals (CIs). The OR was obtained by comparing two genetic models: the allelic model (wild vs. mutant) and the dominant model (heterozygous + mutant vs. wild). The heterogeneity among the selected studies was analyzed using the Higgins inconsistency test (I^2).

The choice of meta-analytic model depends on the heterogeneity test among the studies. When I^2 is less than 25%, the fixed-effect model (Mantel-Haenszel method) was applied, assuming that differences between effect estimates are merely due to chance. Conversely, when I^2 is between 25% and 75%, the random-effects model (DerSimonian- Laird method) is used. I^2 values between 25% and 75% indicate moderate heterogeneity, while values above 75% indicate high heterogeneity.

Publication bias was assessed using a funnel plot, as described by Egger et al. (1997), and asymmetry was estimated using linear regression with the Egger test. A p value < 0.05 in the Egger test indicates a strong likelihood of publication bias. All statistical tests were performed using RStudio® software (version 4.3.2).

3. Results

We identified a total of 4.683 articles after implementing the search strategy across databases. Among these, 3.621 were flagged as duplicates in the search databases and subsequently excluded. Following this exclusion, 2.329 articles remained for Phase I selection, where they were assessed through titles and abstracts. During this phase, 1.623 articles were excluded for not meeting the pre-established criteria. Consequently, we proceeded to Phase II with 706 articles, of which 03 did not have their complete texts identified. Thus, Phase II entailed the full-text reading of 703 articles. During this stage, 668 articles were discarded, and 35 studies were included in the review (Figure 1). We attempted to contact several authors to obtain the full article, but we were unsuccessful.

Among the included studies, 26 were case-control, 05 were cohort, and 04 were cross-sectional. We screened several articles from China, with a predominance of SNP polymorphism types and genotyping methods such as real-time PCR and PCR-RFLP.

3.1. Methodological quality

The studies exhibited heterogeneity in their quality assessment. Remarkably, cross- sectional studies were the only ones to demonstrate a low risk of bias, as evidenced in Figure 2A. Conversely, the case-control study failed to meet criteria 2, 6, and 7 (Q2: Adequacy in combining cases and controls, Q6: Identification of confounding factors, and Q7: Strategies to address these factors), as depicted in Figure 2B.

The cohort studies showed the highest rate of methodological bias, as they failed to meet criteria 4 and 5, which address the identification and handling of confounding factors, as evidenced in Figure 2C. On the other hand, questions 6, 8, 9, and 10, related to study follow-up, were deemed not applicable due to the nature of the study, which focuses on etiology and risk.

3.2. Synthesis of the results

In our systematic review, we identified thirty genes, as shown in Supplementary Table 1 (Supplementary Material), which can be classified into two main groups based on their functions. The first group includes genes involved in immune response, inflammation, and pathogen recognition (*ABO*, *CXCL8*, *HLAG*, *IL1B*, *IL1R1*, *IL1RN*, *IL6*, *IL8*, *IL10*, *IL17A*, *LBP*, *LY96* (MD-2), *TIRAP*, *TLR1*, *TLR2*, *TLR4*, *TLR5*, *TLR9*, *TLR10*, *TNFA*, *TNFB*). The second group comprises genes coding for enzymes and transporters (*ABCB1*, *ACE*, *ATG16L*, *DNMT1*, *DNMT3a*, *GSTT1*, *Le*, *MUC6*, *NQO1*, *TCRBV6S1 (TRBV6-1)*).

For the *ABO* gene, the study by Chen et al. (2018) showed an association between the SNP *ABO* C>T (rs505922) and *H. pylori* infection in children. Individuals with the T allele of *ABO* C>T (rs505922) have a 6.128-fold increased risk of *H. pylori* infection (95% CI = 2.381-15.769; p= < 0.001).

The *CXCL8* gene -251 (rs4073) study by Boonyanugomol et al. (2019) found that heterozygous TA genotypes (OR = 11.60; 95% CI = 4.22-31.94; p= < 0.001) and

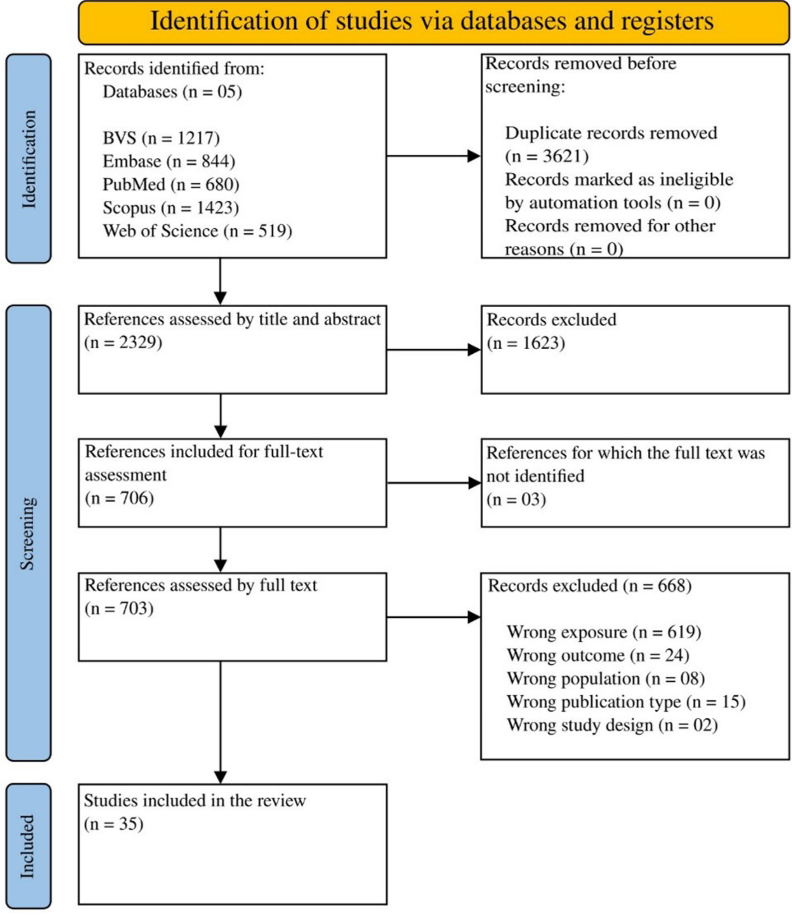


Figure 1. Prisma flowchart demonstrating the process of including studies in this systematic review and metanalysis (Page et al., 2021).

homozygous AA mutants (OR = 6.48; 95% CI = 1.91-22.01; p=0.003) were associated with increased susceptibility to infection. Additionally, the AA genotype acts as a risk factor for the severity of inflammation and gastric cancer induced by *H. pylori* infection.

The *HLAG* 14bp Ins/Del +2960 variation was listed only in the study by Genre et al. (2016), which observed that the odds of having the Ins/Ins genotype (compared to the Del/Del genotype) were 3.77 times higher among positive infection cases than controls (95% CI = 1.21-12.24; p=0.02). This finding suggests that the Ins/Ins 14 bp genotype may be associated with a higher risk of *H. pylor*i infection. For the *IL1B* gene, the SNP -31 C>T (rs1143627) was associated with predisposition to infection in the studies by Hamajima et al. (2001), Caleman Neto et al. (2014), and Ravishankar Ram et al. (2015), with odds ratios of 1.48 and 2.46 (95% CI = 1.19-1.86 and 1.06-5.74, respectively). For SNP -511 C>T (rs16944), the studies by Gao et al. (2009) and Liou et al. (2007) analyzed TT + CT vs. CC genotypes with ORs of 1.88 (1.17-3.02) and 1.51 (1.06-2.15), respectively. Ravishankar Ram et al. (2015) investigated the C allele in different genotypes, finding an OR of 1.17 (0.95-1.45) for CC vs. CT and an OR of 1.40 (1.09-1.80) for homozygous CC vs. TT genotypes. All these studies showed an association with susceptibility to *H. pylori* infection.

Hartland et al. (2004) demonstrated an association between the *IL1R1* 1622 A>G (rs3917225) variation and infection, with individuals carrying the AA genotype showing 1.78-fold more risk than those with the wild-type genotype (p=0.04). Regarding the *IL1RN* A9589T (rs454078) gene, only the study by Gao et al. (2009) was included in our review, showing that this variation increases the chances of *H. pylori* infection by 1.23 times.

Other interleukin gene variants were also listed in relation to susceptibility to *H. pylori* infection. For example, the *IL6* 190 C>T variation (OR: 2.22, 95% CI: 1.03-4.81, p=0.04) was identified in the study by Mărginean et al. (2017). For *IL8* -251 T>A (rs4073), a significant association with susceptibility was observed (OR: 1.13; 95% CI: 0.99-1.29; p=0.038) in the study by Ravishankar Ram et al. (2015) and Caleman Neto et al. (2014) (p=0.039).

