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Pro-inflammatory cytokines of gastric tissues and its role in patients with *H. pylori*

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ABSTRACT

Helicobacter pylori infection, affecting over 50% of the global population, is a major cause of peptic ulcer disease due to its robust induction of pro-inflammatory cytokines like Tumor Necrosis Factor-alpha1 and Interleukin-1 Beta. These cytokines recruit immune cells, leading to tissue damage and ulceration. The aim of the study is to investigate the role of these cytokines in the pathogenesis of *H. pylori*-induced peptic ulcers by quantifying their concentrations in mucous layer of gastric biopsy samples. A total of 65 patients with epigastric pain diagnosed as peptic ulcer and 25 healthy controls have been involved. Gastric biopsies were obtained to detect *H. pylori* using quantitative real-time PCR (qRT-PCR) to measure copy numbers (rpoD gene). The concentration of Interleukin-1 Beta and Tumor Necrosis Factor-alpha1 in biopsy suspension samples were determined using an ELISA assay (Solarbio Human IL-1β ELISA Kit), and absorbance measured with a Fisher Scientific ELISA plate reader. Patients with peptic ulcers and positive to *H. pylori* demonstrated significantly elevated concentrations of both IL-1β (17.78 pg/ml vs. 9.05 pg/ml) and TNFα (89.84 pg/ml vs. 34.67 pg/ml) compared to controls ($p<0.001$). The study highlights elevation of TNFα and IL-1β in *H. pylori*-induced peptic ulcer patients, indicating their critical role in inflammation and ulcer pathogenesis.

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Introduction

Helicobacter pylori is gram-negative bacteria and have spiral-shaped, colonization mainly in the anural portion gastric mucosa human. *Helicobacter. pylori* infection is connected with the progress of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosa associated lymphoid tissue lymphoma (MALT) a (Dunn, Cohen et al. 1997, Abbas et al. 2025, Abid et al. 2025). *H. pylori* infection spread in about 50% of the world's population.

The moment that infected, *Helicobacter. pylori* can be a permanent infection in the human unless eradicated. Eighty-five percent of infected patients experience only mild, asymptomatic gastritis, while 15% may progress to peptic ulcer disease (PUD), and fewer than 1% face the risk of developing gastric cancer (Amieva and El–Omar 2008).

Peptic ulcer disease (PUD) can result in lesions that penetrate the stomach lining, occasionally extending to the muscularis mucosae. Multiple risk factors contribute to the onset and progression of PUD, including infection with *Helicobacter. pylori*, the usage of non- steroidal anti-inflammatory drugs (NSAIDs), smoking, alcohol consumption, stress, unhealthy lifestyle choices, and unhealthy lifestyle choices, and genetic predisposition. These factors play a critical role in the exacerbation and advancement of ulcerative condition (Malik et al. 2024). *Helicobacter. pylori* commonly colonize in gastric mucosa of human during childhood and continues overall

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the life. *Helicobacter. pylori* has evolved multiple mechanisms to evade clearance by the immune system (White et al. 2015).*H. pylori* infection is strongly linked to stomach ulcers, accounting for up to 80% of cases, and to duodenal ulcers, responsible for approximately 90% of cases (Fong 2020).

Interleukin-1 Beta an important pro- inflammatory cytokine essential for immune responses to infection, primarily produced by innate immune cells like macrophage and monocytes. It is produced as inactive precursor, pro-IL1β, which stimulated in response to pathogen-associated molecular patterns (PAMPs) through (PRR). First expression of pro-IL1βis considered a priming step, requiring a subsequent with encounter with another PAMP or danger associated molecular pattern for stimulation. Activation including the cleavage of pro-IL1β by caspase-1, which is recruited into inflammasome complex made by the cytosolic PRRNLRP3 and adaptor proteins(Thornberry, Bull et al. 1992, Dinarello 1996, Schroder and Tschopp 2010, Takeuchi and Akira 2010).

Excessive or dysregulated Interleukin-1 Beta production is associated with chronic inflammatory conditions, including inflammatory bowel disease and rheumatoid arthritis, and even neuroinflammatory conditions like Alzheimer's disease (Schiff 2000, Kinney, Bemiller et al. 2018, Aggeletopoulou et al. 2024). Significantly, polymorphisms in the IL-1β gene influence cytokine production and share with an individual's susceptibility to peptic ulcers, mainly in response to *Helicobacter. pylori* infection (Shakhatreh et al. 2020).

