RESEARCH ARTICLE

Evalution of the Patients with Colon Polyps in Terms of *Helicobacter pylori* with Sydney Criteria

Kolon Polibi Saptanan Hastaların Sydney Kriterleri Eşliğinde *Helicobacter pylori* Açısından İrdelenmesi

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▌▌▌▌▌▌ **ABSTRACT**

Aim: Colorectal cancer (CRC) is one of the leading three cancers with high mortality. Colon polyps are precursors for CRC development. *Helicobacter pylori* is known to increase the risk of gastric cancer by intestinal metaplasia (IM) and glandular atrophy (GA), there are studies suggesting that it increases the risk of CRC by various mechanisms. Sydney criteria have been developed to provide a standardized approach to histopathological changes in gastric mucosa caused by *H. pylori*. The aim of this study was to evaluate *H. pylori* according to the Sydney criteria in patients with colon polyps and to contribute to the literature.

Method: The study cohort included a control group (n=231) with normal colonoscopy findings and a patient group (n=600) who underwent upper gastrointestinal endoscopy and colonoscopy on the same day and had hyperplastic polyps, adenomatous polyps and malignant polyps. Age, gender, complications during endoscopy, number and localization of polyps, and histopathological results of gastric and colon biopsies were analyzed. The relationship between *H. pylori*, IM and GA and colon polyps were investigated with logistic regression model.

Results: *H. pylori* was present in 609 (73.3%) of 831 patients. There was no statistically significant relationship between coexistence of *H. pylori* + IM and hyperplastic polyp and adenomatous polyp (p>0.05). It was found that IM did not increase the risk of CRC without *H. pylori* (p=0.15). There was a statistically significant relationship between CRC and *H. pylori* + IM (p=0.03). GA was detected in 70 patients (8.4%), and there was a statistically significant relationship between the presence of GA and CRC, regardless of the presence of *H. pylori* (p<0.05).

Conclusion: The results of the study showed that the coexistence of *H. pylori* and IM did not increase the risk of colon hyperplastic polyps, adenomatous polyps, but increased the risk of malignant polyps. There was also a statistically significant relationship between colon malignant polyps in the presence of GA regardless of the presence of *H. pylori*. In the light of the data obtained in the study, patients with *H. pylori* and IM and patients with GA should be followed up more closely for malignant colon polyps.

Keywords: Helicobacter pylori, Sydney criteria, colon polyps, glandular atrophy, intestinal metaplasia

▌▌▌▌▌▌ **ÖZ**

Amaç: Kolorektal kanserler (KRK) yüksek mortaliteyle seyreden ilk 3 kanserden biridir. Kolon polipleri KRK gelişimi için prekürsordür. *Helicobacter pylori*'nin intestinal metaplazi (İM) ve glandular atrofi (GA) ile mide kanseri riskini arttırdığı bilinmekte olup ve çeşitli mekanizmalarla KRK riskini artırdığına dair çalışmalar mevcuttur. *H. pylori*'nin gastrik mukozada meydana getirdiği histopatolojik değişikliklere standart bir yaklaşım getirmek için Sydney kriterleri geliştirilmiştir. Amacımız kolon polibi saptanan hastalarda Sydney kriterleri eşliğinde *H. pylori*'yi irdeleyip literatüre katkıda bulunmaktır.

Yöntem: Çalışmaya kolonoskopisi normal olan kontrol grubu (n=231) ile birlikte üst gastrointestinal endoskopisi ve kolonoskopisi aynı gün yapılıp histopatolojisinde hiperplastik polip, adenomatöz polip ve malign polip saptanan hastalar (n=600) dahil edildi. Hastaların yaşı, cinsiyeti, endoskopi sırasındaki komplikasyonlar, polip sayısı ve lokalizasyonu, mide ve kolon biyopsilerinin histopatolojik sonuçları analiz edildi. *H. pylori*, İM ve GA'nın kolon polipleri ile ilişkisi lojistik regresyon modeli ile incelendi.

