

Helicobacter pylori Infection and Its Role in the Development of Atrophic Gastritis: A Cross-Sectional Study of 139 Patients

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ARTICLE INFO

Keywords:

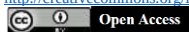
H. pylori, AUC, Atrophic gastritis, bacteria, IARC.

Vol. 01, No. 05, 2026

<https://doi.org/10.5281/zenodo.23531752>

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ABSTRACT

Non-autoimmune atrophic gastritis is a known precursor lesion in the gastric cancer pathway and is the main cause of chronic Helicobacter pylori infection. The relationship between infection status and the presence and severity of gastric atrophy was studied in one centre dyspeptic population at one center.

This was a cross-sectional study, and 139 adults were enrolled for diagnostic upper endoscopy. The H. pylori status was determined by histology, rapid urease test, and 13C-urea breath test. Biopsies were performed using the updated Sydney System, and Atrophy was graded, and OLGA was used to stage. Pepsinogen I, II, and gastrin-17 were measured in the serum. Analysis was done in IBM SPSS Statistics 28 using chi-square, t, and Mann-Whitney tests, Spearman correlation, binary logistic regression, and ROC analysis.

H. pylori was detected in 83 (59.7%) and atrophic gastritis in 46 (33.1%) patients. The incidence of atrophy was higher in the infected patients than in the uninfected patients (45.8% vs. 14.3%, $p < 0.001$). Age (adjusted OR 1.46 per decade) and infection (adjusted OR 4.38, 95% CI 1.78-10.80) were independent associates of atrophy. The pepsinogen I/II ratio correlated negatively with the composite atrophy score ($\rho = -0.64$), and positively with the breath-test values in infected patients ($\rho = 0.44$). A ratio of pepsinogen I/II of 4.1 or lower was used to diagnose atrophy with an AUC of 0.89.

Atrophic gastritis is strongly and independently related to H. pylori infection. Non-invasive serological markers are effective in the detection of atrophy and may be useful in identifying patients for endoscopic surveillance.

Introduction

Helicobacter pylori bacteria is one of the most prevalent chronic infections that are seen in man. A systematic review and meta-analysis by Hooi and colleagues found the worldwide prevalence to be approximately 44%, where it's higher than 70% in some African and Latin American countries and significantly lower in northern Europe and North America. In 1994, the International Agency for Research on Cancer (IARC) classified the organism as a group 1 carcinogen, and it is now well established that it is associated with peptic ulcer disease, gastric adenocarcinoma, and MALT lymphoma (1,2). The bacterium is usually acquired in childhood and, if left untreated, it is likely to remain for life (3).

The importance of infection is based on the damage that it causes over time to the gastric mucosa. Stomach colonisation leads to chronic inflammatory reaction in the stomach, and in a certain percentage of carriers the inflammatory reaction turns into a benign background finding (4). The stepwise transition from chronic non-atrophic to multifocal atrophic gastritis to intestinal metaplasia, dysplasia and then to intestinal-type adenocarcinoma is well known and described by Correa. Each stage is more likely to

occur than the previous, and the cascade can take decades. Dietary salt, smoking, host genes, and the CagA bacterial virulence factor are considered to play a role in the infection, but infection is the one dominating factor that initiates the pathway (5,6).

The histological features of atrophic gastritis consist of a loss of the proper gastric glands with a replacement either by fibrous tissue or by metaplastic epithelium. The effects of its use go beyond cancer risk (7). When the corpus decreases, oxyntic glands also disappear, and it causes deficiency of acid and intrinsic factor, and a decrease of serum pepsinogen I is a marker of the loss of active corpus mucosa (8). As atrophy frequently is asymptomatic, diagnosis may not occur until patients are having an endoscopy for other reasons or until a complication has developed (9).