Tumor Necrosis Factor-alpha as glycoprotein induced by endotoxin, belongs to cytokine family included in acute phase reaction and systemic inflammation .The main function of TNF-α is controlling cells of immune system .TNF-α presence as endogenous pyrogen, is able to stimulate fever, apoptosis, inflammation and cachexia (Tourani et al. 2018). Abnormal regulation of TNF-α production has been associated with numerous human disease, involving cancer major depression, inflammatory bowel disease an various disorders such as gastric cancer and peptic ulcer and Alzheimer ′s disease. . Individuals infected with H. pylori exhibit elevated levels of TNF-α compared to those who are uninfected (Rokkas et al. 2014).

Macrophages are stimulated by *Helicobacter. pylori* secrete various cytokines, such as TNF-α and IL-1β. IL-1β is specifically produced via inflammasome activation in response to the virulence factors of *Helicobacter. pylori* (Ciesielska et al. 2021).

This study aimed to study the expression role of TNFα and IL1β in in *Helicobacter. pylori*-infected gastritis as inflammatory response and their potential roles in the progress of peptic ulcer disease. Specifically.

Materials and Methods

Subjects and sample collection

In this case – control enrolled 2 groups: a case group of patients have peptic ulcer disease and a control group don′t have peptic ulcer disease. Both groups were selected from individuals referred to a gastroenterology hospital in Najaf Al- Ashraf city in March 2024. Gastric biopsies were obtained from 90 person candidate undergoing upper gastrointestinal endoscopy. Before the biopsy collection, all participants took part in interview using a standardized questionnaire to gather demographic information.

Individuals with a history of gastric disorders due to increase stomach acid secretion or NSAID use were not included in the study. Specimens were obtained from patients aged 10 to 70 years. The patient group consisted of 65 individuals diagnosed with *Helicobacter. pylori* (30 males and 35 females), while the control group included 25 individuals without *Helicobacter. pylori* (12 males and 13 females).

DNA extraction

Gastric biopsy specimens were preserved in normal saline at -20°C. DNA extraction from the gastric biopsies was carried out following the manufacturer's instructions using the Geneaid Biotech DNA extraction kit (Presto, UK). The extracted DNA specimens were stored at -20°C until use. The quality and amount of DNA extracts were evaluated using Nano-drop spectrophotometer (DeNovix, USA).

qPCR method for detection H. pylori

DNA extracted from biopsy samples was used for detection of H. pylori copy number. PCR was conducted on DNA extracted from gastric biopsy samples in a reaction volume of 25 µl (Youseq, UK), containing 10 µl of Tetra 2X qPCR Master Mix, 1 µl of *H. pylori*-specific primer/probe (*rpoD* gene), 10 µl of endogenous control primer/probe, and 8 µl of extracted sample DNA.According To qPCR method procedure if copy number of *H. pylori* more than 35 copy the sample consider positive (case), less 35 copy consider negative (control).

Cytokine assay

Centrifuge mucus layer of biopsy at 3000 rpm for 1 minute for homogenies. Perform the assay immediately or aliquot and store samples at or below -20°C. Avoid repeated freeze-thaw cycles.

Enzyme-Linked Immunosorbent Assay (ELISA) method was used to measure cytokines by using

commercial kits for human IL-1β ELISA immunoassay kit (HRP) and human TNF-α ELISA immunoassay kit (HRP) (Solarlab, China). The manufacturer's instructions were carefully followed to and each plate was tested before use to confirm the calibration curve measured IL-1b standards (15.625–1000 pg/ml) and TNF-α standards (15.62 pg\ml) within the stated limits of the assay. An ELISA reader (The BioTek 800 TS absorbance reader/Germany) measured the kits made use of concentrated Biotin-conjugated with anti- IL1β antibody and Biotin-conjugated with anti-TNF-α antibody. The substrate color reaction at 450 nm. The optical density values obtained with the known samples were used to calculate the quantity of IL-1b and TNF-α in the other samples.

Results

Demographic information of the subjects:

Out of the 90 participants included in this study, 65 individuals diagnosed with peptic ulcer disease, with a mean age of 34.63 ± 14.234 years (30 males and 35 females), comprised the case group. The control group consisted of 25 individuals without PUD, with a mean age of 31.24 ± 11.875 years (12 males and 13 females).

Table 1 Demographic comparison of age and gender distribution between PUD patients and control group.

