**Aim** To assess the relationship between *Helicobacter pylori* (*H. pylori*) infection and atrophic gastritis (AG) and intestinal metaplasia (IM) development and to assess the rate of dysplasia or gastric cancer development in patients with AG and/or IM.

**Methods** This retrospective endoscopic follow-up study enrolled 2214 patients. The patients were followed for at least five years between 2007 and 2017 at the Department of Endoscopy at Antalya Ataturk Government Hospital. The results of third-year and five-year surveillance biopsy were assessed.

**Results** The mean follow-up time was 7.77 ± 2.78 years. *H. pylori* was histologically assessed in 1417 (64.6%) patients. Of 198 patients with severe *H. pylori* infection, 32 (16%) and 139 (70.3%) developed extensive AG and extensive IM, respectively. There was a significant relationship between *H. pylori* density and AG and IM degrees. High grade dysplasia, early gastric cancer, and advanced gastric cancer were diagnosed in 73 patients with median age 58.2 (28-80) years, and the incidence rate was 3.29% (73/2214). The annual incidence of gastric neoplastic lesions was 0.46% in total, 0.08% for early GC, and 0.02% for advanced gastric cancer.

**Conclusions** *H. pylori* infection has an important role in the development of AG and IM. *H. pylori* density is directly related to atrophy and metaplasia degree.
Helicobacter pylori (H. pylori) is a widely spread bacterium causing atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia, and eventually gastric cancer (1). Gastric cancer ranks fourth in terms of prevalence and second in terms of the number of cancer-related deaths. The most common gastric cancer type is intestinal type adenocarcinoma, which is closely associated with H. pylori infection (2).

In H. pylori-related AG, the glandular tissue in the stomach disappears, while in IM the surface foveolar and glandular epithelium of the gastric mucosa is replaced with intestinal epithelium. In general, metaplasia is the cell's protective response to changing ambient conditions, since sulfomucins and sialomucins in the intestinal mucosa are resistant to bacterial enzymes. AG and IM are considered the precursors of gastric cancer (3-5). It is widely believed that they could be ameliorated by H. pylori eradication (6). H. pylori infection is a risk factor for developing gastric carcinoma (1). However, only a few infected patients develop gastric cancer, which is why it is important to identify the H. pylori gastritis characteristics that increase the risk for gastric carcinoma. We investigated whether a simple comparison of the gastritis grade and chronic inflammation in the antrum and corpus might help identify patients with H. pylori gastritis with an increased cancer risk. To answer this question, we retrospectively assessed whether patients with AG and/or IM with H. pylori developed gastric cancer or dysplasia in at least 5-year follow up.

**PATIENTS AND METHODS**

In this endoscopic follow-up study, we retrospectively reviewed the charts of patients who underwent first gastroscope at the Department of Endoscopy at Antalya Ataturk Government Hospital. The gastroscope was performed due to epigastric pain, abdominal bulge, nausea, vomiting, and heartburn with at least one premalignant lesion in the stomach biopsy. The patients were followed up for more than 5 years between 2007 and 2017. The exclusion criteria included stomach adenocarcinoma, mucosal associated lymphoid tumor, gastrectomy, previous H. pylori eradication therapy, and age under 18 years. Baseline and surveillance endoscopies were performed by experienced gastroenterologists with Fujinon EG 450 WLS (Fujifilm Europe GmbH, Dusseldorf, Germany) and Pentax EG-2980 K unit (Pentax Medical, Montvale, NJ, USA).

All patients underwent endoscopic examination of the esophagus, stomach, and duodenum. During the first endoscopy, two non-targeted antral and two gastric body biopsies were performed by using Olympus biopsy forceps (Olympus Europa, Hamburg, Germany). All biopsy specimens were fixed in 10% formalin and examined at the Pathology Department. H. pylori density was determined with Giemsa dye.

