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Investigation of the Presence of *Helicobacter Pylori* and the cagA Gene in Nasal Polyp Tissues by PCR

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ÖZ

Amaç: Nazal polipler sinonazal mukozanın inflamatuvar lezyonları olup mikrobiyal faktörlerden etkilenebilir. Helicobacter pylori ve cagA geni, mukozal inflamasyonla olası ilişkileri nedeniyle ilgi çekmektedir. Bu çalışmada nazal polip dokularında H. pylori DNA'sının ve cagA geninin polimeraz zincir reaksiyonu (PCR) ile saptanması amaçlanmıştır.
Araçlar ve Yöntem: Bu kesitsel çalışmaya, nazal polip nedeniyle cerrahi uygulanan hastalardan alınan 45 nazal polip dokusu örneği dahil edildi. Genomik DNA ticari bir kit ile izole edildi. PCR analizinde H. pylori varlığı için glmM geni, virülansla ilişkili genetik materyalin değerlendirilmesi için cagA geni hedeflendi. Çalışmaya pozitif ve negatif kontroller dahil edildi. Demografik değişkenler ve PCR pozitiflik oranları tanımlayıcı olarak, yaş gruplarıyla ilişkiler ise istatistiksel olarak değerlendirildi.
Bulgular: Tüm örnekler başarıyla analiz edildi. Grup 26 erkek (%57,78) ve 19 kadından (%42,22) oluşmakta olup yaş aralığı 15-75 yıl idi. glmM temelli H. pylori pozitifliği 19 örnekte (%42,22) saptanırken 26 örnek (%57,78) negatifti. cagA pozitifliği 16 örnekte (%35,55) bulunurken 29 örnek (%64,45) negatifti. glmM ve cagA pozitiflik oranları 50-59 ve 60-75 yaş gruplarında sayısal olarak daha yüksek olmakla birlikte, yaş grubu ile PCR pozitifliği arasında anlamlı bir ilişki saptanmadı.
Sonuç: PCR analizi, nazal polip dokularının bir kısmında H. pylori DNA'sını ve cagA genini göstermiştir; bu bulgu mikrobiyal genetik materyal ile kronik inflamatuvar mikroçevre arasında olası bir ilişkiye işaret etmektedir. Ancak PCR pozitifliği tek başına canlı bakteri varlığını, aktif kolonizasyonu veya nedenselliği kanıtlamaz. Moleküler, mikrobiyolojik ve klinik parametreleri birleştiren daha geniş, kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: bakteriyel proteinler; glmM; inflamasyon; sinüzit; virülans faktörleri

ABSTRACT

Purpose: Nasal polyps are inflammatory lesions of the sinonasal mucosa and may be influenced by microbial factors. Helicobacter pylori and its cagA gene are of interest because of their possible association with mucosal inflammation. This study aimed to detect H. pylori DNA and the cagA gene in nasal polyp tissues by polymerase chain reaction (PCR).
Materials and Methods: This cross-sectional study included 45 nasal polyp specimens from patients undergoing surgery. Genomic DNA was extracted using a commercial kit. PCR analysis targeted the glmM gene for H. pylori detection and the cagA gene for assessment of virulence-associated genetic material. Positive and negative controls were included. Demographic variables and PCR positivity rates were evaluated descriptively, and associations with age groups were assessed statistically.
Results: All samples were successfully analyzed. The group included 26 men (57.78%) and 19 women (42.22%), aged 15-75 years. glmM-based H. pylori positivity was detected in 19 samples (42.22%), whereas 26 (57.78%) were negative. cagA positivity was found in 16 samples (35.55%), whereas 29 (64.45%) were negative. Although glmM and cagA positivity rates were numerically higher in the 50-59 and 60-75-year age groups, no significant association was found between age group and PCR positivity.
Conclusion: PCR analysis demonstrated H. pylori DNA and the cagA gene in a subset of nasal polyp tissues, suggesting a possible association between microbial genetic material and the chronic inflammatory microenvironment. However, PCR positivity alone does not prove viable bacteria, active colonization, or causality. Larger controlled studies integrating molecular, microbiological, and clinical parameters are needed.

