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Association of Host Interleukin 8 Promoter Polymorphism with *Helicobacter pylori* induced Gastritis among Bangladeshi People

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Abstract

Background: *Helicobacter pylori* induced gastritis involves dense mucosal granulocyte infiltration, driven by pro-inflammatory cytokines like interleukin-8 (IL-8), with cytokine gene polymorphisms influencing secretion levels. **Objective:** The study investigated the association of IL-8–251 A/T polymorphism (Three genotypes: A/A, A/T, T/T) with gastroduodenal diseases in *Helicobacter pylori* infected patients. **Methodology:** This was a prospective observational study that recruited gastritis patients who underwent upper gastrointestinal endoscopic examinations at the outpatient department of Gastroenterology at Bangladesh Medical University, Dhaka, Bangladesh (Former: Bangabandhu Sheikh Mujib Medical University (BSMMU)) and Dhaka Medical College Hospital in Dhaka, Bangladesh, from 2015 to 2020. Patients who received *Helicobacter pylori* eradication treatment in the previous 2 months, elderly individuals aged more than 65 years and those who had severe medical or surgical illnesses or had used proton pump inhibitors, nonsteroidal anti-inflammatory drugs, colloidal bismuth compounds, or antibiotics within 4 weeks of enrollment were excluded from the study. The *Helicobacter pylori* infection was identified using a rapid urease test, PCR of the ureC gene, and histological examination. Grading of gastritis was diagnosed through histopathological analysis and was graded as normal gastric mucosa (Grade - 0, I), Chronic gastritis (Grade-II), and Chronic active gastritis (Grade-III). Interleukin-8 (IL-8) gene polymorphism at the -251 position was detected by Polymerase Chain Reaction restriction fragment length polymorphism. **Results:** The frequencies of IL-8 T/A, A/A genotypes and A carrier were significantly higher in the *Helicobacter pylori* -infected population, whereas T/T genotypes were predominant among the counterparts (P =0.001). The IL-8 A allele carriers with *Helicobacter pylori* infection had an increased risk of developing gastritis (P=0.003). Most Grade III gastritis patients (93.7%) were infected with *Helicobacter pylori*. The frequency of A carrier was much higher (93.3%) than the T/T genotype among *Helicobacter pylori* -infected chronic active gastritis patients (Grade III), whereas the T/T genotype was observed in 100.0% of *Helicobacter pylori*-negative Grade III gastritis population. **Conclusion:** The *Helicobacter pylori*-infected patients carrying the A allele may increase the risk of gastritis, whereas the T/T genotype is protective. [*Bangladesh Journal of Infectious Diseases, June 2025;12(1):85-92*]

Keywords: *Helicobacter pylori*; gastritis; interleukin-8

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Introduction

Helicobacter pylori (*H. pylori*) infection is seemingly associated with various clinical outcomes, including asymptomatic infections, chronic and chronic active gastritis, peptic ulcer disease and gastric carcinoma[1]. However, why some *Helicobacter pylori* -infected patients have only mild asymptomatic gastritis or some develop peptic ulcers and gastric cancer remains a mystery. The complex interplay between the host immune responses, pathogen virulence factors, and environmental factors is responsible for *Helicobacter pylori* -induced pathology[2]. The key event in *Helicobacter pylori* pathogenesis is gastric mucosal inflammation, characterized by dense infiltration of neutrophils and lymphocytes. Accumulation of those inflammatory cells is mediated and regulated by inflammatory cytokines produced by gastric epithelial cells[3-5].