Three *IL10* gene variants were associated with susceptibility to infection: rs1800896 (OR: 1.63, 95% CI: 1.11-2.39, p=0.023), rs3024491 (OR: 1.71, 95% CI: 1.14-2.57, p=0.023), and rs1878672 (OR: 1.79, 95% CI: 1.19-2.68, p=0.015), reported by Assis et al. (2014). Additionally, the *IL17A* A>G (rs2275913) variation (OR: 6.0, 95% CI: 1.22-29.48, p=0.036) was associated with susceptibility to *H. pylori* infection in the study by Hussein and Ali (2020).

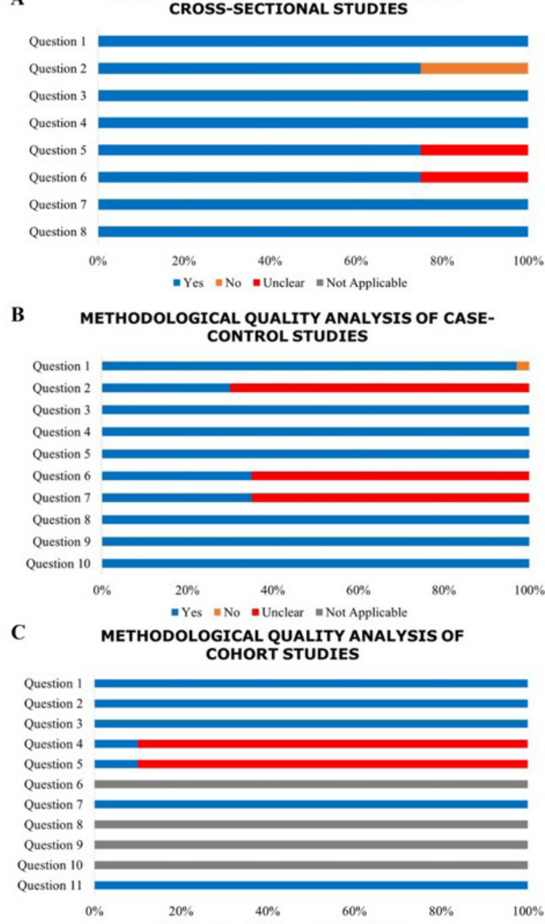


Figure 2. Chart of methodological quality assessment for cross-sectional, case-control and cohort studies. (A) cross-sectional; (B) case-control; (C) cohort.

The study by Castaño-Rodriguez et al. (2014) demonstrated that variations in genes encoding accessory proteins for pathogen recognition could lead to an imbalance in the host-parasite relationship and cause susceptibility to infection, such as SNPs *LBP* rs2232578 (OR: 3.07; 95% CI: 1.24-7.59; p=0.017), *LY96* (MD-2) rs11465996 (OR: 4.83; 95% CI: 2.02-11.57; p=0.0002) and rs16938755 (OR: 3.80; 95% CI: 1.48-9.77; p=0.0082); and *TIRAP* rs7932766 (OR: 6.04; 95% CI: 1.89-19.36; p=0.0032).

In Supplementary Table 1, it can be observed that out of the 35 studies included, 10 addressed variants in *TLR* superfamily genes. Our study highlighted polymorphisms in *TLR1* rs4833095, *TLR2* rs3804100, *TLR4* rs11536889, rs4986790, and rs4986791; *TLR5* rs1640827, rs17163737, and rs5744174; *TLR9* rs352140, and *TLR10* rs10004195, with risks ranging from 1.18 (Xu et al., 2017) to 9.80 (Loganathan et al., 2016) for susceptibility to *H. pylori* infection.

The *TNFA* C-857T variation in the study by Hamajima et al. (2003) demonstrated associations in genotypes: CT (OR: 1.06; 95% CI: 0.82-1.37; p= < 0.001) and TT (OR: 1.69; 95% CI: 0.85-3.35; p= < 0.001). For the SNP *TNFA* T-1030C, this association was observed only by Idris et al. (2022) in individuals with the TC genotype (OR: 2.69; 95% CI: 1.17- 6.17; p=0.020). In the same gene, but with the 308 G>A (rs1800629) variation, susceptibility risk was seen in the studies by Gao et al. (2009) (OR: 1.15; 95% CI: 0.69- 1.91), Mărginean et al. (2017) (genotype GA = OR: 2.26; 95% CI: 1.01-5.04; p=0.04; AA = OR: 3.63; 95% CI: 1.26-10.4; p=0.01; GA + AA vs GG = OR: 2.63; 95% CI: 1.27-5.42; p=0.008) and Yea et al. (2001) (Allele A = OR: 3.683; 95% CI: 1.343-10.101; p=0.011; Allele G = OR: 8.757; 95% CI: 1.413-54.262; p=0.019). Regarding the *TNFB* gene, only Hamajima et al. (2003) studied the A252G variation, where both the AG genotype (95% CI: 0.82-1.34; p= < 0.001) and GG (95% CI: 0.75-1.49; p= < 0.001) showed a 1.05-fold increased probability of susceptibility to the infection.

In our study, only one study was listed for each of the following polymorphisms: *ABCB1* C3435T (rs1045642), *ACE* I>D, *ATG16L* (rs2241880), *DNMT1* (rs2288349), *DNMT3a* (rs13420827 and rs1550117), *GSTT1* (Null/Present), *Le* (Le/le and le/le), *MUC6* (LL: Long-long, LS: Long-short, SS: Short-short), *NQO1* C609T, *TCRBV6S1* (TRBV6-1) GT (12) and BV6S1B(GT)12 or 13. Fifteen polymorphisms were identified in these genes, with risks ranging from 1.14 (Goto et al., 2005) to 9.60 (Kunstmann et al., 2000) for susceptibility in the host. These genes are responsible for encoding enzymes and transporters crucial for the biological response to bacterial infection, as well as for regulating the immune system (Supplementary Table 1).

3.3. Meta-analysis

Of the forty-three polymorphisms identified in this systematic review, only five were included in the meta-analysis: SNPs *IL1B*-C31T (rs1143627), *IL1B*-C511T (rs16944), *TLR1* C>T (rs4833095), *TLR4* A>G (rs4986790), *TLR10* A>T (rs10004195), and *TNF*308 G>A (rs1800629). Meta-analysis was not performed for the remaining polymorphisms due to the insufficient number of relevant articles.

The total number of subjects analyzed was 181 cases and 120 controls for *IL1B*- C31T, 812 cases and 786 controls for *IL1B*-C511T, 613 cases and 587 controls for *TLR1* C>T, 543 cases and 246 controls for *TLR4* A>G, 1046 cases and 884 controls for *TLR10* A>T, and 541 cases and 716 controls for *TNF*308 G>A. The meta-analysis for the SNP *IL1B*-C31T included three studies, which showed no association between the polymorphism and infection, both in the genotype comparison (CC vs. CT + TT) (OR = 1.4165; 95% CI = 0.6399-3.1354; p=0.3904) and in the allele comparison (C vs. T) (OR = 0.70; 95% CI = 0.35-1.43; p=0.3329), as illustrated in Figure 3.

For the SNP *IL1B*-C511T, three studies were included, where only the genotypic comparison (CC vs. CT + TT) was considered significant and risky (OR = 1.34; 95% CI = 1.03-1.74; p=0.0291), while the allele (C vs. T) was not significant comparison (OR = 1.23; 95% CI = 1.23-1.52; p=0.0555) (Figure 4).

Three studies were included in the *TLR1* C>T gene polymorphism (Figure 5). Both the genotype comparison

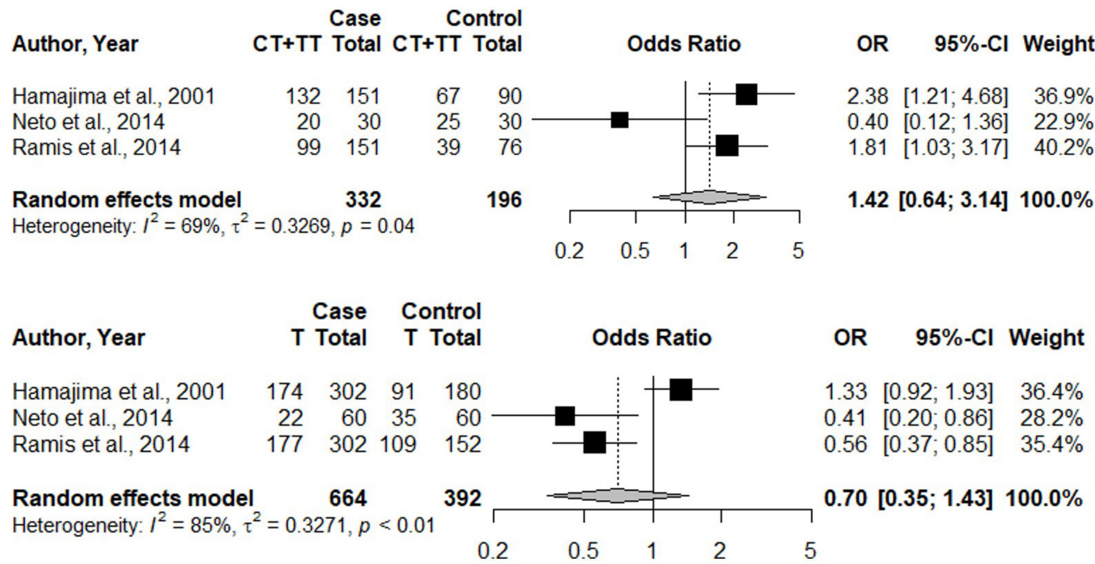


Figure 3. Forest plot for the genotypic and allelic comparison of SNP *IL1B*-C31T (CC vs. CT + TT and C vs. T).