Keywords: bacterial proteins; glmM; inflammation; sinusitis; virulence factors

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INTRODUCTION

Nasal polyps are regarded as an important subphenotype of chronic rhinosinusitis and are benign lesions characterized by prolonged inflammation of the nasal mucosa. 1 These structures are generally bilateral and are histopathologically defined by edematous stroma, dense inflammatory cell infiltration, and structural alterations in the epithelium. 2 Although the exact mechanism underlying nasal polyp formation has not been fully elucidated, it is widely accepted to be a multifactorial process arising from the interaction of immunological responses, environmental factors, allergic processes, and infectious agents. 3 In recent years, growing attention has been directed toward the role of microbial factors in the persistence of chronic inflammation. In particular, bacterial colonization has been suggested to sustain the inflammatory process by influencing the mucosal immune response. Within this context, not only classical respiratory pathogens but also microorganisms originating from the gastrointestinal tract have become the subject of investigation in the upper respiratory tract. 4

Although Helicobacter pylori (H. pylori) is primarily associated with gastric diseases, it has also been identified in extragastric sites, including the nasal cavity. The possible reservoir role of the nasal and oral cavities, the potential for reflux-mediated transfer to the upper airway, and previously reported positivity in nasal polyp tissues make it reasonable to investigate the relationship between this bacterium and nasal polyps. However, although current evidence supports a possible association, it does not demonstrate direct causality. 5,6

The potential biological relevance of H. pylori is related not only to its presence but also to its virulence characteristics. One of the most important virulence factors involved in the pathogenicity of H. pylori is the cytotoxin-associated gene A (cagA). cagA-positive strains are known to enhance inflammatory responses and aggravate tissue damage by affecting host cell signaling pathways. For this reason, the presence of cagA is considered an important biomarker in evaluating the potential clinical impact of the bacterium. 7 Polymerase chain reaction (PCR) is one of the highly sensitive methods used to detect H. pylori in tissue samples. In this method, the glmM gene region is frequently used to determine the presence of H. pylori, whereas specific gene regions such as cagA are used to assess virulence-related characteristics. 8

Findings regarding the presence of H. pylori in nasal polyp tissues have been inconsistent, and data on gene regions reflecting the virulence properties of the bacterium remain limited. In addition, previous studies have often differed in diagnostic methods, target genes, sample types, and the presence or absence of control groups. Therefore, the present study was designed to address this gap by investigating H. pylori DNA in nasal polyp tissues using PCR targeting the glmM gene region and by evaluating cagA gene positivity as a virulence-associated molecular marker. This approach aimed to provide additional molecular data on the possible coexistence of H. pylori-related genetic material in the inflammatory microenvironment of nasal polyps without inferring causality.

MATERIALS and METHODS

Study Design and Sample

This descriptive, cross-sectional study was designed to evaluate the presence of *H. pylori* and cagA gene positivity in nasal polyp tissues. The study material consisted of nasal polyp tissue samples obtained intraoperatively from 45 patients, including 26 men and 19 women, aged 15-75 years, who underwent surgery for nasal polyps at the Department of Otorhinolaryngology, Fırat University Faculty of Medicine, Elazığ, Türkiye. The samples were collected under sterile conditions and transported to the laboratory in an appropriate manner for molecular analysis. The methodological framework of the study was structured on the basis of similarly designed tissue-based prospective/cross-sectional studies.

DNA Isolation

Genomic DNA was isolated from nasal polyp tissues using a commercial DNA extraction kit (Wizard Genomic DNA Purification System, Promega Co., Madison, WI, USA) in accordance with the manufacturer's instructions. The isolated DNA samples were dissolved in sterile dH_2O and stored at -80 °C until analysis.

PCR Analysis of H. pylori and cagA

To detect the presence of *H. pylori*, the glmM gene region was targeted, whereas the cagA gene region was used for virulence assessment. The PCR thermal cycling conditions used for amplification of the glmM and cagA gene regions are summarized in Table 1. Separate primer sets were used for each target, and the primer sequences and expected amplicon lengths are presented in Table 2. The expected PCR product sizes were 294 bp for glmM and 400 bp for cagA. The PCR reaction mixture was prepared in a total volume of 100 µL, containing 10X PCR buffer (100 mM Tris-HCl, pH 8.0, 500 mM potassium chloride, 15 mM magnesium chloride), 250 µM of each deoxynucleotide triphosphate, 2 U of Taq DNA polymerase (Promega Co.), 10 pM of each primer, and 10 µL of template DNA. Following amplification, the products were electrophoresed on 2% agarose gel, stained with ethidium bromide, and evaluated under an ultraviolet transilluminator. [9,10] Representative agarose gel images for glmM and cagA amplification are shown in Figures 1 and 2.