Bulgular: Çalışmada 831 hastanın 609'unda (%73,3) *H. pylori* mevcuttu. *H. pylori* ve İM birlikteliğinde hiperplastik polip ve adenomatöz polip arasında istatistiksel olarak anlamlı ilişki saptanmamıştır (p>0,05). İM'nin *H. pylori* olmaksızının KRK riskini artırmadığı saptanmış olup (p=0,15), *H.*

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pylori + İM birlikteliği ile KRK arasında istatistiksel olarak anlamlı ilişki saptanmıştır (p=0,03). Hastaların 70'inde (%8,4) atrofi saptanırken, *H. pylori* olup olmadığı fark etmeksizin, GA mevcudiyeti ile KRK arasında istatistiksel olarak anlamlı ilişki saptanmıştır (p<0,05).

Sonuç: Çalışma sonucunda *H. pylori* ve İM ile birlikteliğinde kolon hiperplastik polibi, adenomatöz polibi riskini arttırmadığını ancak malign polip riskini artırdığı saptandı. Ayrıca GA mevcudiyetinde, *H. pylori* varlığı fark etmeksizin, kolon malign polipleri arasında istatistiksel olarak anlamlı bir ilişki bulunmaktadır. Çalışmada elde edilen veriler ışığında *H. pylori* ve İM mevcut olan hastalar ile GA mevcut olan hastalar malign kolon polibi açısından daha yakın takip edilmelidir.

Anahtar Kelimeler: *Helicobacter pylori*, Sydney kriterleri, kolon polipleri, glandular atrofi, intestinal metaplazi

Introduction

Colorectal cancers (CRC) are one of the leading three common cancers in the world with high mortality.[1] The environmental and genetic factors play a role in the pathogenesis of CRC and 95% of CRC develop sporadically. Environmental factors play a role in sporadic forms, but not genetic factors.[2] The precursor of the sporadic form is mostly adenomatous polyps; and rarely, CRC may also develop from hyperplastic polyps.[3] *Helicobacter pylori* was detected in 1983 by Marschall and Warren[4] in the gastric epithelium of patients with chronic active gastritis. This microorganism is gram (-), spiral-shaped and produces urease enzyme, and is involved in the etiology of diseases such as chronic gastritis, peptic ulcer, gastric carcinoma and gastric mucosa-associated lymphoid tumor.[5,6] The Sydney criteria were established in 1990, allowing us to histopathologically evaluate the response of gastric mucosa to *H. pylori*. In 1990, Sydney criteria were developed by a group of pathologists to provide a standardized approach to the histopathological changes caused by *H. pylori* in the gastric mucosa. In the revised criteria in 1994, chronic inflammation, neutrophil activity, glandular atrophy (GA), intestinal metaplasia (IM) and *H. pylori* intensity are evaluated and graded.[7] Although *H. pylori* is known to increase the risk of gastric cancer through IM and GA, recent studies have also demonstrated its association with neurodegenerative diseases and ischemic heart disease.[8] *H. pylori* is one of the agents causing more than 90% of cancers related to infections.[9] In addition, there are studies showing that *H. pylori* increases the risk of CRC, as well as studies showing that it does not, and there is no definite consensus.[10,11,12] The aim of our study was to evaluate the patients with colon polyps together with *H. pylori* according to Sydney criteria and to contribute to the literature.

Materials and Methods

The patients who underwent upper gastrointestinal system (GIS) endoscopy and colonoscopy in the general surgery and gastroenterology departments of 4 public hospitals in Ordu province between January 2014 and August 2018 were analyzed retrospectively. In this study, age, gender, complications during endoscopy (bleeding, perforation), number of polyps, localization of polyps (cecum, ascending colon, transverse colon, descending colon, sigmoid, rectum and anal canal), and histopathological results of stomach and colon biopsies were analyzed. Patients who underwent colonoscopic polypectomy and who had mucosal biopsy from the antrum, corpus, fundus or duodenum during simultaneous upper gastrointestinal endoscopy were included in this study. Patients under 18 years of age, patients with malignancy, inflammatory bowel disease, familial adenomatous polyposis, patients with suboptimal colon examination, patients with missing colon or gastric biopsy results, and patients who did not undergo endoscopy on the same day were excluded. The control group consisted of patients who underwent upper GIS endoscopy and had normal colonoscopy findings. Patient data were obtained from hospital data processing system and patient archive system.