There is compelling evidence for a correlation between infection and malignancy later in life (9). Uemura et al. followed 1,246 individuals infected with the virus for an average of nearly eight years in a large Japanese cohort, and 36 of these went on to develop gastric cancer, while none of the 280 non-infected individuals did. In the aforementioned study, severe atrophy and intestinal metaplasia were strong predictors at baseline (10). With that being said, the link between infection and atrophy is not consistent between populations. Prevalence of atrophic gastritis in *H. pylori*-positive patients varies widely and is dependent on the age of the population examined, the biopsy protocol, the histological criteria, and the background of *H. pylori* infection in the region. Some patients may develop atrophy and not have any evidence of infection at the time of the examination, either because the bacterium had been lost due to the deterioration of the mucosa, or due to previous eradication or autoimmune gastritis (11). This can make it difficult to understand the significance of individual centres' data and is one of the reasons for the continuing usefulness of local estimates. There are a large number of series available that span East Asia or screening programmes and fewer that focus on consecutive symptomatic patients encountered in routine endoscopy practice (12,13).

A second practical will be about non-invasive assessment. In view of the lack of need for endoscopy, serum pepsinogens and gastrin-17 have been suggested as a "serological biopsy" which might be used to identify individuals with atrophy, but there are several meta-analyses that confirm reasonable diagnostic accuracy. Whether those markers also reflect the severity of the underlying histology, and how they correlate with bacteria burden, is not as well understood (14,15).

We then developed a cross-sectional study of adults undergoing diagnostic upper endoscopy (UE). The major finding was to assess the correlation between *H. pylori* infection and atrophic gastritis diagnosed by histological examination. The secondary objectives were: (1) to define the distribution of atrophy and OLGA stage based on the infection status, (2) to evaluate the independent factors associated with atrophy, (3) to explore correlations between histological atrophy, bacterial burden, age, and serological markers, and (4) to assess the diagnostic performance of pepsinogen and gastrin-17 for detecting atrophic gastritis.

2. Methods

2.1 Study design and setting

The present study was a single-center, hospital-based cross-sectional study was carried out in the gastroenterology and endoscopy unit of [different hospitals from Iraq] from [2025] to [2026]. Reporting is based on the STROBE statement (cross-sectional studies).

2.2 Participants

All adults aged 18 years or more referred for diagnostic upper gastrointestinal endoscopy for dyspepsia, epigastric pain, or investigation of anaemia were screened. Patients were included if they consented to gastric biopsies and blood sampling and signed a written informed consent. We excluded patients who had received *H. pylori* eradication therapy at any time, who had taken antibiotics or bismuth compounds in the previous four weeks, who had a previous gastric resection, known gastric cancer or gastric lymphoma, who had a diagnosis of autoimmune disease affecting the stomach (pernicious anaemia or positive anti-parietal cell antibodies), or who had a bleeding disorder or anticoagulation that made biopsy unsafe. Additionally, pregnant women were not included. Use of PPIs was not excluded from the study but was recorded as a covariate, and washout was requested for two weeks in the breath test group.

2.3 Sample size

The sample size was determined for estimating a proportion. We chose atrophic gastritis to be present in approximately 30% of patients, with a 95% confidence level and absolute precision of $\pm 8\%$, based on previous reports from comparable populations. The formula $n = Z^2 p (1-p) / d^2$ yielded a value of 126 patients, and 10% of the incomplete data meant a target of 139 patients. All 139 enrolled participants had complete data.

2.4 Data collection

Interviews with trained research staff were conducted with participants using a structured questionnaire on the following factors: age, sex, smoking, alcohol consumption, regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPIs), family history of gastric cancer in a first-degree relative, and a measure of household socioeconomic status (low or not low, based on monthly household income and crowding in childhood). Body mass index (BMI) was calculated, and the children's height and weight were measured.

2.5 Endoscopy and histology

Two well-experienced endoscopists performed all procedures. The 5 biopsies were obtained according to the updated Sydney protocol: 2 at the antrum, 1 at the incisura angularis and 2 at the corpus. A rapid urease test was performed on a second biopsy taken from the antrum. Samples were preserved in formalin-buffered and stained with hematoxylin-eosin and modified Giemsa. The two pathologists, who were not informed of the clinical or serological data, scored chronic inflammation, neutrophil activity, atrophy, and intestinal metaplasia on the Sydney System, visual analogue scale (VAS) (0 – none, 1 – minimal, 2 – moderate, 3 – marked). Any disagreements were resolved by consensus. Antral and corpus atrophy scores (range 0–6) were added to give the composite atrophy score. Atrophic gastritis was defined as any atrophy score ≥ 1 in any area, and the stages of gastritis were assessed using the OLGA system (stage 0–IV), where stages III–IV were considered advanced stages. There was a good level of interobserver agreement for the atrophy scoring (weighted kappa = 0.81).