Chemokines are potential mediators among the cytokines induced by a bacterial infection. The C-X-C chemokines (Two terminal cysteines are separated by one amino acid, indicated by the name C-X-C) provide signals for the migration of granulocytes and are responsible for the inflammatory changes following the contact of bacteria with the epithelium [5]. Interleukin- 8 (IL-8), a potent C-X-C chemokine, induces cell proliferation, migration and angiogenesis and is elevated in gastric biopsy samples of patients with *Helicobacter pylori*-associated gastritis [6-8]. Increased IL-8 levels may amplify the inflammatory response to *Helicobacter pylori* by recruiting neutrophils and monocytes, thereby resulting in an advanced degree of gastritis, which ultimately predisposes to the development of gastric cancer [9]. Additionally, IL-8 is secreted by gastric epithelial cells, which is considered a crucial factor in the immunopathogenesis of peptic ulcer disease and gastric carcinoma [10].

Genetic polymorphisms in inflammatory cytokines are linked to increased production of interleukins, and IL-8 is essential in developing *Helicobacter pylori* infection, a key candidate host gene that affects its outcome[9-11]. The IL-8 gene has been described as having a polymorphism of an A/T base pair in the promoting region (-251), which is associated with an increase in the synthesis of Interleukin-8 by gastric epithelial cells[11-12]. Several studies conducted in some countries like Japan, Italy, and Brazil have found an association of IL-8 -251 A/T polymorphism with *Helicobacter pylori*-induced gastritis, gastric carcinogenesis and peptic ulcer disease[13-16], whereas some countries like Finland and Poland did not find any significant relationship between IL-8 -251 A/T polymorphism and risk of gastric cancer[17-18]. These conflicting results suggest that IL-8 -251 A/T polymorphism may be differently associated with gastric pathogenesis depending on the geographical variation[19].

So, it is important to know the pattern of IL-8 gene polymorphism in the Bangladeshi population to identify *Helicobacter pylori* infected patients who tend to develop severe gastroduodenal diseases. Early identification of persons having IL-8 gene polymorphism and proper treatment can reduce the severity of diseases. The study was aimed to explore the link between host interleukin-8 gene polymorphism and the severity of gastroduodenal disease in *Helicobacter pylori* infections.

Methodology

Study Settings and Population: This was a prospective observational study that recruited 113 gastritis patients who underwent upper gastrointestinal endoscopic examinations at the outpatient department of Gastroenterology at Bangladesh Medical University, Dhaka, Bangladesh (Former: Bangabandhu Sheikh Mujib Medical University (BSMMU)) and Dhaka Medical College Hospital in Dhaka, Bangladesh, from 2015 to 2020. Patients who received *Helicobacter pylori* eradication treatment in the previous 2 months, elderly individuals aged more than 65 years and those who had severe medical or surgical illnesses or had used proton pump inhibitors, nonsteroidal anti-inflammatory drugs, colloidal bismuth compounds, or antibiotics within 4 weeks of enrollment were excluded from the study[19].

Study Procedure: The study population was categorized into *Helicobacter pylori* infection positive and negative groups based on previously established case definitions[20]. Patients were considered *Helicobacter pylori* infection positive when positive results were obtained in at least two of the three tested methods (Rapid urease test, histology for *Helicobacter pylori* and PCR for the ureC gene) and considered negative when all diagnostic tests' results were negative.

Specimen Collection: For *Helicobacter pylori* and gastroduodenal disease detection, three pieces of gastric tissue were taken from non-lesional mucosa of the lesser curvature side of the antrum and midbody, respectively, from each patient. Additional biopsies were taken from the margins of

malignant-looking ulcers or proliferative growths for histopathological examination to confirm the diagnosis[19].

Histopathological Examination: Gastroduodenal diseases were diagnosed by histopathological examinations and established in accordance with the Sydney System Classification[21]. Gastritis was graded as Grade -0, Grade -1, Grade -2, and Grade -3. Histopathological stain haematoxylin and eosin were used to grade gastritis[22] as follows- Grade 0: inflammatory cells rarely seen (Absent); Grade 1: Lymphoid cells present but within normal limits, and no other evidence of inflammation (Mild); Grade 2: Increased number of lymphoid cells or normal cell numbers with evidence of inflammation, oedema, congestion or cell damage (Chronic gastritis); and Grade 3: increased number of lymphoid cells with increased PMN leukocytes or if a few PMNs infiltrated one gland neck or pit, if occasional PMNs were scattered throughout the superficial epithelium or if there was an obvious increase in PMNs in the lamina propria (Chronic active gastritis).