Endoscopy procedures were performed by general surgery and gastroenterology specialists under sedation. Gastric biopsy contents were obtained from the corpus, antrum and suspicious localizations by the clinician performing the endoscopy. Colonoscopic polypectomy was performed piece-by-piece or totally by using forceps and snare. Polyps that could not be removed colonoscopically were either referred to a more advanced center or removed by surgical intervention. Colon and gastric pathology specimens were examined in the pathology laboratory of the hospital. Gastric specimens were evaluated histopathologically according to Sydney criteria for the presence of *H. pylori*, neutrophil activity, chronic inflammation, IM and GA.[7] Pathological evaluation was between 0 and 3 (0. none, 1. mild, 2. moderate, 3. severe) for *H. pylori*, neutrophil activity, and chronic inflammation criteria, and as -/+ (-: negative, +: positive) for IM and GA. Colon specimens were classified as non-neoplastic (hyperplastic) and neoplastic (tubular, tubulovillous, villous, intramucosal carcinoma, adenocarcinoma) histopathologically. Patients with normal colonoscopy were named as control group, patients with hyperplastic polyp as hyperplastic group, patients with neoplastic adenomatous polyp as adenoma group, and patients with malignancy as malignancy group. Patients with both hyperplastic polyps and adenomatous polyps

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were included in the adenoma group, while patients with both adenomatous polyps and malignant polyps were included in the malignancy group. In addition, patients with intramucosal carcinoma histopathology were included in the malignancy group.

The study was carried out in accordance with the Helsinki Declaration 2008 principles. Descriptive statistics for continuous variables included mean, minimum and maximum values, and categorical variables were expressed as numbers and percentages. Chi-square test was used to compare categorical variables. Mann-Whitney U test was used for comparison of continuous data. One-way ANOVA was used for the correlation of Sydney criteria, including *H. pylori* intensity, activation and inflammation. Logistic regression analysis was used to compare the relationship between IM and GA, and CRC. P<0.05 was considered statistically significant. SPSS (IBM SPSS for Windows, Ver.24) statistical package program was used for analysis.

Results

The mean age of 831 patients in our study was 58.85±10.95 (range, 26-88) years. Of the patients, 333 (40.1%) were female and 498 (59.9%) were male. There was no statistically significant difference between the groups in terms of age and gender (p>0.05). Colon polyps were detected in 600 (72.2%) patients, and no colonic polyps were detected in 231 (27.8%) patients in the control group. The total number of polypectomy was 971 and the mean number of polyps per

colonoscopy was 1.55. There were no complications in 816 patients (98.2%) during colonoscopy, while bleeding was seen during polypectomy in 15 patients (1.8%). Bleedings stopped spontaneously without any intervention. There was no perforation during colonoscopy and no complication occurred during upper GIS endoscopy. The number of polypectomy performed during colonoscopy was minimum one and maximum eleven. Polyps could not be excised by colonoscopy in 24 patients. While 23 patients required surgical intervention, one patient underwent colonoscopic polypectomy in the advanced center. The histopathological results of these patients were adenocarcinomas in 18 patients, villous adenoma in five patients and tubulovillous adenoma in one patient. The number of polyps according to colonic localization was as follows: 37 (3.8%) in cecum, 72 (7.3%) in ascending colon, 136 (15.1%) in transverse colon, 97 (10%) in descending colon, 356 (35%) in sigmoid colon, 273 (27.7%) in rectum and 15 (1.5%) in anal canal. Hyperplastic polyps were detected in 200 (24.1%), adenomatous polyps in 371 (44.6%) and malignant polyps in 29 (3.5%) patients. Eight of the malignant polyps were interpreted as intramucosal carcinoma and 21 of them were as colonic adenocarcinoma. There was no statistically significant relationship between histopathology and localization of polyps (p>0.05). Data regarding age, gender, number of polyps, localization and histopathology of the patients are given in Table 1. *H. pylori* was positive in 609 patients (73.3%), while negative in 222 patients (26.7%). *H. pylori* negativity/positivity ratio according to groups was