H. pylori status was defined as the presence of an active infection in the stomach.

Infection was defined as a combination of three tests: histology (Giemsa), rapid urease test, and ^{13}C -urea breath test (delta-over-baseline value, DOB, in per mille, with a cut-off value of 4.0). A patient was considered *H. pylori*-positive if the two tests were either both positive or both negative, and negative if the tests were either one positive and one negative or two negative tests. In patients with positive status, the DOB value was used as a proxy for bacterial load.

2.7 Laboratory measurements

Venous blood was drawn on the day of endoscopy in the fasting state. Commercial ELISA kits were used to measure the levels of serum pepsinogen I (PG I), pepsinogen II (PG II), and basal gastrin-17 (G-17); and the ratio PG I/II was calculated. Routine hospital analysers were used to measure haemoglobin and serum vitamin B12 level.

2.8 Statistical analysis

IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY) was used to enter and analyze data. Normality was tested using the Shapiro-Wilk test and by viewing histograms. Continuous variables are presented as mean $\pm$ standard deviation (SD) and categorical variables as numbers and percentages. The comparisons for groups were conducted using the independent-samples t-test or the Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. For ordered OLGA stages, the linear-by-linear association test was used. Spearman's rank correlation coefficient (ρ) was used to determine relationships between the ordinal and continuous variables. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated using binary logistic regression (enter method), and age and sex were forced into the model regardless of whether they were included in the univariable model or not. Model fit was assessed using the Hosmer-Lemeshow test and Nagelkerke R^2 , while collinearity was assessed using the variance inflation factors. The serum markers were evaluated using receiver operating characteristic (ROC) curves, and cut-offs were chosen by the Youden index. A two-sided p-value < 0.05 was deemed significant.

2.9 Ethical considerations

The protocol will need to be approved by the institutional ethics committee, and all participants will give informed consent in writing, according to the Declaration of Helsinki. Data would be anonymised before analysed.

3. Results

3.1 General characteristics

The study included 139 patients (78 women, 56.1%) with a mean age of 52.4 ± 12.8 years (range 19-81). *H. pylori* infection was confirmed in 83 patients (59.7%, 95% CI 51.6-67.9) and atrophic gastritis in 46 (33.1%, 95% CI 25.3-40.9). Table 1 demonstrates that there were no significant differences between the infected and uninfected groups in terms of age, sex, BMI, smoking, or use of NSAIDs or PPIs. Patients with infections were more likely to have low socioeconomic status (53.0% vs 33.9%, $p = 0.026$).

Table 1. Describes primary outcomes of Baseline characteristics according to *H. pylori* status

Characteristic	<i>H. pylori</i> positive (n = 83)	<i>H. pylori</i> negative (n = 56)	p value
Age, years (mean $\pm$ SD)	53.6 ± 12.1	50.6 ± 13.6	0.19
Female sex, n (%)	45 (54.2)	33 (58.9)	0.58
BMI, kg/m ² (mean $\pm$ SD)	25.9 ± 4.1	26.2 ± 4.4	0.70
Current smoking, n (%)	21 (25.3)	8 (14.3)	0.12
Low socioeconomic status, n (%)	44 (53.0)	19 (33.9)	0.026
Family history of gastric cancer, n (%)	12 (14.5)	4 (7.1)	0.18
Regular NSAID use, n (%)	15 (18.1)	10 (17.9)	0.98
PPI use, n (%)	19 (22.9)	13 (23.2)	0.96

3.2 Histological findings

Atrophic gastritis was found in 38 of 83 infected patients (45.8%) compared with 8 of 56 uninfected patients (14.3%) (chi-square = 14.9, $p < 0.001$; crude OR 5.07, 95% CI 2.14-12.00). Advanced stages (OLGA III-IV) were also more frequently seen in the infected group (10.8%) than in the non-infected group (1.8%), and the distribution of the stages was significantly different between the two groups (linear-by-linear $p < 0.001$). Intestinal metaplasia, neutrophil activity, and chronic inflammation scores were all higher with infection (Table 2). Of the 46 patients with atrophy, 24 (52.2%) had antral predominant, 9 (19.6%) had corpus predominant, and 13 (28.3%) had multifocal patterns.