Two specimens from the antrum and body were fixed in 10.0% buffered formalin and sent to the Pathology Department of BSMMU and DMC hospital for histopathological examination. One specimen from each body and antrum was examined for the presence of *Helicobacter pylori*, utilizing a rapid urease test. One specimen from the antrum and body was preserved in a 1.5ml microcentrifuge tube containing 1 ml phosphate buffer solution to detect the *Helicobacter pylori* ureC gene and host IL-8 gene polymorphism by PCR and PCR-RFLP. All biopsy samples were stored at -20°C until DNA extraction from the samples was performed.

DNA Extraction and PCR for ureC Gene: DNA from gastric tissues was extracted using the QlAamp (QIAGEN) DNA Mini Kit according to the manufacturer's instructions, as mentioned in the published literature [23-25]. To confirm the presence of *H. pylori* DNA in tissue samples, the ureC gene was identified by PCR using the forward primers: 5′-AAGCTTTTAGGGGTGTTAGGGGTTT-3′ as well as reverse primers: 5′-AAGCTTACTTTCTAACACTAACGC -3′ [26]. The DNA was denatured at 94°C for 5 minutes, followed by 35 cycles at 93°C for 1 minute, 55°C for 30 seconds, and 72°C for 1 minute, with a final extension at 72°C for 10 minutes. The PCR product was analysed in 2% agarose gel with ethidium bromide, which was prepared in 1xTAE (Tris Acetic acid EDTA- Ethylene diamine tetra acetic acid) buffer by electrophoresis for 30 minutes to detect a specific band of 294 bp.

PCR-RFLP for IL-8 Gene Polymorphism Analysis: To analyze the polymorphism of the IL-8 gene at position -251, the primers used were forward: 5′-TTCTAACACCTGCCACTCTAG-3′ and reverse: 5′-CTGAAGCTCCACAATTTGGTG-3′. The PCR was performed as previously reported in another study [27]. The DNA was denatured at 94°C for 4 minutes, followed by 35 cycles at 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds, with a final extension at 72°C for 7 minutes. The PCR products were digested with the restriction enzyme MfeI and then visualized by electrophoresis on 5% agarose gel stained with ethidium bromide. The genotypes were coded as follows: T/T, a single band consisting of 108 bp; T/A, three bands composed of 108 bp, 76 bp, and 32 bp; and A/A, two bands composed of 76 bp and 32 bp. Figure 1 illustrates IL-8 polymorphism by PCR- restriction fragment length polymorphism analysis (PCR- RFLP) (1a) and grade 3 chronic active gastritis on H&E stain (1b).