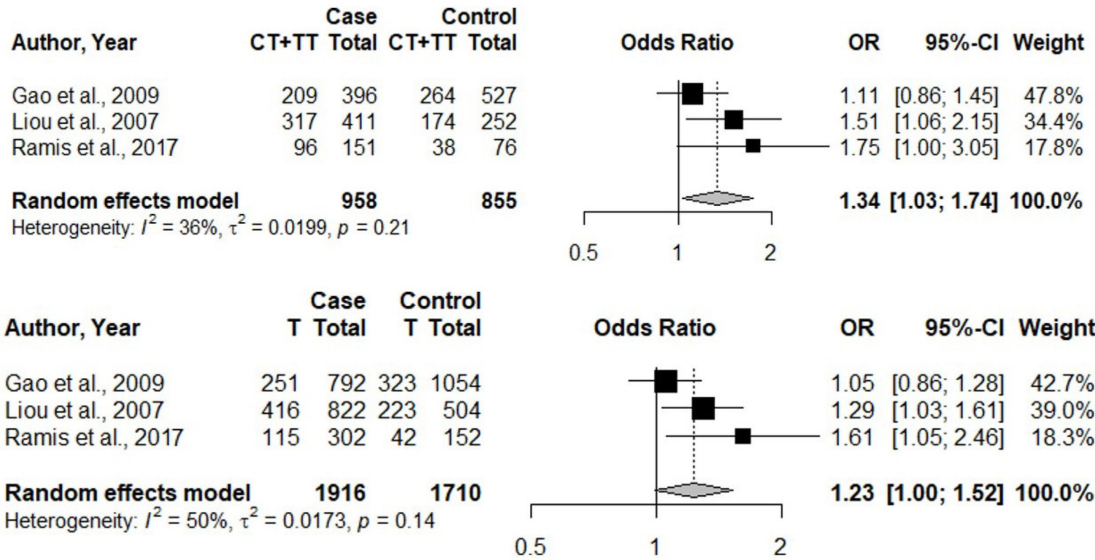


Figure 4. Forest plot for the genotypic and allelic comparison of SNP *IL1B*-C511T (CC vs. CT + TT and C vs. T).
Source: Gao et al. (2009), Liou et al. (2007) and Ramis et al. (2017).

(OR = 0.12; 95% CI = 0.02 - 0.74; p=0.0230) and the allele comparison (OR = 0.79; 95% CI = 0.64-0.99; p=0.0381) were significant for protection. Five studies were included in the analysis for the *TLR4* A>G variability. The genotype comparison (AA vs AG+GG) was insignificant for risk or protection (OR = 2.30; 95% CI = 0.88 - 6.04; p=0.0900). However, the allele comparison (A vs G) demonstrated risk (OR = 1.74; 95% CI = 1.05-2.90; p=0.0330) (Figure 6).

The analysis of the five studies of the SNP *TLR10* A>T showed that the genotype comparison (AA vs AT + TT) was significant for protection (OR = 0.32; 95% CI = 0.20-0.52; p= < 0.0001), while the allele comparison (A vs T) was not significant for either risk or protection (OR = 0.36; 95% CI = 0.10 - 1.24; p=0.1055) (Figure 7). For the SNP *TNF308* G>A, no significant results were found either in the genotypic comparison (GG vs GA+AA) (OR = 1.63; 95% CI = 0.93-2.87; p=0.0908) or in the allelic comparison (G vs A) (OR = 1.53; 95% CI = 0.81-2.88; p=0.1889) (Figure 8).

The publication bias analysis for the SNP *IL1B*-C31T did not indicate publication bias, as evidenced by the funnel plot (Figures 9A and 9B) and the Egger's test for both genotypic (p=0.3277) and allelic comparisons (p=0.5046). For the SNP

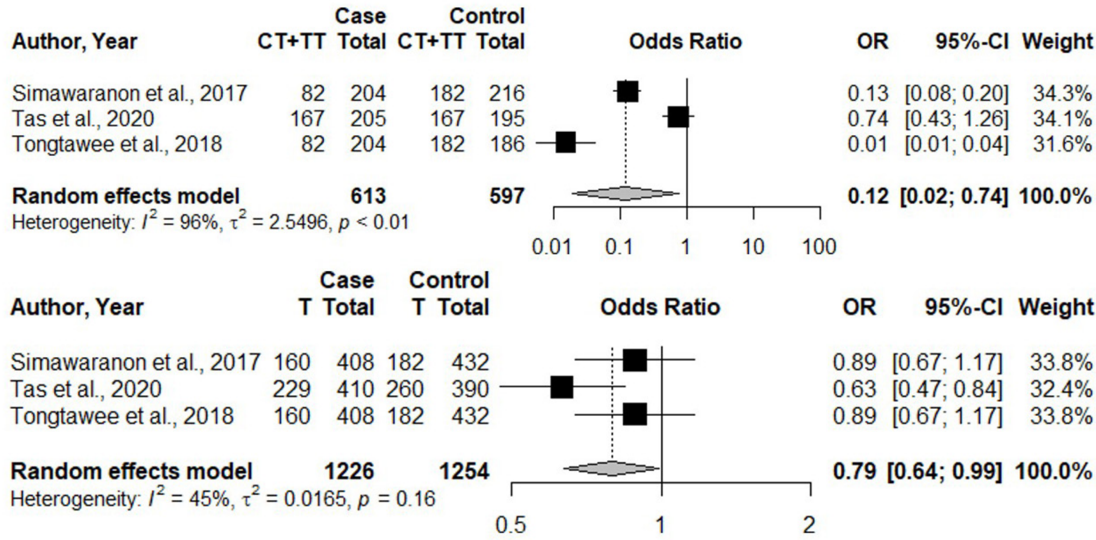


Figure 5. Forest plot for the genotypic and allelic comparison of SNP *TLR1* C>T (CC vs. CT + TT and C vs. T).
Source: Simawaranon et al. (2017), Tas et al. (2020) and Tongtawee et al. (2018).

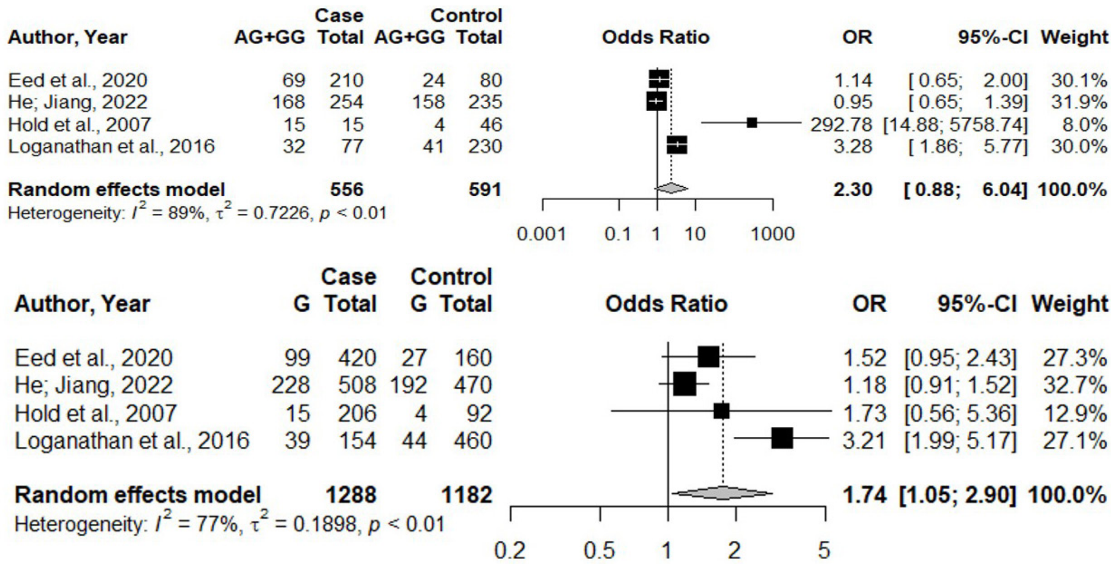


Figure 6. Forest plot for the genotypic and allelic comparison of SNP *TLR4* A>G (AA vs AG+GG and A vs. G).
Source: Eed et al. (2020), He and Jiang (2022), Hold et al. (2007) and Loganathan et al. (2016).

IL1B-C511T, there was no significant publication bias for either genotypic (Figure 9 C) or allelic comparisons (Figure 9D) (Egger's test p=0.2828 and p=0.3706, respectively). In the case of SNP *TLR1* C>T, the genotypic comparison showed no publication bias (Figure 10 A); however, the allelic comparison indicated publication bias in the funnel plot and Egger's test (p = < 0.0001) (Figure 10B).