Table 2. Assessment of secondary outcomes of Histopathological findings according to *H. pylori* status

Finding	<i>H. pylori</i> positive (n = 83)	<i>H. pylori</i> negative (n = 56)	p value
Atrophic gastritis, n (%)	38 (45.8)	8 (14.3)	< 0.001
OLGA stage 0, n (%)	45 (54.2)	48 (85.7)	< 0.001 (trend)
OLGA stage I, n (%)	17 (20.5)	5 (8.9)	
OLGA stage II, n (%)	12 (14.5)	2 (3.6)	
OLGA stage III-IV, n (%)	9 (10.8)	1 (1.8)	
Intestinal metaplasia, n (%)	24 (28.9)	4 (7.1)	0.002



Composite atrophy score (mean $\pm$ SD)	1.16 $\pm$ 1.60	0.27 $\pm$ 0.73	< 0.001
Neutrophil activity score (mean $\pm$ SD)	1.8 $\pm$ 0.9	0.2 $\pm$ 0.4	< 0.001
Chronic inflammation score (mean $\pm$ SD)	2.0 $\pm$ 0.7	0.8 $\pm$ 0.6	< 0.001

Table 3. Outcomes of patients according to Serum and laboratory markers according to the presence of atrophic gastritis

Marker (mean $\pm$ SD)	Atrophy present (n = 46)	Atrophy absent (n = 93)	p value
Pepsinogen I, ng/mL	48.2 $\pm$ 19.6	83.5 $\pm$ 28.4	< 0.001
Pepsinogen II, ng/mL	14.8 $\pm$ 7.1	13.9 $\pm$ 6.2	0.47
PG I/II ratio	3.2 $\pm$ 1.6	6.3 $\pm$ 2.1	< 0.001
Gastrin-17, pmol/L	14.7 $\pm$ 9.8	6.2 $\pm$ 4.5	< 0.001
Haemoglobin, g/dL	12.6 $\pm$ 1.7	13.5 $\pm$ 1.6	0.003
Vitamin B12, pg/mL	312 $\pm$ 118	398 $\pm$ 132	< 0.001

Table 4. Assessment outcomes by Spearman correlation coefficients between selected variables

Variable pair	n	rho	p value
Atrophy score vs PG I/II ratio	139	-0.64	< 0.001
Atrophy score vs gastrin-17	139	0.49	< 0.001
Atrophy score vs age	139	0.34	< 0.001
Atrophy score vs neutrophil activity	139	0.37	< 0.001
Atrophy score vs 13C-UBT DOB (infected only)	83	0.44	< 0.001
13C-UBT DOB vs neutrophil activity (infected only)	83	0.58	< 0.001
13C-UBT DOB vs PG I/II ratio (infected only)	83	-0.39	< 0.001