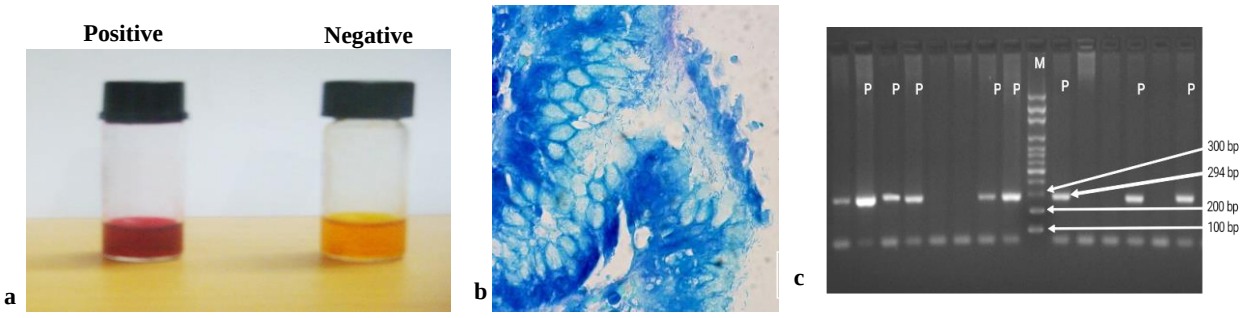
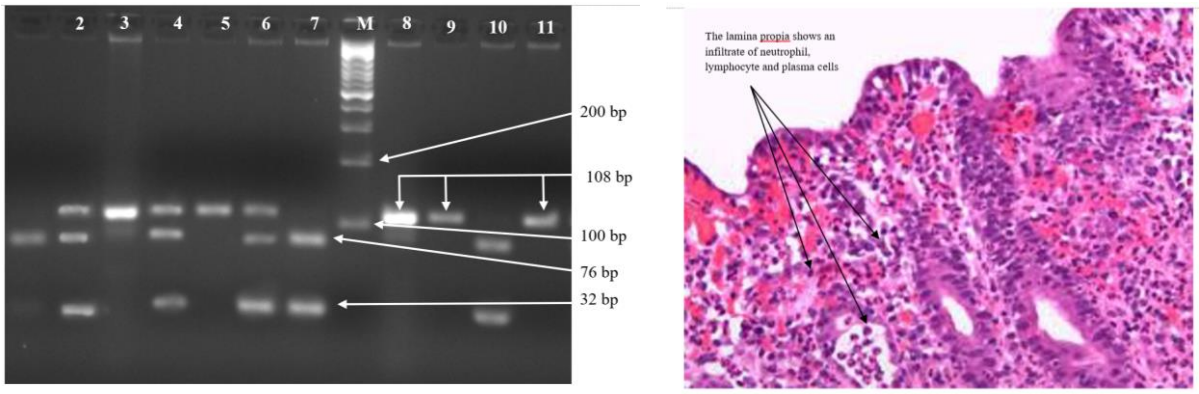


Figure 1: (a) Photography of positive and negative rapid urease test. (b) Histological section of the gastric mucosa of antrum showing *H. pylori* over the surface mucosa (Modified Giemsa stain X 100). (c) Amplification of 294 bp product of *H. pylori* ureC gene. (M = ladder marker, Lane-p = positive results).



a **b**

Figure 2: (a) PCR- RFLP analysis of IL-8 (-251) polymorphism by MfeI enzyme after gel electrophoresis.(M = ladder marker) (b) Photomicrograph of the gastric mucosa of antrum showing chronic active gastritis (Grade 3 gastritis) (H&E stainX 100)

Statistical Analysis: The statistical analysis was conducted using the Statistical Program for the Social Sciences (SPSS) version 28 (Inc., Chicago, USA). The sample size was calculated using the $n= Z^2pq/e^2$ formula. A 95% confidence interval was used. The seroprevalence of *Helicobacter pylori* infection in Bangladesh (p) is 92%, with an acceptable error (e) of 5%. The Chi-square or Fisher's exact test was used to compare the proportions, as appropriate. The effect of IL-8–251 genotypes on the risk of each gastroduodenal disease was expressed as the odds ratio (OR) with a 95% confidence interval (CI) using unconditional logistic regression analysis. Values of P <0.05 were considered statistically significant.

Ethical Clearance: This study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh (BSMMU/2015/10008) and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients, and collected data were encrypted.