Table 1. PCR thermal cycling conditions used for amplification of the glmM and cagA gene regions.

Step	Temperature	Time	Cycles
Initial denaturation	94 °C	5 min	1 cycle
Denaturation	94 °C	30 s	35 cycles
Annealing	58 °C	30 s	35 cycles
Extension	72 °C	30 s	35 cycles
Final extension	72 °C	8 min	1 cycle

Note: PCR amplification was performed in 35 cycles following the initial denaturation step. Amplification products were evaluated by 2% agarose gel electrophoresis. Abbreviations: cagA: cytotoxin-associated gene A; glmM: phosphoglucosamine mutase gene; min: minute; PCR: polymerase chain reaction; s: second.

Table 2. Primer sequences and expected amplicon lengths used for amplification of *H. pylori* (glmM) and cagA gene regions in nasal polyp tissue samples. [9]

Target gene	Forward primer sequence (5′→3′)	Reverse primer sequence (5′→3′)	Expected amplicon length
glmM	AAGCTTTTAGGGGTGTTAGGGGTTT	AAGCTTACTTTCTAACACTAAACGC	294 bp
cagA	AATACACCAACGCCTCCA	TTGTTGCCGCTTTTGCTC	400 bp

Note: Primer sequences are presented in the 5′→3′ direction. The glmM gene was used to detect *H. pylori* DNA, whereas the cagA gene was used to evaluate the virulence-associated gene region. Abbreviations: bp: base pair; cagA: cytotoxin-associated gene A; glmM: phosphoglucosamine mutase gene; H. pylori: Helicobacter pylori; PCR: polymerase chain reaction.

Contamination Control

To minimize contamination risk, DNA extraction, PCR mixture preparation, template addition, amplification, and post-PCR electrophoresis were performed in separate work areas using dedicated equipment. Aerosol-resistant filter tips, nuclease-free consumables, and separate pipettes were used. Negative controls were included in each PCR run, and amplified products were handled separately from pre-amplification materials. Work surfaces and equipment were routinely decontaminated before PCR setup.

Quality Control and Analytical Sensitivity

Helicobacter pylori ATCC 43504 reference strain was used as the positive control during both the DNA extraction and PCR procedures. Nuclease-free water was included in the reactions as the negative control. The analytical sensitivity of the method was assessed using 10-fold serial dilutions of DNA obtained from the reference strain, ranging from 50 ng to 5 fg, and the detection limit was determined to be approximately 7 bacteria per reaction (0.05 pg DNA).

Statistical Analysis

Categorical variables were summarized as number and percentage. Age was evaluated using predefined age groups. The distribution of glmM and cagA positivity according to age groups was assessed using Pearson's chi-square test. Because several age categories included small cell counts, subgroup findings were interpreted cautiously and were also presented descriptively. Aggregate sex distribution was summarized; however, sex-specific PCR comparisons were not performed because paired sex-PCR data were not available in the dataset used for subgroup analysis. A p value of <0.05 was considered statistically significant.

Ethical Approval

Ethical approval was obtained from the Fırat University Faculty of Medicine Clinical Research Ethics Committee prior to the study (Approval No: 12-08/2024). Written informed consent was obtained from all patients before surgery. Throughout the study, patient information was anonymized, and all procedures were conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

All 45 nasal polyp tissue samples included in the study were evaluated by molecular analysis. The study population consisted of 26 men (57.78%) and 19 women (42.22%). The age distribution was as follows: 15-19 years, 1 patient (2.22%); 20-29 years, 5 patients (11.11%); 30-39 years, 10 patients (22.22%); 40-49 years, 3 patients (6.67%); 50-59 years, 14 patients (31.11%); and 60-75 years, 12 patients (26.67%). The age-group distribution and sex distribution of the study population are presented in Tables 4 and 5, respectively.