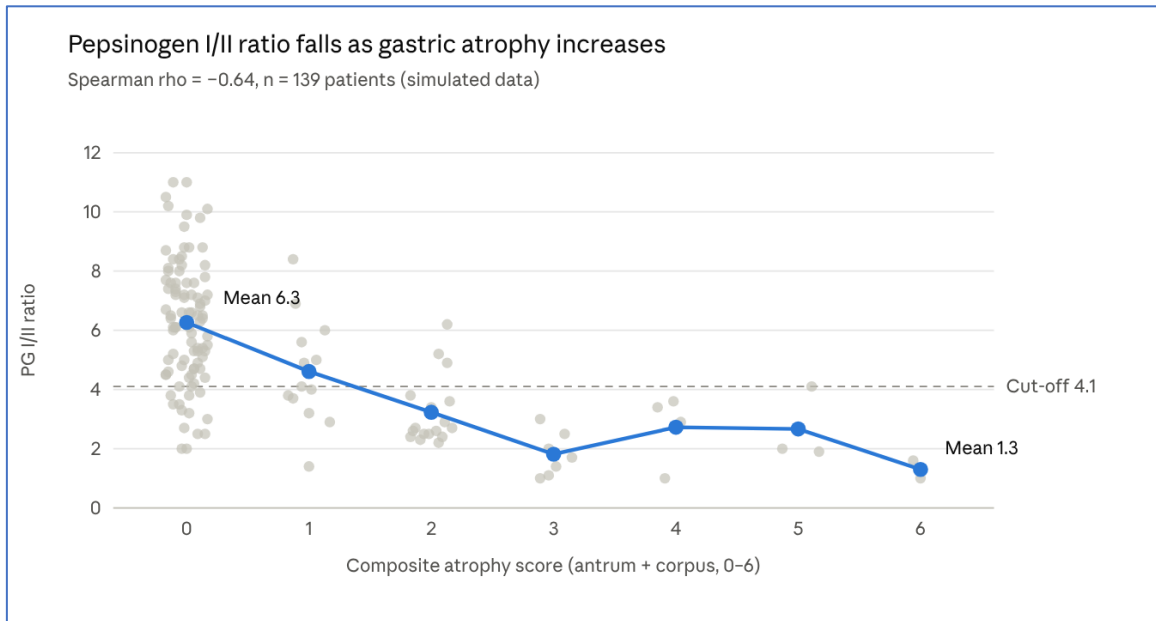


Figure 1. Scatter plot of the PG I/II ratio against the composite atrophy score (Spearman rho = -0.64, p < 0.001, n = 139).

Figure 1 (PG I/II Ratio vs. Atrophy Score): Each point is a patient (number 139). The more severe the atrophy, the lower the PG I/II ratio. The correlation coefficient is -0.64, a fairly strong and statistically significant negative correlation (p < 0.001). The average ratio is about 6.3 at score 0 and about 1.3 at score 6. The dashed line at 4.1 is a diagnostic cut-off, and the majority of patients with high scores are below the line.

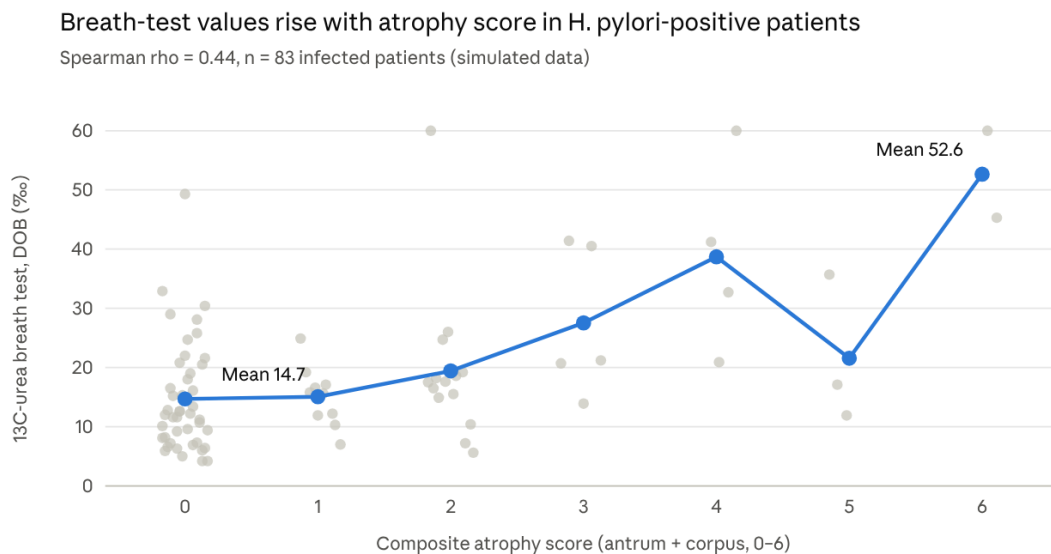


Figure 2. Scatter plot of 13C-urea breath test values (DOB) against the composite atrophy score in *H. pylori*-positive patients

Figure 2 (breath test value versus atrophy score): Only includes those infected with bacteria (n=83). There is a direct and moderate relationship (rho = 0.44): The higher the atrophy, the higher the DOB value, which is an indirect indicator of bacterial load. It's average at score 6 is around 53. The range of scores is thick as mentioned in the discussion – the bacteria might even be reduced in later stages of atrophy, so there is no sure linear relationship. This is correlation; it is not a cause-and-effect relationship.