Demographic	Control (NPUD) (n = 25)	PUD (n = 65)	P-value
Age (years)	31.24 ± 11.875	34.63 ± 14.234	0.284
Gender	12/13	35/30	0.887
N (%)	(48.0/52)	(48.8/51.3)	

Mean ± SD

The study population was modified for both age and gender, as detailed in Table 1.

Diagnosis of H. pylori infection

For diagnosis *Helicobacter pylori* infection in patient's biopsy specimens were used specific qPCR (copy number) as shown in table (2). In figure (1), this is the first run for 88 samples only, yellow circle represents a standard curve amplification, other lines represent amplification of patient samples. dRn means Baseline corrected fluorescence with reference (ROX).

Also, in figure (2), this standard curve is used in a qPCR assay to quantify *Helicobacter. pylori* DNA copy number in samples. Each point on the graph represents a sample with a known amount of DNA, spanning a range of concentrations from lower on the left to higher starting quantities of DNA have lower Ct (cycle threshold) values, meaning they detect earlier in PCR cycles. The close alignment of these points along the line, with R2 value of 0.994, indicates strong consistency and reliability in the assay, allowing unknown DNA quantities to be estimated accurately. This curve effectively enables the quantification of *Helicobacter*. *pylori* in patients samples by matching their Ct values to this reference, even through efficiency, at 82.9%, is slightly below the ideal range.

Table 2 Comparison of Cq (Ct) and copy number of *H. pylori* between control and patient groups

Results	Values
Cq	31.07±0.66
Copy number	35108.90±8311.88

The results indicate a stable average Cq value (31.07 ± 0.66) across *Helicobacter. pylori* samples, suggesting consistent detection thresholds. However, the copy number (35,108.90 ± 8,311.88) varies more widely, reflecting differences in bacterial load, which may correspond to variations in infection severity or progression among samples. Overall, these findings highlight detectable *H. pylori* levels with varying bacterial concentration.

Table 3 Significant variable in copy number between patients and controls

Groups	Number	Copies group (mean± Std.)	p-value
Patients	65	34219.99 ± 72671.592	>0.001**
Controls	25	18.400 ± 7.789	

* Represent a significant difference at p≤ 0.05.

The results from qPCR on biopsy specimen specimens for diagnosis *H. pylori* infection show a significantly higher mean cop number in patients (34219.99) compared to controls (18.4), indicating a marked presence of the infection in patients. The high standard deviation in patients suggest variability in infection levels, while the low deviation in controls shows consistent low copy number. The p-value (<0.001) confirm this difference is statistically significant, supporting qPCR's diagnostic accuracy.

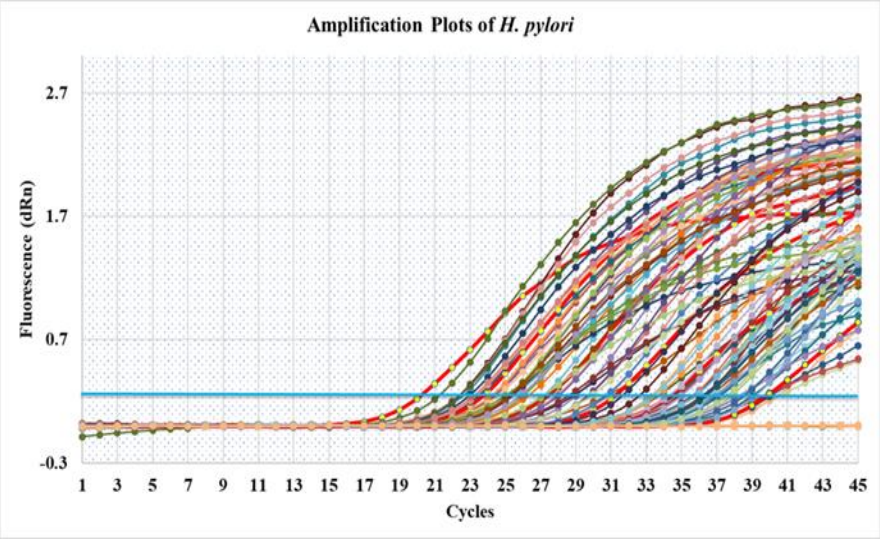

Fig 1. Identification and quantification of *H. pylori* copy number by qPCR assay.