Table 1. Data on age, gender, number of polyps, localization and histopathology

Variables	Group 1 (n=231) (control)	Group 2 (n=200) (hyperplastic)	Group 3 (n=371) (adenoma)	Group 4 (n=29) (malignant)	Total (n=831)	p
Age (min-max)	56.97±10.48 (31-79)	58.16±11.11 (30-78)	60.54±10.69 (26-88)	61.97±11.92 (39-86)	59.03±10.89 (26-88)	0.139*
Gender						0.169**
Female	105	71	144	13	333	
Male	126	129	227	16	498	
Polyp localization						
Cecum		7	26	3	36	
Ascending colon		15	54	2	71	
Transverse colon		25	105	3	133	
Descending colon		24	69	2	95	
Sigmoid colon		117	227	8	352	>0.05*
Rectum		119	140	11	270	
Anus		9	5	-	14	
Total		316	626	29	971	

Min: Minimum, Max: Maximum, *Mann-Whitney U test was used, **Chi-square test was used

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as follows: 65/166 in Group 1, 52/148 in Group 2, 100/271 in Group 3, and 5/24 in Group 4. There was no statistically significant relationship between *H. pylori* positivity and colon polyps (p=0.65). When the intensity of *H. pylori* was examined, *H. pylori* was negative in 215 patients (25.9%), (+) in 367 patients (44.2%), (++) in 231 patients (27.8%) and (+++) in 18 patients (2.2%). There was no statistically significant relationship between *H. pylori* intensity and neoplastic status of colon polyps (p=0.65). Activation values of gastric biopsies were negative in 125 patients (15%), (+) in 400 patients (48.1%), (++) in 1261 patients (31.4%) and (+++) in 45 patients (5.4%). Inflammation values were negative in 14 patients (1.7%), (+) in 410 patients (49.3%), (++) in 344 patients (41.4%) and (+++) in 63 patients (7.6%). According to the Sydney criteria, no significant correlation was found between *H. pylori* intensity, activation and inflammation and colon polyp neoplasms (p=0.65, p=0.99, p=0.31, respectively). The neoplastic data and statistical data of the patients according to chi-square test of IM, GA and colon polyps are shown in Table 2. Although the relationship between IM and CRC patients was significant (p=0.003), Table 3 shows that IM was not a single risk factor in the presence of *H. pylori* and GA when evaluated by multiple logistic regression analysis. When the relationship between colon polyps and the presence of *H. pylori*, IM and GA were examined together, the data of the multiple logistic regression analyzes are shown in Table 3.

In the study, it was shown in Table 2 that IM was found to be proportionally high in patients compared to GA, and it was found that GA decreased proportionally less than IM in patients with CRC and that IM was more homogeneous in all patients than GA. Data showing the distribution between GA, IM and CRC is shown in Figure 1. In logistic regression analysis, when the IM and GA values of *H. pylori* negative patients were examined, no statistically significant relationship was found between CRC and IM (p=0.15), and a significant relationship was found between CRC and GA (p=0.041).

Discussion

CRCs are an important cause of morbidity and mortality in the world, accounting for 9% of the incidence of cancer.[13] Although multiple factors play a role in colon cancerogenesis, environmental factors constitute 95% of this rate.[14] *H. pylori* is a microorganism that is found in about 50% of the population and the rate increases to 80% in developing countries.[15] *H. pylori* is a type of bacteria classified as Group 1 carcinogen and is in the same category as smoking and asbestos.[16] The high rate of environmental factors in CRC and the fact that *H. pylori* is carcinogenic and common in the population has led to the necessity to investigate *H. pylori* in the etiology of CRC. In addition, in recent studies, the cultivation of some *H. species* in the colon mucosa of patients with inflammatory bowel disease has

Table 2. Neoplastic information of colon polyps with intestinal metaplasia and atrophy parameters of Sydney criteria