Results

A total of 113 age and sex-adjusted patients were enrolled in this study, with male predominance (n=72, 63.7%) and a mean ±SD age of 39.4 ±12.8 years. The age (46.9 ±17.7 vs 42.5 ±15.6, P =0.15) and male sex distribution (45.8% vs 54.2%, P=0.58) were similar between *Helicobacter pylori* positive and negative groups. Of the total cases, the majority (61, 53.98%) were histopathologically diagnosed as gastritis, followed by 17 cases of duodenal ulcers, 12 cases of gastric ulcers, 8 cases of intestinal metaplasia, 1 case of gastric dysplasia, and 14 cases of gastric carcinomas. Out of 113 patients, 46 (40.7%) cases had the T/T genotype, 48 (42.5%) had the T/A genotype, and 19 (16.8%) had the A/A genotype. The frequencies of IL-8 T/A (55.7%) and A/A (27.8%) genotypes were significantly higher in the *H. pylori*-positive cases than in negative patients, whereas the IL-8 T/T genotype frequency was significantly higher in *Helicobacter pylori*-negative patients (62.7%) compared to *Helicobacter pylori* -positive patients. We identified a significant link between the A allele at position -251 of the IL-8 gene and increased susceptibility to *Helicobacter pylori* infections. The likelihood of *Helicobacter pylori* infections increased for individuals with the T/A genotype (Odds Ratio [OR] 6.8; 95% Confidence Interval [CI] 2.6-17.4, P <0.001), those with the A/A genotype (OR 15.4; 95% CI 4.1-57.8, P <0.001), and the carriers of the A allele showed an OR of 8.4 (95% CI 3.5-20.5, P <0.001) (Table 1).

Table 1: The frequency of host IL-8 gene polymorphisms at -251 position in *Helicobacter pylori* positive cases and *Helicobacter pylori* negative cases (*n* =113)

Variables		*H. pylori*		Total	OR (95% CI)	P value
		Positive	Negative			
Age (mean ±SD)		46.9 ±17.7	42.5 ±15.6	113	-	0.15
Sex	Men	33 (45.8%)	39 (54.2%)	72	1.1 (0.8-1.7)	0.58
	Women	21 (51.2%)	20 (48.8%)	41		

Genotypes IL-8 (-251)					
T/T	9 (16.7%)	37 (62.7%)	46(40.7%)	1.0	Reference
T/A	30 (55.7%)	18 (30.5%)	48(42.5%)	6.8 (2.6-17.4)	<0.001
A/A	15 (27.8%)	4 (6.8%)	19(16.8%)	15.4 (4.1-57.8)	<0.001
A carrier	45 (83.3%)	22 (37.3%)	67 (59.3%)	8.4 (3.5-20.5)	<0.001[b]
Total n (%)	54 (100.0%)	59 (100.0%)	113 (100.0%)		

OR- Odds Ratio; CI- Confidence Interval; P was determined by chi-square and independent t-test, as appropriate. Additionally, [b]P was determined by binary logistic regression analysis. Risk assessment was done by Binary logistic regression; T= Thymine, A= Adenine; A carrier = A/A+A/T.

The frequency of IL-8 genotypes in gastritis patients, distinguishing between those who are positive and negative for *Helicobacter pylori*. The IL-8 T/T genotype frequency was higher in the *H. pylori* infection-negative gastritis patients (62.1%) than those who were *Helicobacter pylori* infection-positive. Conversely, the frequencies of the T/A (41.7%) and A/A (33.3%) genotypes were significantly greater in patients with *Helicobacter pylori*-positive gastritis compared to their *Helicobacter pylori* infection-negative counterparts. This finding suggests that individuals with *Helicobacter pylori* infections and carriers of the A allele (comprising both the T/A and A/A genotypes, which account for 75%) have an increased risk of developing gastritis associated with the A/A genotype (OR 15.3, 95% CI 2.6-91.9, P =0.003). Additionally, carriers of the A allele showed an OR of 4.9 (95% CI: 1.6-15.4, P =0.005) (Table 2).

The distribution of the IL-8 genotype related to the histopathological grading of gastritis is illustrated in Table 3. Out of 61 patients, 13 (21.3%) were Grade-0, 15 (24.6%) were Grade-1, 17 (27.9%) were Grade-2 and 16 (26.2%) were Grade-3 gastritis patients. Most of the Grade-0 gastritis (92.3%), Grade-1 gastritis (73.3%) cases and Grade-2 gastritis cases (76.5%) were not infected with *H. pylori*, whereas the majority of Grade-3 gastritis patients (93.7%) were infected with *H. pylori*. In contrast to T/T genotypes (reference group), the A carrier genotype was insignificantly higher in all grades of gastritis, 93.3% in *H. pylori*-infected Grade 3, whereas A carrier was 75% among Grade 2 and 25% among Grade 1 gastritis (P >0.05) (Table 3).