In the analysis of publication bias for SNP *TLR4* A>G, no significant publication bias was identified according to the funnel plot (Figure 10C for genotypic and Figure 10D for the allelic comparison) and Egger's test (p=0.1612 for the genotypic comparison and p=0.4541 for the allelic comparison). For the SNP *TLR10* A>T, no biases were observed in the genotypic comparison (Egger's test p=0.5833) (Figure 10E); however, the allelic comparison showed publication bias, as illustrated in Figure 10F (Egger's test p=0.0114). The SNP *TNF308* G>A did not present significant publication bias, according to the funnel plot (Figure 11A for genotypic and Figure 11B for the allelic comparison) and Egger's test (p=0.3518 for the genotypic comparison and p=0.4301 for the allelic comparison).

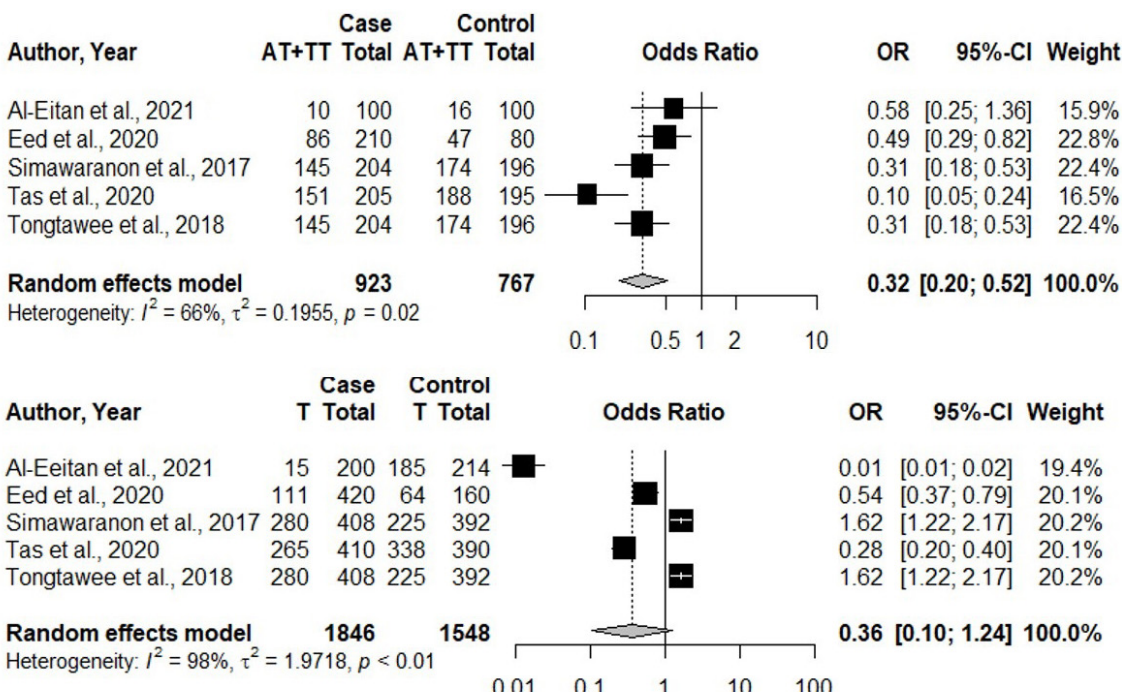


Figure 7. Forest plot for the genotypic and allelic comparison of SNP *TLR10* A>T (AA vs AT + TT and A vs. T).
Source: Al-Eitan et al. (2021), Eed et al. (2020), Simawaranon et al. (2017), Tas et al. (2020) and Tongtawee et al. (2018).

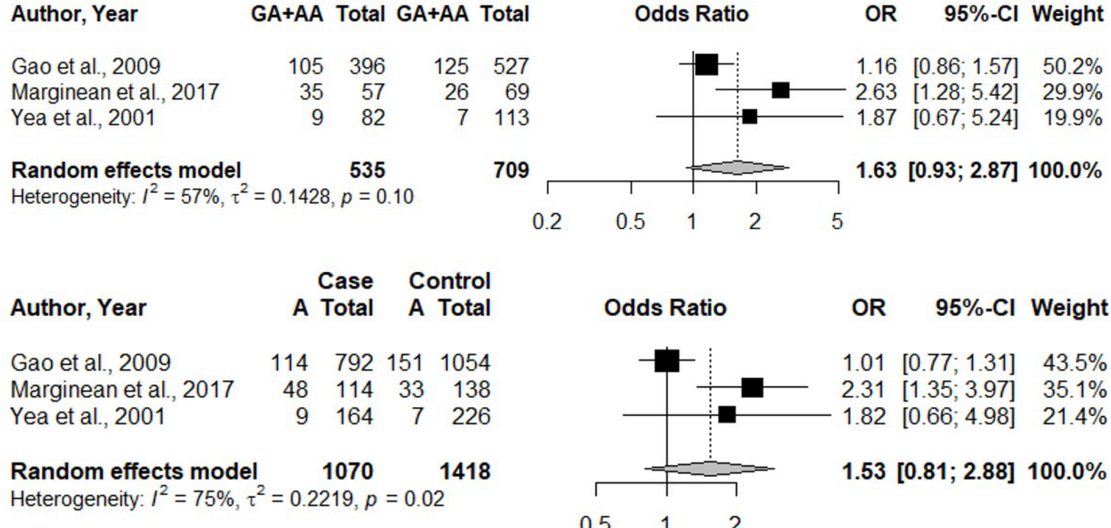


Figure 8. Forest plot for the genotypic and allelic comparison of SNP *TNF308* G>A (GG vs GA+AA and G vs. A).
Source: Gao et al. (2009), Mărginean et al. (2017) and Yea et al. (2001).

4. Discussion

Infection by *H. pylori* can be influenced by various factors, including those related to the bacterial strain and the host. Genetic polymorphisms are crucial in determining susceptibility to infection, as they can impact the prognosis and clinical course of the disease. This review aims to highlight the key host genes and polymorphisms that contribute to increased susceptibility to infection by this bacterium.

The genes identified in this review are predominantly associated with the immune system and involved in inflammatory responses and pathogen recognition (*ABO*, *CXCL8*, *HLAG*, *IL1R1*, *IL1RN*, *IL1B*, *IL6*, *IL8*, *IL10*, *IL17A*, *LBP*,

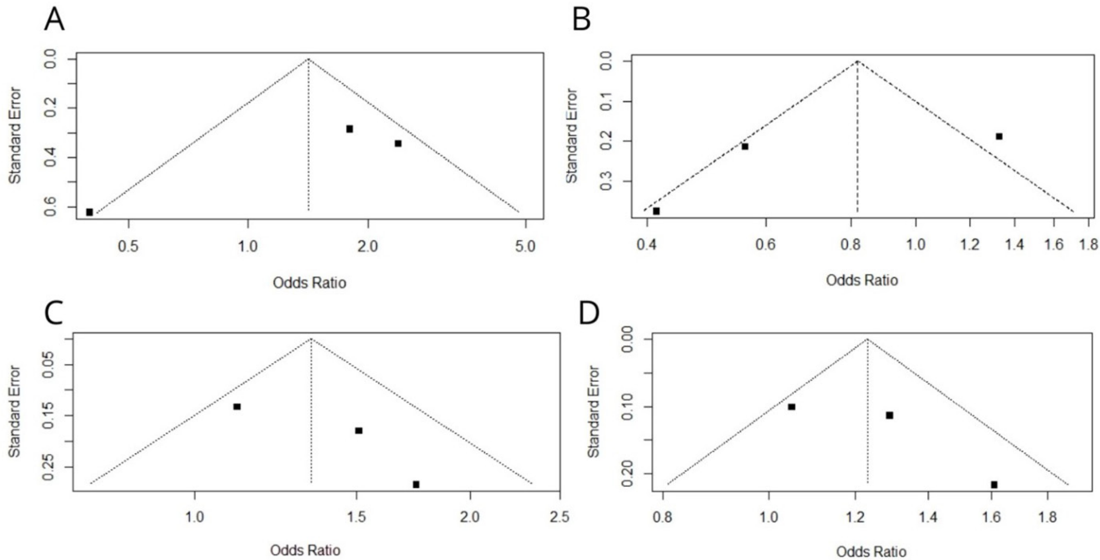
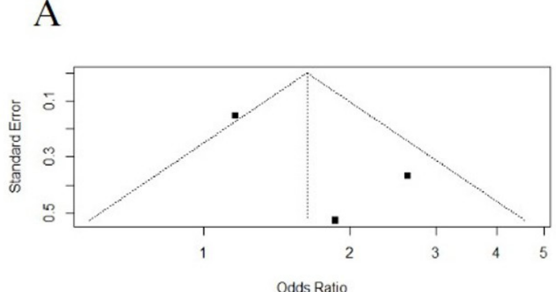


Figure 9. Funnel plots for the publication bias of the *IL1B* studies included in the meta- analysis. (A) genotypic comparison (CC vs. CT + TT) for SNP C31T; (B) allelic comparison (C vs. T) SNP C31T; (C) genotypic comparison (CC vs. CT + TT) for SNP C511T; (D) allelic comparison (C vs. T) for SNP C511T.