PCR targeting the glmM gene region showed *H. pylori* positivity in 19 samples (42.22%), whereas 26 samples (57.78%) were negative. In the PCR analysis targeting the cagA gene region, positivity was detected in 16 samples (35.55%), while 29 samples (64.45%) were negative. The distribution of PCR results for the glmM and cagA targets is presented in Table 3.

Table 3. Distribution of PCR results for glmM and cagA targets in nasal polyp tissue samples.

PCR target	PCR positive n (%)	PCR negative n (%)	Total n (%)
glmM	19 (42.22)	26 (57.78)	45 (100.00)
cagA	16 (35.55)	29 (64.45)	45 (100.00)

Note: Data are presented as n (%). glmM positivity indicates the presence of *H. pylori* DNA, whereas cagA positivity indicates detection of the relevant virulence gene. Abbreviations: cagA: cytotoxin-associated gene A; glmM: phosphoglucosamine mutase gene; H. pylori: Helicobacter pylori; PCR: polymerase chain reaction.

Table 4. Distribution of nasal polyp patients according to age groups.

Age group	n	%
15-19 years	1	2.22
20-29 years	5	11.11
30-39 years	10	22.22
40-49 years	3	6.67
50-59 years	14	31.11
60-75 years	12	26.67
Total	**45**	**100.00**

Note: n: number of patients; %: percentage within the total study population (n=45).

Table 5. Distribution of nasal polyp patients according to sex.

Sex	n	%
Male	26	57.78
Female	19	42.22
Total	**45**	**100.00**

Note: n: number of patients; %: percentage within the total study population (n=45).

When PCR results were evaluated according to age groups, glmM positivity was highest in the 50-59-year group (8/14, 57.14%), followed by the 60-75-year group (6/12, 50.00%) (Table 6). Similar findings were observed for cagA positivity, which was highest in the 50-59-year group (7/14, 50.00%), followed by the 60-75-year group (5/12, 41.67%) (Table 7). However, no statistically significant association was detected between age group and glmM positivity (p=0.545) or cagA positivity (p=0.606).

Table 6. Distribution of glmM PCR results according to age groups.

Age group	PCR positive n (%)	PCR negative n (%)	Total
15-19 years	0 (0.00)	1 (100.00)	1
20-29 years	1 (20.00)	4 (80.00)	5
30-39 years	3 (30.00)	7 (70.00)	10
40-49 years	1 (33.33)	2 (66.67)	3
50-59 years	8 (57.14)	6 (42.86)	14
60-75 years	6 (50.00)	6 (50.00)	12
Total	**19 (42.22)**	**26 (57.78)**	**45**

Note: No statistically significant association was detected between age group and glmM positivity (p=0.545). Abbreviations: glmM: phosphoglucosamine mutase gene; n: number of patients; PCR: polymerase chain reaction.

Table 7. Distribution of cagA PCR results according to age groups.

Age group	PCR positive n (%)	PCR negative n (%)	Total
15-19 years	0 (0.00)	1 (100.00)	1
20-29 years	1 (20.00)	4 (80.00)	5
30-39 years	2 (20.00)	8 (80.00)	10
40-49 years	1 (33.33)	2 (66.67)	3
50-59 years	7 (50.00)	7 (50.00)	14
60-75 years	5 (41.67)	7 (58.33)	12
Total	**16 (35.55)**	**29 (64.45)**	**45**

Note: No statistically significant association was detected between age group and cagA positivity (p=0.606). Abbreviations: cagA: cytotoxin-associated gene A; n: number of patients; PCR: polymerase chain reaction.

The relationship between glmM and cagA PCR positivity is presented in Table 8. Among glmM-positive samples, 16 were cagA-positive and 3 were cagA-negative. cagA positivity was not detected among glmM-negative samples in the cross-tabulated PCR results. Representative agarose gel images show the expected 294 bp glmM band and the 400 bp cagA band (Figures 1 and 2).