Table 2: Frequency of Host IL-8 Genotypes among *H. pylori* positive and negative gastritis cases (*n*=61)

Genotypes IL-8 (-251)	**Gastritis**		**OR (95% CI)**	**P value**
	***H. pylori* positive cases**	***H. pylori* negative cases**		
T/T	6 (25.0%)	23 (62.2%)	1.0	Reference
T/A	10 (41.7%)	12 (32.4%)	3.2 (0.9-10.9)	0.064
A/A	8 (33.3%)	2 (5.4%)	15.3 (2.6-91.9)	0.003
A carrier	18 (75.0%)	14 (37.8%)	4.9 (1.6-15.4)	0.005
Total	24 (100.0%)	37 (100.0%)		

OR- Odds Ratio; CI- Confidence Interval; P value was compared between IL-8 genotype and H. pylori infection. P value was determined by Binary logistic regression. T= Thymine, A= Adenine; A carrier = A/A+A/T

Table 3: Distribution of IL-8 Genotype in Relation to Histopathological Grading of Among Gastritis Patients (n=61)

Histopathological findings		**A carrier**	**T/T Genotype**	**Total**	**P value**
Grade 0 (n =13)	*H. pylori* Positive	0 (0.0%)	1 (7.7%)	1 (100)	0.52
	H. pylori Negative	5 (41.7%)	12 (92.3%)	7 (58.3)	
Grade 1 (n =15)	*H. pylori* Positive	1 (25.0%)	4 (36.4%)	3 (75)	0.94
	H. pylori Negative	3 (27.3%)	11 (73.3%)	8 (72.7)	
Grade 2 (n =17)	*H. pylori* Positive	3 (75.0%)	4 (23.5%)	1 (25)	0.59
	H. pylori Negative	6 (46.25)	13 (76.5%)	7 (53.8)	

Grade 3 (n =16)	*H. pylori* Positive	14 (93.3%)	15 (93.7%)	1 (6.7)	0.34
	H. pylori Negative	0 (0.0%)	1 (6.3%)	1 (100)	

P value was compared between A carrier and T/T genotype and was determined by χ^2 test; T= Thymine, A= Adenine, A carrier = A/A+A/T genotype; Grade 0= Normal; Grade 1= Normal; Grade 2= Chronic gastritis; Grade 3= Chronic active gastritis

Discussion

We found that the frequency of IL-8 T/A, and A/A genotypes was significantly higher in the *Helicobacter pylori* infected population than in negative patients. In contrast, the IL-8 T/T genotype frequency was significantly higher in patients who were *Helicobacter pylori*-negative compared to those who were positive.

Transepithelial signal transmission and hypochlorhydria by *Helicobacter pylori* play a significant role in initiating the inflammatory response in *Helicobacter pylori*-associated gastritis[28-30]. Among the inflammatory cytokines, chemokines are possible candidates to act as second signals following the contact of bacteria with the epithelium. IL-8 may have a major role in *Helicobacter pylori* -induced gastritis because *Helicobacter pylori* infections are histologically characterized by neutrophil infiltration [23]. When an individual is exposed to *Helicobacter pylori*, the variation of clinical outcomes depends on host-pathogen interaction. Moreover, Rad et al. observed that the cytokine gene expression and susceptibility to infectious disease are influenced by allelic variation in the cytokine gene[31]. So, the determination of allelic variation of the host interleukin -8 gene has been suggested to predict outcomes of *Helicobacter pylori* -associated pathologies[15,19,32-34]. Despite controversies [35-37], Ramis and colleagues found the IL-8 T/A genotype in 52.3% and the A/A genotype in 26.5% of the *Helicobacter pylori* -infected population; similar findings were also noted in Brazil [13,15], supporting the current study results. A genome-wide linkage analysis[38] identified the host genetic factor contributing to the prevalence of *Helicobacter pylori* infection and observed the possible linkage of the host factors with chromosomes 4 and 6, similar to other study findings[39]. This is the first Bangladeshi study demonstrating that IL-8 polymorphism at position -251 on chromosome 4 (4q13-q21) is linked to a higher risk of gastritis in *Helicobacter pylori* infected patients.