Variables	Group 1 (n=231) (control)	Group 2 (n=200) (hyperplastic)	Group 3 (n=371) (adenoma)	Group 4 (n=29) (malignant)
Intestinal metaplasia				
Present	35	29	58	11
Absent	196	171	313	18
Atrophy				
Present	8	16	37	9
Absent	223	184	334	20

Table 3. Data regarding colon polyps and presence of hyperplastic polyps, intestinal metaplasia and atrophy

	HP OR (95% CI)	p*	T OR (95% CI)	p*	TV OR (95% CI)	p*	V OR (95% CI)	p*	M OR (95% CI)	p*
HP	0.95 (0.66-1.36)	0.76	1.12 (0.81-1.53)	0.50	0.88 (0.51-1.51)	0.63	2.78 (0.59-13.13)	0.20	0.66 (0.24-1.77)	0.40
Intestinal metaplasia	0.85 (0.52-1.41)	0.53	0.85 (0.55-1.31)	0.46	1.07 (0.54-2.12)	0.84	1.48 (0.19-11.46)	0.71	1.86 (0.72-4.86)	0.20
Atrophy	1.02 (0.53-1.96)	0.96	1.35 (0.77-2.37)	0.30	1.76 (0.79-3.94)	0.17	7.87 (0.98-63.06)	0.06	3.57 (1.29-9.89)	0.02

OR: Odds ratio, HP: Hyperplastic polyp, T: Tubular polyp, TV: Tubulovillous polyp, V: Villous polyp, M: Malignant polyp, CI: Confidence interval, *Logistic regression analysis was applied
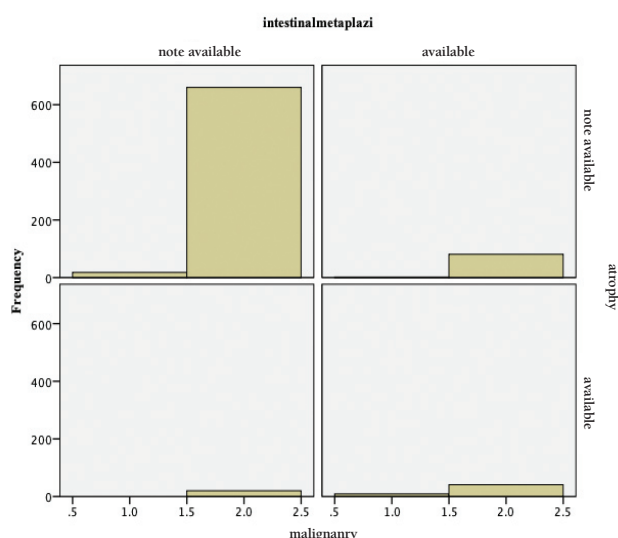
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Figure 1. Information showing the distribution between glandular atrophy, intestinal metaplasia and colorectal cancer

aroused more interest between *Helicobacter species* and colon pathologies.[17,18] *H. pylori* diagnosis can be made with non-invasive and invasive diagnostic methods and histological method, which is the gold standard method, was used in our study.[19] This diagnostic method also gave us the advantage of examining the Sydney criteria with colon polyps, except for *H. pylori* intensity. Buso et al.[20] and Fujimori et al.[21] found no significant relationship between the presence of *H. pylori* and CRC in women. We think that these clinical results are caused by gynecological hormones. In our study, no significant relationship was found between female gender and colon hyperplastic and adenomatous polyps, and adenocarcinoma. Fujimori et al.[21] and Brim et al.[22] found no significant relationship between the localization of *H. pylori* and colorectal neoplastic polyps. In our study, we did not find any significant relationship between *H. pylori* and the localization of hyperplastic, adenomatous and malignant polyps. *H. pylori* has a virulence factor called cytotoxin-associated gene A (Cag-A), which can cause ulcers and cancer. There are studies stating that this factor is colonized in the gastric mucosa and leads to hypergastrinemia through long-term inflammation and leads to the risk of CRC.[23] In a prospective study, Strofilas et al.[24] examined gastrin and Cag-A levels in 93 CRC patients, and found no significant relationship between CRC and *H. pylori*. Zhao et al.[25] revealed a significant relationship between *H. pylori* and CRC in patients analyzed by Anti-*H. pylori* immunoglobulin G. In a case-control study by Wang et al.[26], a significant relationship was found between Cag-A levels and CRC in 27 patients. They also found that the risk of tubular and villous