Table 8. Cross-tabulation of glmM and cagA PCR positivity in nasal polyp tissue samples.

glmM PCR result	cagA positive n (%)	cagA negative n (%)	Total n (%)
glmM positive	16 (84.21)	3 (15.79)	19 (100.00)
glmM negative	0 (0.00)	26 (100.00)	26 (100.00)
Total	**16 (35.55)**	**29 (64.45)**	**45 (100.00)**

Note: Percentages in the glmM-positive and glmM-negative rows are calculated within each row. Percentages in the total row are calculated using the total sample size (n=45). Abbreviations: cagA: cytotoxin-associated gene A; glmM: phosphoglucosamine mutase gene; H. pylori: Helicobacter pylori; PCR: polymerase chain reaction.

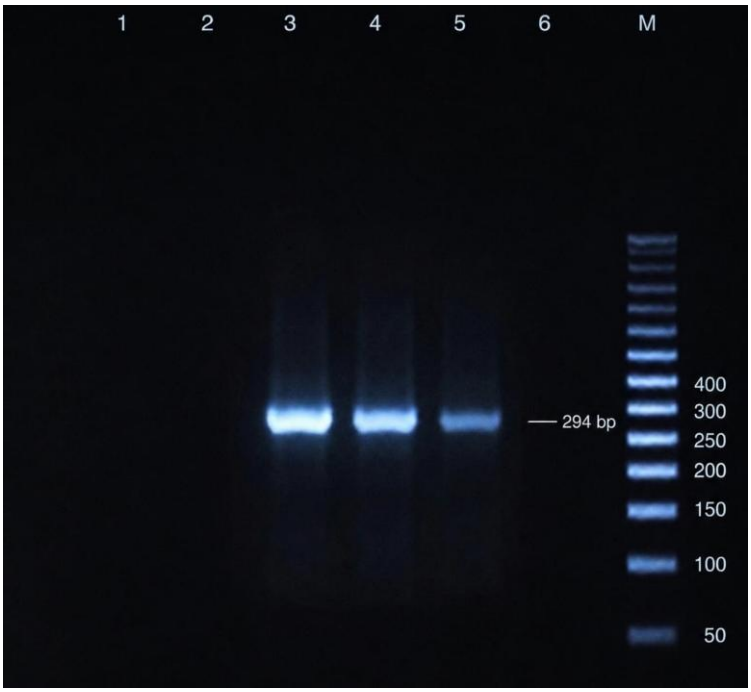


Figure 1. glmM PCR image.

The 294 bp bands obtained with glmM primers indicate positivity. M: 50 bp ladder; 1: negative control; 2: negative sample; 3: positive control; 4 and 5: positive samples; 6: negative sample. Abbreviations: bp: base pair; glmM: phosphoglucosamine mutase gene; M: molecular weight marker (DNA ladder); PCR: polymerase chain reaction.

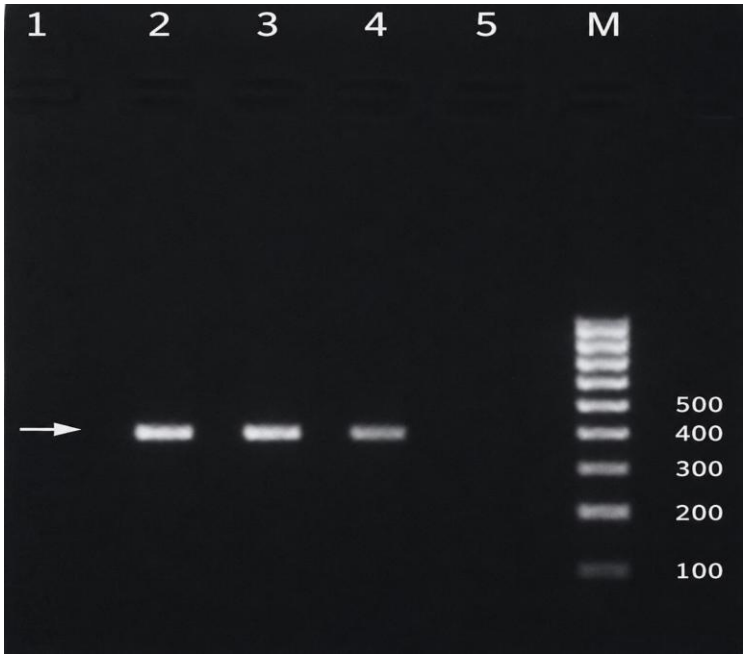


Figure 2. cagA PCR image.