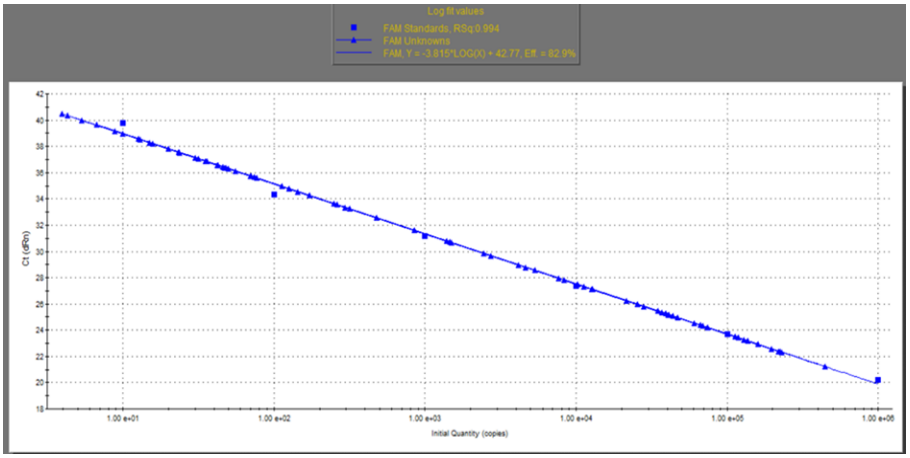

Fig 2. Amplification standard curve for quantification of *H. pylori* copy number by qPCR assay.

Interpretation of different IL1 beta concentration between patients and controls groups

Date represented in table (4) showed the comparison of IL1β levels between *Helicobacter. pylori* infected patients and controls shows a significantly higher mean in patients (17.78) compared to controls (9.05). The patients also exhibit greater variability in IL1β levels (standard deviation 13.96) versus the controls (1.40), indicating inconsistent inflammatory responses among patients. The p-value (<0.001) suggest that this difference is statistically significant, highlighting the role of IL1β in *Helicobacter. pylori* infection.

Table 4: Comparison of IL-1β level between patients and controls

Groups	Number	IL-1β (M ±S.D.)	p-value
Patients	65	17.78±13.961	<0.001**
Controls	25	9.05±1.404	

Interpretation of different TNF-α beta concentration between patients and controls groups

In table 5, the comparison of TNF-α levels between *Helicobacter. pylori* infected patients and controls reveals a statically significant difference (p<0.001). Patients exhibited a notably higher mean TNF-α level (89.84± 120.359) compared to controls (34.67± 30.304), indicating elevated inflammatory response in the infected group. This suggests a strong association

between peptic ulcers induced by *Helicobacter. pylori* and increased TNF-α production as in table 5.

Table 5 Comparison of TNF alpha level between patients and controls.

Groups	Number	TNF-α(mean±Std. deviation)	p-value
Patients	65	89.84±120.359	0.001**
Controls	25	34.67±30.304	

Discussion

Helicobacter. pylori is clinically isolates of adapt rapidly to their host. The bacterium is acquire the ability colonization in epithelium cells of stomach, which can produce to human gastric diseases. Chronic gastritis stimulates microorganisms to alter the host, leading to variations in the severity of the disease induced by *Helicobacter. pylori* in various individuals (Li et al. 2018). *Helicobacter. pylori* infection required effective diagnosis is essential for effective clinical management, symptom relief, and bacterial eradication. Both molecular techniques and culture have their advantages and drawbacks. Molecular methods for diagnosing *Helicobacter. pylori* offer very high sensitivity (over 95%) and specificity (close to 100%), detecting more positive cases than culture. Unlike culture, which depends on the viability of the bacteria, molecular techniques do not have this limitation. Additionally, some molecular procedures can be applied to gastric biopsy or non-invasive specimens. Moreover, PCR-based techniques allow for faster identification by amplifying genome-specific regions, providing results more quickly than culture, which typically requires 10-14 days to yield a negative result(Fernandez-Caso et al. 2022).

PCR is a valuable tool for routine laboratory testing to detect *Helicobacter. pylori* in stomach tissue, providing high sensitivity and specificity. However, it requires careful analysis and standardized procedures to ensure reliable results (Nevoa et al. 2017).