Histopathological classification was made according to the updated Sydney System (7) (Table 1). All biopsy samples were evaluated for H. pylori, IM, AG, and dysplasia and graded according to their density as absent, mild (grade 1), moderate (grade 2), and severe (grade 3). The dysplasia degree was assessed using the Vienna system; dysplasia was graded as low-grade to high-grade or neoplasia. A control endoscopy was performed after 3 years, with biopsies performed and evaluated in the same manner as at baseline. H. pylori infection was treated by triple (proton pump inhibitor, clarithromycin, and amoxicillin) and quadruple therapy (proton pump inhibitor, bismuth, metronidazole, and tetracycline). The patients underwent endoscopic examination after having given written and verbal consent. This study was approved by the institutional review board of the University of Health Sciences Antalya Training and Research Hospital (13.08.2020-12/10).

**Statistical analysis**

The Pearson and Kruskal-Wallis tests were used to evaluate the differences in outcome proportions (at least LGD or at least HGD) and to assess the differences in patients’ age, sex, Hp infection prevalence, and disease duration. Survival analysis was performed to define the rate of progression to outcome at the third- and fifth-year follow up endoscopy. Outcome was considered as progression to lesions as severe as LGD. Age was presented with median, minimum,
and maximum value. The level of significance was set at 0.05. The analysis was conducted with SPSS, version 17.0 (SPSS, Chicago, IL, USA).

RESULTS

The study enrolled 2214 patients (1285 or 58.3% male). Men and women did not significantly differ in median age (54.5 [18-64] women and 58.5 [18-69] men, \( P = 0.495 \)) (Table 2). The mean follow-up period was 7.77 ± 2.78 years. \( H. \) pylori was histologically confirmed in 1417 (64.6%) of 2214 patients.

\( H. \) pylori density was significantly associated with chronic inflammation degree (\( P = 0.001 \)), atrophy degree (\( P = 0.0001 \)), and IM degree (\( P = 0.0028 \)). Significantly more patients with \( H. \) pylori had chronic inflammation, atrophy, and IM compared with patients without \( H. \) pylori (Table 3, Table 4, Table 5). A total of 493 patients with \( H. \) pylori infection simultaneously had histologic features of IM and AG.

IM was most frequently detected by follow-up endoscopy. High grade dysplasia (HGD), early gastric adenocarcinoma (early gastric cancer), and advanced gastric adenocarcinoma (advanced gastric cancer) were diagnosed in 73 patients (24 women, median age 58.2 [49-68] years), with the crude incidence rate of 3.29% (Table 6). These patients were followed-up more closely. In 28 of the 73 gastric cancer patients, biopsy was taken from the suspicious areas

| TABLE 2. Age and sex of participants with and without \( H. \) pylori infection |
|---------------------------|-----------------|-----------------|-----------------|
| Age (years)               | \( H. \) pylori-negative \( (n = 797) \) | \( H. \) pylori-positive \( (n = 1417) \) | total \( (n = 2214) \) |
| <30                       | 133 (55.2)       | 108 (44.8)       | 241             |
| 30-49                     | 261 (36.7)       | 451 (63.3)       | 712             |
| 50-59                     | 146 (26.5)       | 405 (73.5)       | 551             |
| >60                       | 257 (36.2)       | 453 (63.8)       | 710             |
| Sex                       |                 |                 |                 |
| female                    | 393 (42.4)       | 536 (57.6)       | 929 (41.7)      |
| male                      | 404 (31.5)       | 881 (68.5)       | 1285 (58.3)     |

| TABLE 3. The prevalence of chronic inflammation in patients with and without \( H. \) pylori infection |
|-----------------------------|-----------------|-----------------|-----------------|
| Chronic inflammation        | \( H. \) pylori-negative \( (N = 797) \) | \( H. \) pylori-positive \( (N = 1417) \) | total |
| none                        | 605 (75.9)       | 654 (81.3)       | 1259 |
| mild (+)                    | 151 (18.9)       | 121 (15.5)       | 272 |
| moderate (++)               | 41 (5.2)         | 32 (3.3)         | 73 |
| severe (+++)                | 226 (34.6)       | 226 (34.6)       | 452 |
| 95% confidence interval     | 3.47-3.47        | 3.47-3.47        |       |
| P                           | <0.01            | <0.01            |       |