Figure 10. Funnel plots for the publication bias of the studies included in the meta- analysis. (A) genotypic comparison (CC vs. CT + TT) for SNP *TLR1* C>T; (B) allelic comparison (C vs. T) for SNP *TLR1* C>T; (C) genotypic comparison (AA vs AG+GG) for SNP *TLR4* A>G; (D) allelic comparison (A vs. G) for SNP *TLR4* A>G; (E) genotypic comparison (AA vs AT + TT) for SNP *TLR10* A>T; (F) allelic comparison (A vs. T) for SNP *TLR10* A>T.



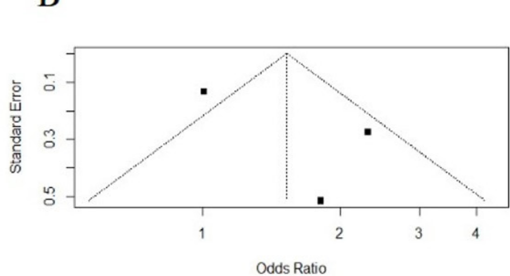


Figure 11. Funnel plots for the publication bias of the *TNF308* G>A studies included in the meta-analysis. (A) genotypic comparison (GG vs GA+AA); (B) allelic comparison (G vs. A).

LY96 (MD-2), *TIRAP*, *TLR1*, *TLR2*, *TLR4*, *TLR5*, *TLR9*, *TLR10*, *TNFA*, and *TNFB*). The high frequency of identification of these genes may explain why some individuals have never been affected by the bacterium or are asymptomatic or symptomatic carrier.

Genetic variations in the components of the immune system can significantly influence the body's response to infection, being essential for understanding the complex inflammatory cascades induced by this pathogen. Additionally, various genes coding for proteins involved in the inflammatory process (e.g., *TLR* responses) and enzymes important for detoxification and gene expression regulation have often been identified (*ABCB1*, *ACE*, *ATG16L*, *DNMT1*, *DNMT3a*, *GSTT1*, *Le*, *MUC6*, *NQO1*, *TCRBV6S1* (*TRBV6-1*)).

Most of the genes identified in our study are linked to inflammatory pathways activated by TLRs. These receptors play key roles in detecting pathogenic microorganisms in the human body, balancing infection control. TLRs belong to a superfamily of transmembrane proteins that identify pattern recognition, such as pathogen-associated molecular patterns (PAMPs) expressed by a wide range of microorganisms (Tas et al., 2020).

H. pylori is initially recognized by the innate immune system, particularly by TLRs (*TLR1*, *TLR2*, *TLR4*, *TLR5*, *TLR9*, *TLR10*), and in the adaptive immune system, it is mediated by Human Leukocyte Antigen (HLA), sometimes referred to as the Major Histocompatibility Complex (MHC). TLR-1, together with TLR-2, after heterodimerization, are considered the main receptors responsible for recognizing pathogens and virulence factors in the extracellular space (Akira and Takeda, 2004).

The activation of innate immune system cells through TLR responses is also crucial for the development of adaptive immunity. Polymorphisms in *TLR* genes have shown to enhance susceptibility to *H. pylori* in the human body, both by altering recognition patterns and by reducing anti-inflammatory and mucin-producing cytokines, as well as increasing the secretion of pro-inflammatory cytokines.

Our meta-analysis was conducted with six polymorphisms in five genes: *IL1B*- C31T (rs1143627), *IL1B*-C511T (rs16944), *TLR1* C>T (rs4833095), *TLR4* A>G (rs4986790), *TLR10* A>T (rs10004195), and *TNFA* 308 G>A (rs1800629). Studies on the polymorphism rs4833095 *TLR1* C>T have associated the genetic alteration with susceptibility to *H. pylori* infection and predisposition to gastritis (Ravishankar Ram et al., 2015), as well as the occurrence and progression of gastric cancer (Dang et al., 2024). However, in our meta-analysis, the genotypic (CC vs. CT + TT) (OR = 0.12; 95% CI = 0.02-0.74; p=0.0230) and allelic (C vs. T) (OR = 0.79; 95% CI = 0.64-0.99; p=0.0381) comparisons demonstrated an association with protection against infection. Our findings support other data on genetic variation.

Yang et al. (2013) also associated the CT genotype with a decreased risk of infection by the bacteria, gastritis, and metaplasia in Chinese individuals. It is possible that this polymorphism reduces interaction with innate and adaptive immune cells, such as natural killer cells and T cells, and induces lower secretion of pro-inflammatory molecules, such as IFN-gamma (Yang et al., 2013).

The *TLR4* gene has a well-established interaction with bacterial lipopolysaccharide (LPS). The SNP *TLR4* A>G (rs4986790), which involves a change from adenine (A) to guanine (G), was analyzed in our meta-analysis. We identified that this polymorphism, in the allelic comparison (A vs G), showed a 1.74-fold increased risk for susceptibility to infection compared to individuals without bacterial infection (95% CI = 1.05-2.90; p=0.0330).

Similarly to our data, the study by Hold et al. (2007) demonstrated a high association in the allelic comparison (A vs. G), increasing the susceptibility to infection by 11 times (95% CI: 2.50-48.0). It is hypothesized that this polymorphism decreases the receptor's affinity in interacting with bacterial LPS, resulting in a less effective immune response and contributing to the establishment of the infection (Uno et al., 2014). However, the association of this SNP with increased susceptibility to *H. pylori* infection still requires further studies. Kupcinskas et al. (2011) showed no association between the polymorphism and infection. It is important to consider that ethnic diversity of the population as well as different genotyping techniques and statistical power of analyses in each study can influence the reproducibility of results.

According to our meta-analysis, the SNP rs10004195 (T>A) in the *TLR10* gene showed that, in the genotypic comparison (AA vs AT + TT), there was a protective association against infection (OR = 0.32; 95% CI = 0.20-0.52; p= < 0.0001), while in the allelic comparison (A vs T), the variant did not show statistical significance.

The SNP rs10004195 may affect susceptibility by modulating the immune response signaling pathway. This variant may also influence immune responses mediated by TLRs 1 and 2, reducing antigen recognition activity, such as *H. pylori*, in the gastric mucosa. As a result, bacterial proliferation in the stomach is diminished, and consequently, the production of pro-inflammatory molecules that could increase the risk of gastric lesions is reduced (Mikacenic et al., 2013).

The data collected by Tang et al. (2015) were similar to those of our study, considering the Chinese population included in their research. However, they contradict much of the scientific literature regarding the variant and infection, as Al-Eitan et al. (2021), Eed et al. (2020), and Tas et al. (2020) found risks associated with the polymorphism and infection ranging from 1.42 to 3.7 times.

Although not statistically assessed in our meta-analysis, studies with genetic variants in *TLR5* were identified through systematic review. This receptor plays a crucial role in identifying bacterial motility structures. *H. pylori* has about 5 to 7 flagella, equipped with the flagellin protein, which is specifically recognized by *TLR5* present in gastric epithelial cells. Xu et al. (2017) investigated the association of gene polymorphisms with infection, where *TLR5* rs1640827 (OR: 2.13, 95% CI: 1.79-2.53, p=0.009) and *TLR5* rs17163737 (OR: 2.17, 95% CI: 1.81-2.61, p=0.006) were related to predisposition to *H. pylori* infection. According to Xu et al. (2017), abnormal functioning of *TLR5* is related to the onset of gastric cancers. Patients with polymorphisms in *TLR5* expressed significantly lower levels of IL-1β, TNF-α, IL-6, and IL-10 in gastric tissue (Xu et al., 2017).

After antigen recognition by receptors through presenting molecules, cytokines are released, playing a crucial role in the immune system signaling cascade. In our meta- analysis, we identified two relevant polymorphisms in the *IL1B* gene (C31T rs1143627 and C511T rs16944), which codes for an important pro-inflammatory cytokine involved in the initiation and amplification of inflammatory responses against the bacterium. For the SNP C31T (rs1143627), we observed no association in the genotypic model (CC vs. CT + TT) (OR = 1.4165; 95% CI = 0.6399-3.1354; p=0.3904) and a protective association in the allelic model (C vs. T) (OR = 0.70; 95% CI = 0.35-1.43; p=0.3329). The SNP C511T (rs16944) showed an association with susceptibility to infection only in the genotypic model (CC vs. CT + TT) (OR = 1.34; 95% CI = 1.03-1.74; p=0.0291).