The 400 bp bands corresponding to the cagA gene region indicate positivity. M: 100 bp ladder; 1: negative control; 2: positive control; 3 and 4: positive samples; 5: negative sample. Abbreviations: bp: base pair; cagA: cytotoxin-associated gene A; M: molecular weight marker (DNA ladder); PCR: polymerase chain reaction.

DISCUSSION

In this study, the presence of *H. pylori* DNA in nasal polyp tissues was detected at a rate of 42.22% based on the glmM gene region, while cagA gene positivity was identified in 35.55% of samples. These findings demonstrate that not only *H. pylori* DNA, but also a virulence-associated gene region, can be detected in nasal polyp tissue by molecular methods. The data suggests that nasal polyp tissue may not be a completely sterile microbial environment and that, in some cases, genetic material belonging to *H. pylori* can be present within this tissue. However, this observation should be interpreted as evidence of microbial DNA detection rather than proof of active infection or causation.

The rate of *H. pylori* positivity identified in our study falls within the broad range reported in the literature. In the systematic review and meta-analysis by Doulberis et al. [11], the cumulative prevalence of *H. pylori* was reported as 32.3% in the nasal polyp group and 17.8% in the control group, indicating a higher likelihood of detecting *H. pylori* in nasal polyps. However, the high heterogeneity reported in the same study suggests that this association should not be interpreted in a uniform or definitive manner. Zika et al. [12] reported the presence of *H. pylori* in nasal polyp tissue at rates of 25% by histological examination and 30.5% by rapid urease test. From this perspective, the 42.22% positivity rate observed in our study is not entirely inconsistent with the existing literature; however, direct comparison remains limited because of differences in sample characteristics, methodological approaches, and the study populations examined.

One of the main reasons for variability across studies is the diversity of diagnostic methods used. For this reason, the use of reliable molecular techniques is of particular importance in investigations of *H. pylori* in nasal polyp tissue. [13] Although conventional invasive methods such as histology, culture, and rapid urease testing are still used, their diagnostic performance may be influenced by several variables, including the sampling site, bacterial density, transport conditions, and the use of proton pump inhibitors or antibiotics. In contrast, PCR has emerged as a method that provides high sensitivity and specificity for the detection of *H. pylori* DNA. In their meta-analysis, Doulberis et al. [11] reported lower heterogeneity in studies using immunohistochemistry, whereas PCR-based studies showed more variable results. Zika et al. [12] also emphasized that rapid

urease testing may yield higher positivity rates because of the presence of other urease-producing microorganisms in nasal tissue. Within this framework, the use of molecular methods represents one of the strengths of our study. PCR-based approaches may provide sensitive results, particularly in samples with low bacterial DNA levels or in cases where conventional methods remain limited. Indeed, Bogiel et al. [14] reported that samples found to be positive by PCR may be consistent with histopathological evidence of inflammation and that this method may serve as a valuable diagnostic adjunct. Gillet et al. [15] further demonstrated that virulome analysis can be performed on tissue samples, although sample quality and bacterial load may affect the results.

On the other hand, the specific gene region targeted in molecular assays may also influence the findings. The literature reports the use of a variety of gene targets, including 16S rRNA, 23S rRNA, ureA, vacA, cagA, and glmM. [16] In particular, the glmM gene is considered one of the reliable targets that can be detected in biopsy specimens and is widely preferred for diagnostic purposes. [14] In the present study, the PCR method enabled detection of *H. pylori*-related genetic material in nasal polyp tissues and allowed parallel evaluation of the cagA gene. Similarly, previous studies have shown that sensitivity and specificity may vary according to the gene target used for *H. pylori* detection, while glmM remains one of the widely accepted diagnostic targets. [17] Therefore, the selection of glmM and cagA as targets in our study is methodologically consistent with the literature. Nevertheless, it should be taken into account that different primer sets, expected amplicon sizes, and laboratory protocols may influence prevalence rates. [11] In this respect, the demonstration of *H. pylori* and cagA in nasal polyp tissue by PCR is scientifically meaningful, but the detection of genetic material by PCR alone does not prove the presence of viable bacteria or active colonization.