| TABLE 4. The prevalence of gastric atrophy in patients with and without \( H. \) pylori infection |
|-----------------------------|-----------------|-----------------|-----------------|
| Gastric atrophy             | \( H. \) pylori-negative \( (N = 797) \) | \( H. \) pylori-positive \( (N = 1417) \) | total |
| none                        | 713 (89.4)       | 582 (72)        | 1295 |
| mild (+)                    | 84 (10.5)        | 225 (28)        | 309 |
| moderate (++)               | 0               | 0               | 0 |
| severe (+++)                | 0               | 43 (10.4)       | 43 |
| 95% confidence interval     | 3.13-3.47        | 3.13-3.47        |       |
| P                           | <0.01            | <0.01            |       |
of IM or visible lesions. Biopsies from visible lesions were evaluated as high-grade advanced GC in 3 patients, as IM in 14 patients, as early GC in 4 patients, and as high-grade dysplasia in 6 patients.

Among 73 patients with neoplastic lesions, 57 patients had lesions localized in the antrum (35 low-grade dysplasia, 14 high-grade dysplasia, 5 early GC, and 3 advanced GC). Sixteen patients had lesions localized in the gastric body (9 LGD, 4 HGD, and 3 early GC) (Table 7).

The annual incidence rate of total gastric neoplastic lesions per person was 0.46%. The annual incidence of LGD, HGD, early GC, and advanced GC was 0.37%, 0.18%, 0.08%, and 0.02%, respectively.

A total of 364 patients had moderate and severe IM and/or moderate and severe AG. Severe metaplasia and atrophy at first biopsy progressed at a higher rate than others, both at 3 and 5 years after diagnosis.

**TABLE 5.** The prevalence of intestinal metaplasia in patients with and without *Helicobacter pylori* infection

| Intestinal metaplasia | H. pylori-negative (N = 797) | H. pylori-positive (N = 1417) |
|-----------------------|-----------------------------|------------------------------|
| none                  | none                        | mild (+)                     |
| mild                  | 713 (89.4)                  | 583 (72)                     |
| moderate              | 84 (10.5)                   | 170 (21.4)                   |
| severe                | 0                           | 246 (30.7)                   |
| total                 | 797                         | 807 (56.9)                   |
| Odds ratio            | 5.6                         | 5.12-5.96                    |
| 95% confidence interval|                            |                              |
| P                     | 0.0028                      |                              |

**TABLE 6.** Histological lesions found at outcome endoscopic biopsy at the first, third, and fifth year after diagnosis according the lesion found at entry biopsy, n (%)

|                   | Third-year biopsy | Fifth-year biopsy |
|-------------------|-------------------|-------------------|
|                   | LGD | HGD | EGC | AGC | LGD | HGD | EGC | AGC |
| Atrophy           |     |     |     |     |     |     |     |     |
| +                 | 225 | 24 (10.6) | 1 (0.4) | 0 | 0 | 29 (12.8) | 4 (1.7) | 0 | 0 |
| ++                | 193 | 21 (10.8) | 3 (1.5) | 0 | 0 | 32 (16.5) | 12 (6.2) | 0 | 0 |
| +++               | 75  | 8 (10.6) | 2 (2.6) | 0 | 0 | 11 (14.6) | 6 (8) | 0 | 2 (2.6) |
| Metaplasia        |     |     |     |     |     |     |     |     |
| +                 | 416 | 21 (5) | 4 (0.9) | 0 | 0 | 32 (7.6) | 14 (3.3) | 0 | 0 |
| ++                | 359 | 18 (5) | 5 (1.3) | 0 | 0 | 28 (7.7) | 19 (5.2) | 0 | 5 (1.3) |
| +++               | 59  | 4 (6.7) | 2 (3.3) | 0 | 0 | 7 (11.8) | 9 (15.2) | 0 | 2 (3.3) |

*LGD – low grade dysplasia; HGD – high grade dysplasia; EGC – early gastric carcinoma; AGC – advanced gastric carcinoma.*