The results in table (3) likely appear the *Helicobacter. pylori* copies number detected in biopsy samples from two groups. The patient group, with a mean of 34,219.99 *Helicobacter. pylori* copies number represents a significantly higher bacterial number in biopsies compared to the control group, which had mean only 18.40 copies number. This suggests that the patients have severe infection with *Helicobacter. pylori* progress to peptic ulcer. The large standard deviation in the patient group 72,671.59 indicates substantial variability in the bacterial copies number in samples, implying that some patients may have extremely high levels of *Helicobacter. pylori* related to develop to peptic ulcer disease; others might have lower but still significantly elevated levels compared to controls due to low number of *Helicobacter. pylori* in biopsies not reach to infected dose don't cause peptic ulcer in controls. In contrast, the low standard deviation in the control group 7.79 suggests that *H. pylori* presence in healthy individuals is minimal, likely to represent secondary or background bacterial levels. The p-value < 0.001 emphasize that the observed difference in *Helicobacter. pylori* copies number between patients and controls is statistically significant, meaning that the higher bacterial number in patients is highly unlikely to be due to link to *Helicobacter. pylori* the main causative agent for peptic ulcer disease (Mutar et al. 2025).

This study suggests that elevated (IL-1β) levels in patients with peptic ulcer disease may be directly linked to the mechanisms by which *Helicobacter pylori* induces ulcers. *Helicobacter. pylori* infection triggers a strong immune and inflammatory response in the gastric mucosa, with IL-1β playing a crucial role in this inflammatory cascade. Upon infection, *Helicobacter. pylori* stimulates secretion of IL-1β, which in turn recruits inflammatory cells such as macrophages and neutrophils to the site of infection. This influx of immune cells produce inflammatory mediators, causing tissue injury.IL-1β also inhibition gastric acid secretion, generating an environment suitable for *H. pylori* colonization while damaging mucus layer against the acid. Additionally, IL-1β disorders the normal processes of tissue repair, corporation with ongoing damage and preventing the healing of ulcers. IL-1β levels in patients higher significant compared to controls, as demonstrated by the strong statistical significance ($p< 0.001$), highlight its essential function in the development of peptic ulcers. This suggests that the chronic inflammatory response produced by IL-1β exacerbates *Helicobacter. pylori* pathogenesis, leading to the development from gastritis to peptic ulcer disease.

The study investigates the association between *Helicobacter. pylori* infection and TNF-α levels, highlighting a significant elevation in inflammatory response among infected individuals. Statistical analysis reveals a pronounced difference in TNF-α levels between *Helicobacter. pylori* infected patients and controls, with a p-value lower than 0.001, indicating strong role of TNF- α in peptic ulcer formation.

In the infected cohort, the mean TNF-α level was 89.84 ± 120.359, contrasted with 34.67 ± 30.304 in the control group. This substantial increase in THF-α among patients suggests that *Helicobacter. pylori* infection is closely related to heightened inflammatory activity. The elevated TNF-α levels in infected persons underscore the

potential role of this cytokine in pathogenesis of *H. pylori* related disease.

These findings emphasize the importance of TNF-α`as biomarker for peptic ulcer induced by *Helicobacter. pylori* and may inform future therapeutic strategies amid at mitigating inflammation –related damage in infected patients. The results contribute to a growing body of evidence linking *Helicobacter. pylori* infection progression gastric cancer, highlighting the need for further research into targeted anti- inflammatory treatments (Sabah & AL-Oqaili 2024).

Recent evidence has highlighted the link between pro-inflammatory cytokines and pro- inflammatory, showing that a series of reactions including in the dysregulation of stomach secretion occur due to *Helicobacter. pylori* infection. This creates a conducive environment for the development of peptic ulcers (Haruma et al. 2000). Damage to the barriers in strict cell junctions increases antigen presentation to immune cells, which enhances the activation of the human immune system and elevates the production of pro-inflammatory cytokines for example IL-1β, IL-2, and TNF-α (Algood and Cover 2006). Pro inflammatory cytokines increased production, in return consequences in raised progression of peptic ulcer (Larussa et al. 2015).

Conclusion

This study identifies increase in IL-1β and TNFα levels in patients with *H. pylori*–induced peptic ulcers, emphasizing the crucial role these cytokines play in development of ulceration. The results suggest that IL-1β and TNFα are central mediators of inflammation and tissue damage, pointing to their potential as therapeutic targets for managing this challenging condition.

Ethical approval

Two biopsies' specimens were prepared from stomach or duodenum for patient. The study received approval NO.12268 in 28\3\2024 from the Research Ethics Committee of the Faculty of Medicine at Babylon University. In addition, informed consent was obtained from all participants before their inclusion in the study.

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Authors' contributions

The authors conceived and designed the experiment, performed the experiment, analyzed the data participated in its design and coordination, and helped to draft the manuscript. All authors read and approved of the final manuscript.

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Conflicts of interest

The authors report no conflict of interest.

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