These polymorphisms may affect the biological transcription of the gene, promoting overproduction of this cytokine, leading to a heightened inflammatory response and increased suppression of gastric acid, creating an environment conducive to the infection's establishment. Our data for the SNP C511T (rs16944) are similar to Liou et al. (2007) (OR: 1.51, 95% CI: 1.06-2.15, p=0.022) and Ravishankar Ram et al. (2015) TT vs CC (OR: 1.48, 95% CI: 1.09-1.80, p=0.004) and TT vs TC (OR: 1.16, 95% CI: 0.95-1.45, p=0.004). In our systematic review, we also identified studies evaluating polymorphisms in IL-1B receptor genes, such as *IL1RN* A9589T (rs454078) (OR: 1.23; 95% CI: 0.78-1.94) (Gao et al., 2009) and *IL1R1* 1622 A>G (rs3917225) (OR: 1.78; p=0.04) (Hartland et al., 2004). The association of genetic variants in cytokine genes and their receptors may contribute to the intensification of the inflammatory process in the body and increase the likelihood of developing gastric lesions (Hartland et al., 2004).

The TLR signaling pathway induces the expression of various pro-inflammatory cytokines, such as tumor necrosis factors (TNF), specifically TNF-A and TNF-B, which have similar characteristics in inhibiting gastric acid secretion. TNF-A, mainly derived from macrophages, plays a crucial role in the immune response against the bacterium. In our meta-analysis, the SNP rs1800629 in the *TNFA* gene did not show statistically significant association with risk or protection. Despite this, associations of imbalance in the host-pathogen interaction can be evidenced. Gao et al. (2009) related the SNP (rs1800629) to an increased risk of *H. pylori* infection in the host (OR: 1.15, 95% CI: 0.69- 1.91). Given the uncertain role of this SNP in the pathophysiological mechanisms mediated by *H. pylori*, further studies are needed to establish the relationship between this variant and susceptibility to bacterial infection, especially considering the host's genetic background and ethnicities.

This systematic review and meta-analysis showed a risk for susceptibility to *H. pylori* infection with the genes *IL1B*-C511T (rs16944) for the genotype (OR: 1.34; 95% CI: 1.03-1.74; p=0.0291) and *TLR4* A>G in the allelic comparison (OR: 1.74; 95% CI: 1.05-2.90; p=0.0330) with increased function. Additionally, there was protection against infection considering the gene *TLR1* C>T (allelic comparison = OR: 0.79; 95% CI: 0.64-0.99; p=0.0381 and genotypic comparison = OR: 0.12; 95% CI: 0.02-0.74; p=0.0230) and genotypic *TLR10* A>T (OR = 0.32; 95% CI = 0.20-0.52; p= < 0.0001). Our results indicate that SNPs in genes involved in the host's immune system may become strong indicators of susceptibility to infection.

Despite the large number of studies included in our systematic review, our study has some limitations, primarily related to the small final sample of studies included. Many studies evaluated in the first phase of our review were excluded due to the lack of correlation between genetic variants and *H. pylori* infection. Several studies, on the other hand, assessed the contribution of polymorphisms to complications caused by the imbalance of the host-parasite relationship, such as gastritis, ulcers, and gastric cancers. Multiple studies also assessed the association between SNPs and resistance to pharmacological treatment of the bacterium. Furthermore, our review aimed to construct a genetic panel with risk variants for infection. In this sense, studies that demonstrated protective associations with polymorphisms were excluded.

It is important to consider that the establishment of the pathophysiological process mediated by *H. pylori* is complex and involves the activation of bacterial virulence mechanisms as well as molecules from the host's immune system. Thus, our meta-analysis should also be interpreted cautiously due to high heterogeneity values. However, subgroup analyses for the included polymorphisms were not possible due to the small number of available studies. The Cochrane Handbook (Higgins and Green, 2009) recommends that no bias tests be performed in reviews with fewer than ten studies.

This study took genetic diversity into account, including genetic variants associated with susceptibility to infection, in populations of different ethnicities and genetic backgrounds. The reviewed literature encompassed data from several countries, reflecting variability in immune responses and the prevalence of genetic variants among distinct populations.

Host genetic factors are key markers in influencing the development of gastric infection by *H. pylori*. Identifying target genes involved in this response is challenging, as it requires associating the complexity of molecular and genetic interactions with the pathophysiological mechanisms of infection in the host.

Genes related to decreased gastric acid secretion and inflammatory signaling in response to infections stood out in our study. Although no strong genetic determinants of increased susceptibility to this infection were identified, our findings are crucial for advancing the understanding of host-parasite interactions. In this regard, personalized approaches in clinical management of the infection can be developed through improved prevention, efficient diagnosis, and precise treatment, benefiting medical research, public health, and precision medicine. Personalized medicine, based on the patient's genetic characteristics, will allow for the identification of individual susceptibility to infection and its more severe forms, such as gastric cancer, enabling early interventions and more effective treatments tailored to the genetic profile of each patient.

Data Availability Statement

The entire data set that supports the results of this study was published in the article itself.

References

ABDIEV, S., AHN, K.S., KHADJIBAEV, A., MALIKOV, Y., BAHRAMOV, S., RAKHIMOV, B., SAKAMOTO, J., KODERA, Y., NAKAO, A. and HAMAJIMA, N., 2010. *Helicobacter pylori* infection and cytokine gene polymorphisms in Uzbeks. *Nagoya Journal of Medical Science*, vol. 72, no. 3-4, pp. 167-172. PMid:20942272.

AKIRA, S. and TAKEDA, K., 2004. Toll-like receptor signalling. *Nature Reviews. Immunology*, vol. 4, no. 7, pp. 499-511. http://doi.org/10.1038/nri1391. PMid:15229469.

AL-EITAN, L., ALMOMANI, F.A., AL-KHATIB, S.M., ALJAMAL, H.A., AL-QUSAMI, M.N. and ALJAMAL, R.A., 2021. Association of toll-like receptor 4, 5 and 10 polymorphisms with *Helicobacter pylori*-positive peptic ulcer disease in a center in Jordan. *Annals of Saudi Medicine*, vol. 41, no. 4, pp. 206-215. http://doi.org/10.5144/0256-4947.2021.206. PMid:34420402.

AMIEVA, M. and PEEK JUNIOR, R.M., 2016. Pathobiology of *Helicobacter pylori*-Induced Gastric Cancer. *Gastroenterology*, vol. 150, no. 1, pp. 64-78. http://doi.org/10.1053/j.gastro.2015.09.004. PMid:26385073.

ASSIS, S., MARQUES, C.R., SILVA, T.M., COSTA, R.S., ALCANTARA-NEVES, N.M., BARRETO, M.L., BARNES, K.C. and FIGUEIREDO, C.A., 2014. *IL10* single nucleotide polymorphisms are related to upregulation of constitutive IL-10 production and susceptibility to *Helicobacter pylori* infection. *Helicobacter*, vol. 19, no. 3, pp. 168-173. http://doi.org/10.1111/hel.12119. PMid:24628819.

ATAPOOR, S., DEHKORDI, F.S. and RAHIMI, E., 2014. Detection of *Helicobacter pylori* in various types of vegetables and salads. *Jundishapur Journal of Microbiology*, vol. 7, no. 5, e10013. http://doi.org/10.5812/jjm.10013. PMid:25147709.

BASSAGH, A., JAFARZADEH, A., KAZEMIPOUR, N., NEMATI, M., AMINIZADEH, N., LARUSSA, T., GHAZIZADEH, M., ABASI, M.H. and MIRKAMANDAR, E., 2019. Decreased circulating interleukin-33 concentration in *Helicobacter pylori*-infected patients with peptic ulcer: evaluation of its association with a cytokine gene polymorphism, gender of patients and bacterial virulence factor CagA. *Microbial Pathogenesis*, vol. 136, pp. 103708. http://doi.org/10.1016/j.micpath.2019.103708. PMid:31491552.

BOONYANUGOMOL, W., RUKSEREE, K., KONGKASAME, W., PALITTAPONGARNPIM, P., BAIK, S.C. and MANWONG, M., 2019. Genetic polymorphisms of *CXCL8* (-251) are associated with the susceptibility of *helicobacter pylori* infection increased the risk of inflammation and gastric cancer in Thai gastroduodenal patients. *Iranian Journal of Allergy, Asthma, and Immunology*, vol. 18, no. 4, pp. 393-401. http://doi.org/10.18502/ijaai.v18i4.1417. PMid:31522447.

CALEMAN NETO, A., RASMUSSEN, L.T., DE LABIO, R.W., DE QUEIROZ, V.F., SMITH, M.D.E.A., VIANI, G.A. and PAYÃO, S.L., 2014. Gene polymorphism of interleukin 1 and 8 in chronic gastritis patients infected with *Helicobacter pylori*. *The Journal of Venomous Animals and Toxins Including Tropical Diseases*, vol. 20, no. 1, pp. 17. http://doi.org/10.1186/1678-9199-20-17. PMid:24803922.

CASTAÑO-RODRÍGUEZ, N., KAAKOUSH, N.O., PARDO, A.L., GOH, K.L., FOCK, K.M. and MITCHELL, H.M., 2014. Genetic polymorphisms in the Toll-like receptor signalling pathway in *Helicobacter pylori* infection and related gastric cancer. *Human Immunology*, vol. 75, no. 8, pp. 808-815. http://doi.org/10.1016/j.humimm.2014.06.001. PMid:24929142.