**TABLE 7.** Characteristics of patients who developed gastric neoplastic lesions at follow-up

|                   | LGD | HGD | Early GC | Advanced GC |
|-------------------|-----|-----|----------|-------------|
| Antrum            | 35  | 14  | 5        | 3           |
| Corpus            | 9   | 4   | 3        | -           |
| Age               |     |     | 49 to 68 years, median age 58.2 ± 5.74 years |
| Gender            |     |     | 24 women, 49 men (P < 0.05) |
| Crude incidence rate |    | 73/2214 |
| Average length of follow-up |    | 7.77 ± 2.78 year |

*LGD – low grade dysplasia; HGD – high grade dysplasia; GC – gastric carcinoma.*
DISCUSSION

In this study, at baseline biopsy, all lesions (AG, IM, LGD) were equally prevalent. The patients with AG or IM at first biopsy did not develop cancer during the following three years, and less than 5% progressed to HGD. Although we did not confirm the direct effect of H. pylori infection on lesion progression, it is a potential risk factor for cancer, because it causes chronic gastritis and leads to atrophy. We found no significant differences in age, sex, H. pylori infection prevalence, and follow up duration according to the histological diagnosis of the first lesion.

Several studies have shown that the presence and severity of H. pylori infection correlates with chronic gastritis, AG, and IM (8). As is well known, AG and IM are important risk factors for gastric cancer, together with genetic and other environmental factors (9). In AG cases, the risk of gastric cancer development increases with disease duration, atrophy severity, IM presence, dysplasia, epigenetic changes, and H. pylori infection. In 10% of cases with AG, gastric cancer can develop within 10-20 years (10-12).

A 20-year prospective study by Lahner et al showed a person-year incidence of gastric cancer in patients with AG to be 0.25% (4). Another study (13) observed 8.4% cases of gastric cancer among patients with IM and AG who were followed up for 10 years, with endoscopy being performed once a year. The risk of developing malignancy in these patients was 11% (13).

A Dutch nationwide cohort study found the annual gastric cancer incidence to be 0.1%, 0.25%, 0.6%, and 6% in 5 years in patients with AG, IM, mild, and moderate and severe dysplasia (14). East Asian countries have higher gastric adenocarcinoma prevalence than Western countries (15), and the prevalence of H. pylori in Turkey is similar to Asian countries. Since patients with extensive IM have a high risk of gastric cancer, they are recommended to undergo follow-up endoscopy (16-18). Similar to other studies, our study found extensive AG and/or IM to be risk factors for gastric cancer and dysplasia. As we have already noted, H. pylori infection is an important etiological factor for gastric cancer, and its eradication reduces the risk of cancer development (19). Some authors have also reported that IM areas in the stomach after H. pylori treatment convert into normal mucosa, meaning that the progression to gastric cancer can be prevented. However, complete prevention can only be achieved by H. pylori eradication therapy before AG and IM develop (20). Although chronic AG may be cured after bact-
sion and the reliability of the study. However, NBI endoscopy is not commonly used in routine practice in Turkey. In addition, we did not assess the IM subtypes in accordance with recent studies, as it was not clinically significant.

In conclusion, patients with chronic gastritis with *H. pylori*, IM, and AG had an increased risk for gastric cancer. In these patients, screening endoscopy can detect early gastric cancer. Further prospective, long-term, large-scale follow-up studies with immunohistochemical methods and double-blind assessment by two or three pathologists are necessary to assess gastric intestinal adenocarcinoma development in *H. pylori* patients.

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**Declaration of authorship** BB and BD conceived and designed the study; BB acquired the data; BB and BD analyzed and interpreted the data; BB and BD drafted the manuscript; BB and BD critically revised the manuscript for important intellectual content; BB and BD gave approval of the version to be submitted; BB and BD agree to be accountable for all aspects of the work.

**Competing interests** All authors have completed the Unified Competing Interest form at www.cmj.org/doi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization or entity; no financial relationships with any organization or entity that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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