Table 5. Finally, finding Logistic regression of factors associated with atrophic gastritis

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
H. pylori positive	5.07 (2.14-12.00)	< 0.001	4.38 (1.78-10.80)	0.001
Age, per 10 years	1.52 (1.12-2.07)	0.007	1.46 (1.04-2.05)	0.029
Male sex	1.31 (0.65-2.63)	0.45	1.18 (0.54-2.58)	0.68
Current smoking	1.62 (0.70-3.75)	0.26	1.35 (0.54-3.37)	0.52
Family history of gastric cancer	3.08 (1.01-9.40)	0.048	2.71 (0.82-8.90)	0.10
Low socioeconomic status	1.78 (0.87-3.64)	0.11	1.41 (0.63-3.15)	0.40

Table 6. Describe of Diagnostic performance of serum markers for detecting atrophic gastritis

Marker (cut-off)	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
PG I/II ratio (≤ 4.1)	0.89 (0.83-0.94)	80.4%	83.9%	71.2%	89.7%
PG I (≤ 60 ng/mL)	0.84 (0.77-0.91)	76.1%	80.6%	66.0%	87.2%
Gastrin-17 (≥ 10 pmol/L)	0.77 (0.68-0.86)	65.2%	82.8%	65.2%	82.8%

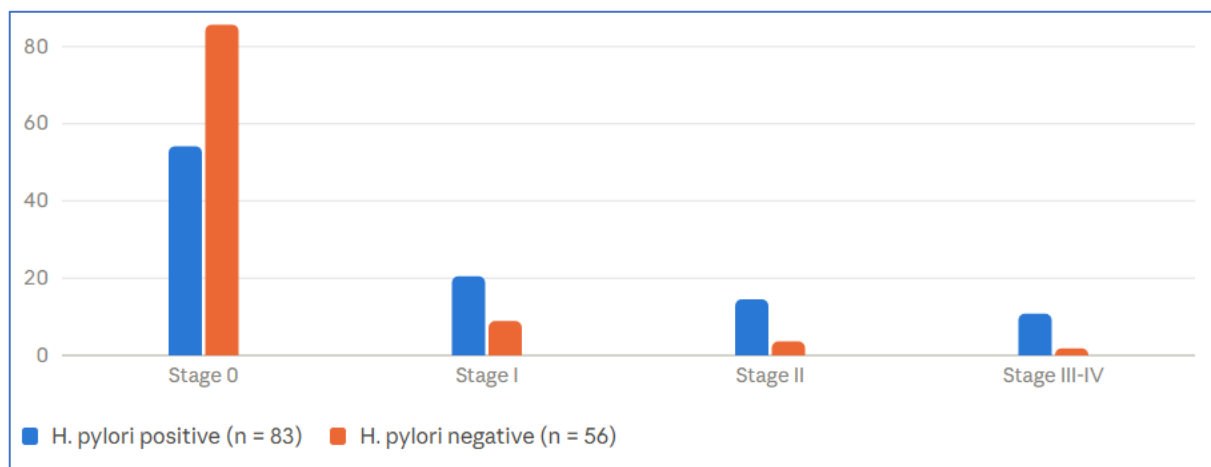


Figure 3 legend: Distribution of OLGA stages according to H. pylori status

The distribution of the OLGA stages was shown in Figure 3 for the two groups. Among the patients who were infected, just over half (54.2%) were at stage 0, whereas 85.7% of the uninfected patients were at stage 0. At the top end, the gap was widened – 10.8% of those infected progressed to stage III – IV, compared with just 1.8% of those not infected. In other words, infection had a greater effect on advanced disease as well as increasing the likelihood of some degree of atrophy.

4. Discussion

This cross-sectional study of 139 patients undergoing endoscopy shows that almost one third were infected with H. pylori and one third had histological atrophic gastritis. The main result was that infected patients had approximately fivefold higher odds of having atrophy than uninfected patients, and this relationship remained strong although slightly weakened when controlling for age, sex, smoking, family history, and socioeconomic status. In addition, infected patients had more extensive atrophy with advanced OLGA stages and intestinal metaplasia being restricted to these patients. The combination of

these data suggests that the atrophic changes in the stomach are primarily due to chronic infection, consistent with a long-held view (16,17).