CHEN, S.T., NI, Y.H. and LIU, S.H., 2018. Potential Association of *IL1B* Polymorphism with Iron Deficiency Risk in Childhood *Helicobacter pylori* Infection. *Journal of Pediatric Gastroenterology and Nutrition*, vol. 66, no. 2, pp. e36-e40. http://doi.org/10.1097/MPG.0000000000001687. PMid:28727656.

DANG, Y., HUANG, J., LIN, C. and XU, S., 2024. Investigation of the association between the Toll-like receptor 1 rs4833095 variation and gastric adenocarcinoma recurrence. *Annals of Human Genetics*, vol. 88, no. 4, pp. 287-299. http://doi.org/10.1111/ahg.12548. PMid:38196279.

EED, E.M., HAWASH, Y.A., KHALIFA, A.S., ALSHARIF, K.F., ALGHAMDI, S.A., ALMALKI, A.A., ALMEHMADI, M.M., ISMAIL, K.A., TAHA, A.A. and SABER, T., 2020. Association of toll-like receptors 2, 4, 9 and 10 genes polymorphisms and *Helicobacter pylori*-related gastric diseases in Saudi patients. *Indian Journal of Medical Microbiology*, vol. 38, no. 1, pp. 94-100. http://doi.org/10.4103/ijmm.IJMM_20_164. PMid:32719215.

EGGER, M., SMITH, G.D., SCHNEIDER, M. and MINDER, C., 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ*, vol. 315, no. 7109, pp. 629-634. http://doi.org/10.1136/bmj.315.7109.629. PMid:9310563.

FISCHBACH, W. and MALFERTHEINER, P., 2018. *Helicobacter pylori* Infection. *Deutsches Ärzteblatt International*, vol. 115, no. 25, pp. 429-436. PMid:29999489.

GAO, L., WECK, M.N., NIETERS, A. and BRENNER, H., 2009. Inverse association between a pro-inflammatory genetic profile and *Helicobacter pylori* seropositivity among patients with chronic atrophic gastritis: enhanced elimination of the infection during disease progression? *European Journal of Cancer*, vol. 45, no.

16, pp. 2860-2866. http://doi.org/10.1016/j.ejca.2009.04.015. PMid:19427781.

GENRE, J., REGINALDO, F.P., ANDRADE, J.M., LIMA, F.P., CAMARA, A.V., DONADI, E.A. and CRISPIM, J.C., 2016. HLA-G 14-bp Ins/Ins genotype in patients harbouring *Helicobacter pylori* infection: a potential risk factor? *Scandinavian Journal of Immunology*, vol. 83, no. 1, pp. 52-57. http://doi.org/10.1111/sji.12390. PMid:26368842.

GOTO, Y., HAMAJIMA, N., HONDA, H., MATSUO, K., YAMAMOTO, K., TAMAKOSHI, A., ANDO, T. and GOTO, H., 2005. Association between *Helicobacter pylori* seropositivity and NAD(P)H:quinone oxidoreductase 1 (*NQO1*) C609T polymorphism observed in outpatients and health checkup examinees. *Gastric Cancer*, vol. 8, no. 1, pp. 12-17. http://doi.org/10.1007/s10120-004-0308-1. PMid:15747169.

HAMAJIMA, N., MATSUO, K., SAITO, T., TAJIMA, K., OKUMA, K., YAMAO, K. and TOMINAGA, S., 2001. Interleukin 1 polymorphisms, lifestyle factors, and *Helicobacter pylori* infection. *Japanese Journal of Cancer Research*, vol. 92, no. 4, pp. 383-389. http://doi.org/10.1111/j.1349-7006.2001.tb01106.x. PMid:11346459.

HAMAJIMA, N., SHIBATA, A., KATSUDA, N., MATSUO, K., ITO, H., SAITO, T., TAJIMA, K. and TOMINAGA, S., 2003. Subjects with TNF-A-857TT and -1031TT genotypes showed the highest *Helicobacter pylori* seropositive rate compared with those with other genotypes. *Gastric Cancer*, vol. 6, no. 4, pp. 230-236. http://doi.org/10.1007/s10120-003-0258-z. PMid:14716517.

HARTLAND, S., NEWTON, J.L., GRIFFIN, S.M. and DONALDSON, P.T., 2004. A functional polymorphism in the interleukin-1 receptor-1 gene is associated with increased risk of *Helicobacter pylori* infection but not with gastric cancer. *Digestive Diseases and Sciences*, vol. 49, no. 9, pp. 1545-1550. http://doi.org/10.1023/B:DDAS.0000042262.14969.2d. PMid:15481335.

HE, W. and JIANG, M., 2022. *TLR4* rs4986790 polymorphism confers risk to *Helicobacter pylori* infection in Zhejiang, China and its enlightenment to nursing care. *Journal of Clinical Laboratory Analysis*, vol. 36, no. 6, e24453. http://doi.org/10.1002/jcla.24453. PMid:35500224.

HIGGINS, J.P.T. and GREEN, S., 2009. *Cochrane handbook for systematic reviews of interventions. Version 5.0.2*. Oxford: Cochrane Collaboration.

HOLD, G.L., RABKIN, C.S., CHOW, W.H., SMITH, M.G., GAMMON, M.D., RISCH, H.A., VAUGHAN, T.L., MCCOLL, K.E., LISSOWSKA, J., ZATONSKI, W., SCHOENBERG, J.B., BLOT, W.J., MOWAT, N.A., FRAUMENI, J.F. Jr. and EL-OMAR, E.M., 2007. A functional polymorphism of toll-like receptor 4 gene increases risk of gastric carcinoma and its precursors. *Gastroenterology*, vol. 132, no. 3, pp. 905-912. http://doi.org/10.1053/j.gastro.2006.12.026. PMid:17324405.

HUSSEIN, A. and ALI, A.A., 2020. The influence of genetic polymorphisms of *il17a* in the acquisition of *Helicobacter pylori* and PUD (Peptic Ulcer Disease) development. *Plant Archives*, vol. 20, no. 1, pp. 2893-2896.

IDRIS, A.B., IDRIS, A.B., GUMAA, M.A., IDRIS, M.B., ELGORAISH, A., MANSOUR, M., ALLAM, D., ARBAB, B.M., BEIRAG, N., IBRAHIM, E.M. and HASSAN, M.A., 2022. Identification of functional tumor necrosis factor-alpha promoter variants associated with *Helicobacter pylori* infection in the Sudanese population: computational approach. *World Journal of Gastroenterology*, vol. 28, no. 2, pp. 242-262. http://doi.org/10.3748/wjg.v28.i2.242.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER – IARC, 2014. *Helicobacter pylori eradication as a strategy for preventing gastric cancer.* Lyon: IARC, vol. 8.

KUNSTMANN, E., HARDT, C., ELITOK, E., HARDER, M., SUERBAUM, S., PEITZ, U., SCHMIEGEL, W. and EPPLEN, J.T., 2000. The nonfunctional allele *TCRBV6S1B* is strongly associated with *Helicobacter pylori* infection. *Infection and Immunity*, vol. 68, no. 11, pp. 6493-6495. http://doi.org/10.1128/IAI.68.11.6493-6495.2000. PMid:11035766.

KUPCINSKAS, J., WEX, T., BORNSCHEIN, J., SELGRAD, M., LEJA, M., JUOZAITYTE, E., KIUDELIS, G., JONAITIS, L. and MALFERTHEINER, P., 2011. Lack of association between gene polymorphisms of Angiotensin converting enzyme, Nod-like receptor 1, Toll-like receptor 4, FAS/FASL and the presence of *Helicobacter pylori* induced premalignant gastric lesions and gastric cancer in Caucasians. *BMC Medical Genetics*, vol. 12, no. 12, pp. 112. http://doi.org/10.1186/1471-2350-12-112. PMid:21864388.

LI, Y., CHOI, H., LEUNG, K., JIANG, F., GRAHAM, D.Y. and LEUNG, W.K., 2023. Global prevalence of *Helicobacter pylori* infection between 1980 and 2022: A systematic review and meta-analysis. *The Lancet. Gastroenterology & Hepatology*, vol. 8, no. 6, pp. 553-564. http://doi.org/10.1016/S2468-1253(23)00070-5. PMid:37086739.

LIOU, J.M., LIN, J.T., WANG, H.P., HUANG, S.P., LEE, Y.C., CHIU, H.M., SHUN, C.T. and WU, M.S., 2007. IL-1B-511 C-->T polymorphism is associated with increased host susceptibility to *Helicobacter pylori* infection in Chinese. *Helicobacter*, vol. 12, no. 2, pp. 142-149. http://doi.org/10.1111/j.1523-5378.2007.00484.x. PMid:17309751.

LOGANATHAN, R., NAZEER, M., GODA, V., DEVARAJU, P., ALI, M., KARUNAKARAN, P. and JAYARAMAN, M., 2016. Genetic variants of *TLR4* and *TLR9* are risk factors for chronic *Helicobacter pylori* infection in South Indian Tamils. *Human Immunology*, vol. 78, no. 2, pp. 216-220. http://doi.org/10.1016/j.humimm.2016.12.002. PMid:27993530.