The IL-8 A carrier was significantly associated with *Helicobacter pylori* infected gastritis patients; a similar association was found in Japan [14] and the Hungary population[39,40]. Previous studies indicate that 90.2% of patients[41] with Grade 3 gastritis are infected with *Helicobacter pylori*, and neutrophil activity is typically present in active cases[42], which makes neutrophils a sensitive indicator of *Helicobacter pylori*, supporting our study's findings. A Korean study [19] found that neutrophil infiltration, atrophy, and intestinal metaplasia in the gastric body mucosa were more significant in individuals with the IL-8-251 A genotype compared to the T/T genotype. Patients with the A/A genotype exhibited higher IL-8 levels and greater neutrophil infiltration compared to those with the T/T genotype, thereby increasing the risk of atrophic gastritis in *Helicobacter pylori*-infected individuals[14,26]. *Helicobacter pylori* infections can lead to gastric cancer, gastric ulcers, and duodenal ulcers through two main pathways. The first pathway involves significant neutrophil infiltration, which damages the surface epithelium and can result in multifocal atrophic gastritis, gastric ulcers, or dysplastic changes linked to gastric cancer[43]. Another pathway is characterized by diffuse antral gastritis in which lymphocytes and plasma cells infiltrate the mucosa typically found in duodenal ulcer patients [44], who are considered at no increased risk of gastric cancer[45].

Although the study is novel, it has several limitations, particularly the small sample sizes and the cross-sectional nature of the research on the Bangladeshi population, which may not apply to other ancestries. The IL-8 genotypes identified by PCR-RFLP cannot be confirmed by sequencing due to time, budget and resource constraints. Moreover, *Helicobacter pylori* colonized individuals cannot be assessed as asymptomatic individuals excluded from the study. However, a multicentre evaluation of the association of various pro-inflammatory and anti-inflammatory cytokine gene polymorphisms in *Helicobacter pylori* infections in different ethnicities could prove a more reliable correlation and also establish the role of host factors in developing gastroduodenal diseases. Finally, likely, merely one polymorphism cannot determine the outcome of the disease, but the higher IL-8-producing genotypes appear to confer a higher risk of developing gastritis and peptic ulcer disease in *Helicobacter pylori* -infected patients. Novel therapies can also inhibit or reduce the

inflammation induced by this mucosal pathogen if the host genetic factors and their role in the disease process are studied in detail.

Conclusion

Carriers of the A allele at position -251 of the IL-8 gene are significantly associated with increased susceptibility to *Helicobacter pylori* infection, while the T/T genotype appears to have protective effects against *Helicobacter pylori* infections. Individuals with the IL-8 A allele (those with T/A or A/A genotypes) may have a higher risk of developing gastritis and peptic ulcer diseases when infected with *Helicobacter pylori*. Additionally, the IL-8 A allele may be linked to more severe inflammation (Grade 3 gastritis) compared to the T/T genotype in cases of *Helicobacter pylori* infection. Therefore, intensive endoscopic screening and/or eradication therapy for patients at higher risk of developing gastric cancer can reduce the disease progression.

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Conflict of Interest
The authors declare no conflict of interest in the publication of this paper.

Financial Disclosure
None

Authors' contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Data Availability and Data Sharing Statement
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Dr. Ritu Saha had full access to all of the study data and took complete responsibility for the integrity of the data and the accuracy of the data analysis..

Ethics Approval and Consent to Participate
The Institutional Review Board granted the study ethical approval. Since this was a prospective study, every study participant provided formal informed consent. Each method followed the appropriate rules and regulations.

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