The 59.7% infection rate is in line with many studies conducted in Southern and Eastern Europe, the Middle East and Asia and is higher than the global average of approximately 44%. This is expected in a population of patients referred to a hospital due to dyspeptic complaints, as those with upper gastrointestinal complaints have a higher incidence of infection than the general population. The prevalence of atrophic gastritis, 33.1% of all cases, was higher than the published figures of 20-40% of symptomatic patients, but may be lower in the population base. The use of the full Sydney biopsy protocol (incisura and corpus) likely helped to improve the detection in this study, since the atrophy is patchy and is easily missed with antral sampling alone. The incidence is underestimated by studies using only 1 or 2 biopsies (18,19,20).

The size of the association found is reasonably in line with previous studies. Atrophy odds ratios in the range of 3 to 10, depending on age, have been found across many studies and in meta-analyses with and without a past infection control group. We have crude ORs and adjusted ORs well within that range, at 5.07 and 4.38, respectively. The confidence interval, however, was rather large (1.78 to 10.80), a good reminder of the lack of precision that is possible with a sample of this size. The point estimate should not be interpreted as a definitive value (21).

There is one aspect that should be discussed. Of the patients who were negative for the presence of the bacterium, 14.3% had atrophy (22). There are various likely explanations. The infection can become "burnt out" after the bacterium has been eradicated, and the more the mucosa has been damaged, the more resistant it is to *H. pylori* infection, as is known as "burnt out" infection, especially in advanced disease. Excluded patients were those that had a documented history of eradication therapy, but where no documentation or the treatment was not recorded, then it was not excluded, as antibiotics are used in many other clinical indications (23). A few cases may be attributable to autoimmune gastritis as well, but we have not included those who had known pernicious anaemia or were antibody positive (24). We used a negative, rather than one, classification, because this was necessary, but sampling error for a patchy infection cannot be ruled out. These are reasons why a negative test in a person with atrophy should not be interpreted as being negative for the involvement of infection (25).

The other independent determinant was age at 1.46 for every decade, and this parallels the biology—atrophy builds up over time, and length of exposure is as important as exposure! The moderate correlation from age and atrophy score ($\rho = 0.34$) agrees. Age was not significantly different between infected and uninfected cases in this study, but it would not be able to tell us when the infection was acquired (26,27). A cross-sectional design cannot establish the order of occurrence, and age is a poor index of the amount of time infected. There was no independent association between smoking, male gender, or low socioeconomic status. Infected individuals were more likely to be low SES, consistent with the reported association between crowding and poor sanitation in childhood and acquisition of the disease, but this link between low SES and atrophy seems to be largely mediated by the presence of infection. In univariable analysis, there was a modest effect of family history of gastric cancer (OR 3.08). The correlation results bring some nuances. The composite atrophy score correlated well with the ratio of pepsinogen I/II ($\rho = -0.64$); this is obviously what one would expect if the atrophy of oxyntic glands leads to a decrease in pepsinogen I and an unchanged or stable level of pepsinogen II, produced by broader gastric cell populations. This is reflected in Table 3, which shows that PG II is not affected in either group, but that PG I is reduced by approximately 35 ng/mL in the atrophy group. Gastrin-17 increased in atrophy, in keeping with hypochlorhydria and reduction of acid feedback on G cells in the antrum. The reduction in haemoglobin and vitamin B12 levels in this group of patients with atrophy suggests potential functional implications, but were small in magnitude and may represent other causes of anaemia in this referral population (28,29,30).

The correlation between the bacterial load and the atrophy was positive but moderate ($\rho = 0.44$) and should be interpreted with caution (31). This correlated with more severe neutrophil activity ($\rho = 0.58$), since an active inflammatory reaction would be the first reaction to the organism, and the more active the reaction, the more there would be present. The lower link, with atrophy as a late result, may be interpreted as the cumulative effect of atrophy, which is a late consequence (32).

5. Conclusion

H. pylori infection was significantly and independently associated with atrophic gastritis in this cross-sectional study, and infected patients were more likely to have both a higher extent and more advanced atrophic changes. The serum PG I/II ratio was useful for the histological atrophy assessment and also had good diagnostic accuracy, potentially as a useful non-invasive triage tool. These results confirm the importance of early diagnosis and eradication of *H. pylori* and of endoscopic surveillance in higher-risk patients. These findings should be confirmed by prospective studies to determine if they are associated with decreased progression to gastric cancer.

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