MĂRGINEAN, M.O., MĂRGINEAN, C.O., MELIŢ, L.E., VOIDĂZAN, S., MOLDOVAN, V. and BĂNESCU, C., 2017. The impact of host's genetic susceptibility on *Helicobacter pylori* infection in children. *Medicine*, vol. 96, no. 30, e7612. http://doi.org/10.1097/MD.0000000000007612. PMid:28746216.

MIKACENIC, C., REINER, A.P., HOLDEN, T.D., NICKERSON, D.A. and WURFEL, M.M., 2013. Variation in the *TLR10/TLR1/TLR6* locus is the major genetic determinant of interindividual difference in *TLR1/2*-mediated responses. *Genes and Immunity*, vol. 14, no. 1, pp. 52-57. http://doi.org/10.1038/gene.2012.53. PMid:23151486.

MOOLA, S., MUNN, Z., TUFANARU, C., AROMATARIS, E., SEARS, K., SFETCU, R., CURRIE, M., LISY, K., QURESHI, R., MATTIS, P. and MU, P. 2020. Systematic reviews of etiology and risk. In: JOANNA BRIGGS INSTITUTE, ed. *JBI manual for evidence synthesis.* Adelaide: JBI, chap. 7. http://doi.org/10.46658/JBIMES-20-08.

MUKA, T., GLISIC, M., MILIC, J., VERHOOG, S., BOHLIUS, J., BRAMER, W., CHOWDHURY, R. and FRANCO, O.H., 2020. A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. *European Journal of Epidemiology*, vol. 35, no. 1, pp. 49-60. http://doi.org/10.1007/s10654-019-00576-5. PMid:31720912.

PAGE, M.J., MCKENZIE, J.E., BOSSUYT, P.M., BOUTRON, I., HOFFMANN, T.C., MULROW, C.D., SHAMSEER, L., TETZLAFF, J.M., AKL, E.A., BRENNAN, S.E., CHOU, R., GLANVILLE, J., GRIMSHAW, J.M., HRÓBJARTSSON, A., LALU, M.M., LI, T., LODER, E.W., MAYO-WILSON, E., MCDONALD, S., MCGUINNESS, L.A., STEWART, L.A., THOMAS, J., TRICCO, A.C., WELCH, V.A., WHITING, P. and MOHER, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, vol. 372, pp. n71. http://doi.org/10.1136/bmj.n71. PMid:33782057.

RAMIS, I.B., VIANNA, J.S., GONÇALVES, C.V., VON GROLL, A., DELLAGOSTIN, O.A. and SILVA, P.E.A., 2017. Polymorphisms of

the IL-6, IL-8 and IL-10 genes and the risk of gastric pathology in patients infected with *Helicobacter pylori*. *Journal of Microbiology, Immunology, and Infection*, vol. 50, no. 2, pp. 153-159. http://doi.org/10.1016/j.jmii.2015.03.002. PMid:25888319.

RAVISHANKAR RAM, M., GOH, K.L., LEOW, A.H., POH, B.H., LOKE, M.F., HARRISON, R., SHANKAR, E.M. and VADIVELU, J., 2015. Polymorphisms at locus 4p14 of Toll-like receptors *TLR-1* and *TLR-10* confer susceptibility to gastric carcinoma in *Helicobacter pylori* infection. *PLoS One*, vol. 10, no. 11, e0141865. http://doi.org/10.1371/journal.pone.0141865. PMid:26559190.

SANTOS, H.C.O., MACIEL, D.N., RAMOS, A.F.P.L., SANTIAGO, S.B., COSTA, C.C.P., SANTOS, R.S. and BARBOSA, M.S., 2023. Association between host genetic polymorphisms and susceptibility to *Helicobacter pylori* infection: a systematic review protocol. *Genetics and Molecular Research*, vol. 22, no. 4, pp. GMR19198. http://doi.org/10.4238/gmr19198.

SAVOLDI, A., CARRARA, E., GRAHAM, D.Y., CONTI, M. and TACCONELLI, E., 2018. Prevalence of antibiotic resistance in *helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions. *Gastroenterology*, vol. 155, no. 5, pp. 1372-1382.e17. http://doi.org/10.1053/j.gastro.2018.07.007. PMid:29990487.

SCHMAUSSER, B., ANDRULIS, M., ENDRICH, S., LEE, S.K., JOSENHANS, C., MÜLLER-HERMELINK, H.K. and ECK, M., 2004. Expression and subcellular distribution of toll-like receptors TLR4, TLR5 and TLR9 on the gastric epithelium in *Helicobacter pylori* infection. *Clinical and Experimental Immunology*, vol. 136, no. 3, pp. 521-526. http://doi.org/10.1111/j.1365-2249.2004.02464.x. PMid:15147355.

SIMAWARANON, T., WATTANAWONGDON, W. and TONGTAWEE, T., 2017. Toll-like receptors are associated with *Helicobacter pylori* infection and gastric mucosa pathology. *Jundishapur Journal of Microbiology*, vol. 10, no. 12, e58351. http://doi.org/10.5812/jjm.58351.

SUNG, H., FERLAY, J., SIEGEL, R.L., LAVERSANNE, M., SOERJOMATARAM, I., JEMAL, A. and BRAY, F., 2021. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians*, vol. 71, no. 3, pp. 209-249. http://doi.org/10.3322/caac.21660. PMid:33538338.

TANG, F.B., LI, Z.X., WANG, Y.M., ZHANG, L., MA, J.L., ZHOU, T., ZHANG, Y., GAO, J.J., WU, S., YANG, T., YOU, W.C. and PAN, K.F., 2015. Toll-like receptor 1 and 10 polymorphisms, *Helicobacter pylori* susceptibility and risk of gastric lesions in a high- risk Chinese population. *Infection, Genetics and Evolution*, vol. 31, pp. 263-269. http://doi.org/10.1016/j.meegid.2015.02.005. PMid:25687912.

TAS, S.K., KIRKIK, D., TANOGLU, A., KAHRAMAN, R., OZTURK, K., ESEN, M.F., COSKUNPINAR, M.E. and CAGILTAY, E., 2020. Polymorphisms in Toll-like receptors 1, 2, 5, and 10 are associated with predisposition to *Helicobacter pylori* infection. *European Journal of Gastroenterology & Hepatology*, vol. 32, no. 9, pp. 1141-1146. http://doi.org/10.1097/MEG.0000000000001797. PMid:32541244.

TONGTAWEE, T., BARTPHO, T., KAEWPITOON, S., KAEWPITOON, N., DECHSUKHUM, C., LEEANANSAKSIRI, W., LOYD, R.A., TALABNIN, K., MATRAKOOL, L. and PANPIMANMAS, S., 2018. Genetic polymorphisms in *TLR1, TLR2, TLR4*, and *TLR10* of *Helicobacter pylori*-associated gastritis: a prospective cross- sectional study in Thailand. *European Journal of Cancer Prevention*, vol. 27, no. 2, pp. 118-123. http://doi.org/10.1097/CEJ.0000000000000347. PMid:28368946.

UNO, K., KATO, K. and SHIMOSEGAWA, T., 2014. Novel role of toll-like receptors in *Helicobacter pylori*- induced gastric malignancy. *World Journal of Gastroenterology*, vol. 20, no. 18, pp. 5244-5251. http://doi.org/10.3748/wjg.v20.i18.5244. PMid:24833854.

XU, T., FU, D., REN, Y., DAI, Y., LIN, J., TANG, L. and JI, J., 2017. Genetic variations of *TLR5* gene interacted with *Helicobacter pylori* infection among carcinogenesis of gastric cancer. *Oncotarget*, vol. 8, no. 19, pp. 31016-31022. http://doi.org/10.18632/oncotarget.16050. PMid:28404962.

YANG, C.A., SCHEIBENBOGEN, C., BAUER, S., KLEINLE, C., WEX, T., BORNSCHEIN, J., MALFERTHEINER, P., HELLMIG, S., SCHUMANN, R.R. and HAMANN, L., 2013. A frequent Toll-like receptor 1 gene polymorphism affects NK- and T-cell IFN-γ production and is associated with *Helicobacter pylori*-induced gastric disease. *Helicobacter*, vol. 18, no. 1, pp. 13-21. http://doi.org/10.1111/hel.12001. PMid:23067142.

YEA, S.S., YANG, Y.I., JANG, W.H., LEE, Y.J., BAE, H.S. and PAIK, K.H., 2001. Association between TNF-alpha promoter polymorphism and *Helicobacter pylori* cagA subtype infection. *Journal of Clinical Pathology*, vol. 54, no. 9, pp. 703-706. http://doi.org/10.1136/jcp.54.9.703. PMid:11533078.

Supplementary Material

Supplementary material accompanies this paper.
Supplementary Table 1. Systematic Review Data Extraction Table.

This material is available as part of the online article from https://doi.org/ 10.1590/1519-6984.290851