adenomas was associated with increased Cag-A levels. In our study, a non-serological histological method was used for the diagnosis of *H. pylori* and the result of our study was not consistent with the study of Wang et al.[26] Sonenberg and Genta[27] examined simultaneous gastric and colon biopsies of 156.000 patients and found a significant relationship between *H. pylori* and hyperplastic polyps, adenomatous polyps, villous adenomas, and CRC. However, considering active gastritis patients as a result of upper GIS endoscopy pathology as *H. pylori* (+) was a limitation of this study.[28] In our study, patients diagnosed as *H. pylori* histologically were included in the study.

There are studies showing that chronic gastritis caused by *H. pylori* triggers a series of events in gastric carcinogenesis known as GA-IM-dysplasia-cancer sequence.[29] In addition, there are studies stating that IM leads to bacterial overgrowth in colon and contributes to CRC.[30] Therefore, IM associated with *H. pylori* may increase colorectal carcinogenesis. Yan et al.[31] found that IM increases CRC. In our study, a statistically significant relationship was found between IM and the risk of CRC in the presence of *H. pylori*. Considering the *H. pylori*-associated cancer sequence,[29] we can explain the fact that the risk of CRC does not increase in the group of patients with IM who do not have *H. pylori*, although GA occurs before IM. Prolonged exposure to *H. pylori* increases gastrin levels.[32] Hypochlorhydria caused by long-lasting hypergastrinemia and chronic GA may disrupt acid-sensitive microflora and increase the risk of CRC.[32] In addition, increased hypergastrinemia in GA cases may lead to increased intraluminal ammonia and increased systemic inflammation, which can trigger intracellular tumor mechanisms.[25] Lee et al.[33] found that *H. pylori* and especially *H. pylori* positivity in patients with GA increased the risk of CRC. Gastrin has a trophic effect on epithelial cell growth and proliferation that may contribute to colorectal carcinogenesis, which is likely to increase the risk of CRC.[34] In a prospective study, Thorburn et al.[34] found that increased serum gastrin levels increased the risk of CRC. Kikendall et al.[35] found that increased serum gastrin level did not increase the risk of CRC. In our study, patients with GA had significant *H. pylori* positivity and a significant correlation was found between GA level and CRC. In addition, increased risk of CRC in patients with GA without *H. pylori* suggests the possibility that hypergastrinemia may be the precursor of CRC other than *H. pylori*. Limitations of the study include retrospective nature and the inability to question environmental factors such as obesity and smoking, which may increase the risk of CRC in patients. The advantages of the study include the diagnosis of *H. pylori* by histological diagnosis, which is the gold standard, the inclusion of hyperplastic polyps other than neoplastic colon polyps and the examination of

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Sydney criteria together with colon polyps. As a result of the study, it was determined that *H. pylori* did not increase the risk of colon hyperplastic polyps, adenomatous polyps, but increased the risk of malignant polyps in association with IM. In the presence of GA, there is also a statistically significant relationship between colon malignant polyps regardless of the presence of *H. pylori*. In the light of the data obtained in this study, patients with GA and patients with *H. pylori* and IM should be followed-up more closely for malignant colon polyps.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Ordu University Faculty of Medicine (approval no: 2019-19, date: 7/2/2019).

Informed Consent: Informed consent form was obtained from patients for surgical intervention and subsequent care, necessary permissions were obtained for the use of their data.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.A., Concept: Ç.A., Ö.Ö., Design: Ç.A., Data Collection or Processing: Ç.A., Ö.Ö., Analysis or Interpretation: Ç.A., Ö.Ö., Literature Search: Ö.Ö., Writing: Ç.A.

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