One of the notable findings of our study is the demonstration of cagA gene positivity in nasal polyp samples. It is well established that the clinical impact of *H. pylori* depends not only on the presence of the bacterium itself, but also on the virulence factors it carries. [18] When the findings are considered together, it cannot be stated with certainty that *H. pylori* is a direct determinant in the pathogenesis of nasal polyps. Rather, the results suggest that *H. pylori*-related genetic material, including cagA, may coexist with the chronic inflammatory environment of nasal polyps in a subset of patients. Hassan Khater and AlFaki 10 reported that virulence-associated genes such as cagA may be associated with mucosal irritation and inflammatory responses. Similarly, Jiang et al. [8] noted that high-virulence *H. pylori* genotypes in the upper aerodigestive tract may be associated with higher bacterial load and an unfavorable clinical course. In addition, strains harboring the cagA gene can affect host cell signaling pathways, enhance cytokine production, and intensify inflammation. [19] However, because our study examined only gene presence in nasal polyp tissue, it does not establish a direct relationship between cagA positivity and tissue damage, clinical severity, or prognosis. Even so, the investigation of virulence genes may be valuable for understanding the nature of microbial involvement in chronic inflammatory tissue environments. [18,20]

The age-based analysis showed numerically higher glmM and cagA positivity in the 50-59 and 60-75-year age groups. However, no statistically significant relationship was detected between age group and PCR positivity. Therefore, these findings should be regarded as descriptive rather than conclusive. The observed pattern may reflect cumulative exposure, age-related changes in mucosal immunity, or sampling variability, but the present data do not allow definitive interpretation. Additional studies with larger cohorts and detailed clinical variables are needed to clarify whether age, sex, reflux history, antibiotic exposure, or other clinical features influence *H. pylori*-related DNA detection in nasal polyp tissues.

In conclusion, this study demonstrated that *H. pylori* DNA and the cagA gene region can be detected in nasal polyp tissues by PCR. These findings suggest that *H. pylori*-related genetic material may be present in nasal polyp tissue and, in some cases, may include virulence-associated genetic characteristics. This observation supports a possible association between microbial factors and the inflammatory microenvironment of nasal polyps, but it does not demonstrate that the bacterium is a direct determinant in the pathogenesis of nasal polyps.

Accordingly, molecular diagnostic methods may be beneficial in the evaluation of microbial factors in patients with nasal polyps. Future studies involving larger and more heterogeneous sample groups, control tissues, combined assessment of different molecular and immunological parameters, and integration of clinical findings with molecular data may contribute to a more comprehensive understanding of the pathophysiology of the disease. Clarifying the role of *H. pylori*-related genetic material in the nasal mucosa may also provide a basis for future targeted research approaches.

Limitations

This study has several limitations. First, PCR demonstrates the presence of bacterial DNA but does not prove the presence of viable bacteria or active colonization. Therefore, culture, immunohistochemistry, RNA-based methods, or quantitative molecular approaches would be useful in future studies. Second, although contamination-control procedures were applied, the possibility of low-level contamination cannot be completely excluded in PCR-based studies. Third, detection of *H. pylori*-related DNA in nasal polyp tissue may reflect nasopharyngeal or upper airway colonization rather than true tissue invasion. Fourth, the study did not include a control group of non-polyp sinonasal tissues, which limits interpretation of whether the observed positivity is specific to nasal polyps. Fifth, the sample size was limited, and only aggregate demographic data were available for some subgroup analyses. Detailed clinical variables such as reflux status, allergy, asthma, medication exposure, disease severity, and recurrence were not available for integrated clinicopathological analysis. Finally, because the study was cross-sectional, causal inference cannot be made.

Conflict of Interest

The authors have no conflicts of interest to declare.

Ethics Committee Permission

Ethical approval was obtained from the Fırat University Faculty of Medicine Clinical Research Ethics Committee prior to the study (Approval No: 12-08/2024).

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Authors' Contributions

Concept/Design: YÜ, AK, ZAT, MT. Data Collection and/or Processing: YÜ, AK, ZAT, MT, PÖ. Data analysis and interpretation: YÜ, AK, MT, YK. Literature Search: YÜ, AK, PÖ, ZAT, KZK. Drafting manuscript: YÜ, AK, PÖ, MT, KZK, YK. Critical revision of manuscript: YÜ, AK, PÖ, MT, YK. Supervision: PÖ, ZAT, KZK.

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