PREVALENCE OF GASTRIC CANCER PRECURSOR LESIONS IN PATIENTS OF A SECONDARY CARE CENTER IN A STATE IN SOUTH OF BRAZIL

PREVALÊNCIA DE LESÕES GÁSTRICAS PRÉ NEOPLÁSICAS EM PACIENTES DE UM CENTRO DE ATENÇÃO SECUNDÁRIA EM UM ESTADO DO SUL DO BRASIL

AUTHORS

Dominique Valentina TEREBINTO[1]

Celso Nilo Didoné FILHO[1]

Guilherme Ribas TAQUES[2]

Michelle Gusmão de ASSIS[3]

1.Centro Universitário Campo Real, Guarapuava, PR, Brasil.

2.Centro de Apoio em Patologia de Guarapuava (CAPG), Guarapuava, PR, Brasil.

3.Centro de Anatomia e Patologia HISTOCENTER, Guarapuava, PR, Brasil.

Dominique Valentina TEREBINTO: ORCID https://orcid.org/0000-0001-8191-5242

Celso Nilo Didoné FILHO: ORCID https://orcid.org/0000-0003-1238-4999

Guilherme Ribas TAQUES: ORCID https://orcid.org/0000-0002-2880-759X

Michelle Gusmão de ASSIS: ORCID https://orcid.org/0000-0002-1049-1734

Corresponding author: Dominique Valentina Terebinto. E-mail: dominiqueterebinto@yahoo.com.br. Telefone: +55 42 9 9991-9951

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ABSTRACT

BACKGROUND: Atrophy of the gastric mucosa and intestinal metaplasia is considered malignant precursor lesions of gastric cancer, which is considered the fifth most common neoplasm in the world and the third cause of death from cancer. The main risk factor is the infection by *Helicobacter pylori (H. pylori)*, which increases up to six times the risk of gastric cancer, through gastritis, atrophy, and hypochlorhydria, consequences of the infection. Other risk factors are also worth noting, like smoking and family history of gastric cancer.

OBJECTIVE: To investigate the prevalence of malignant precursor lesions and their associated factors in patients who underwent upper gastrointestinal endoscopy.

METHODS: A descriptive, observational study was performed based on an analysis of endoscopic gastric biopsies performed in two affiliated private laboratories to the Unified Health System (Sistema Único de Saúde [SUS]) in a city in Paraná state. Patients were assessed for age, sex, active or recent smoking, family history of gastric cancer, and previous treatment for *H. pylori.* The samples were evaluated for the presence of glandular atrophy, intestinal metaplasia, dysplasia and *H. pylori* infection.

RESULTS: A total of 1,549 medical records and patient reports were evaluated and 945 were eligible, the average age was 52.2 (±14.3) years old and most patients (73.3%) were female. The prevalence of *H. pylori* infection was 47.5% (n=449) and the highest percentage was between 30-39 years (58.7%). Among *H. pylori* positive (+) patients who had developed intestinal metaplasia, there is more risk of having incomplete than complete metaplasia (OR: 4.34; 1.1–17.1; 95%CI). Patients who smoke are more increase the risk to developed glandular atrophy (OR: 1.91; 1.09–3.33; 95%CI) and intestinal metaplasia (OR: 1.93; 0.72 – 5.11; 95%CI). T

CONCLUSION: The study reinforces risk factors such as smoking and *H. pylori* infection as precursors for developing pre-neoplastic lesions in a population in southern Brazil, highlighting the importance of smoking cessation and prevention of *H. pylori* infection and the treatment of infected patients.

HEADINGS: Metaplasia; *Helicobacter pylori;* Atrophy; Stomach Neoplasms

RESUMO

CONTEXTO: A atrofia da mucosa gástrica e a metaplasia intestinal são consideradas lesões precursoras malignas de câncer gástrico, sendo essa considerada a quinta neoplasia mais comum no mundo e a terceira causa de morte por câncer. O principal fator de risco é a infecção pelo *Helicobacter pylori (H. pylori)*, a qual chega a aumentar em até 6 vezes o risco de desenvolvimento do câncer gástrico, através da gastrite, atrofia e hipocloridria, consequências da infecção. Outros fatores de risco também devem ser mencionados como tabagismo e histórico familiar de câncer gástrico.

OBJETIVO: Investigar a prevalência das lesões precursoras malignas e seus fatores associados em pacientes que foram submetidos à endoscopia digestiva alta.

MÉTODOS: Estudo descritivo, observacional, individulizado, realizado com base em análise de biópsias endoscópicas gástricas realizadas em dois laboratórios privados afiliados ao Sistema Único de Saúde (SUS) em uma cidade do Paraná. Os pacientes foram avaliados quanto à idade, sexo, tabagismo ativo ou recente, histórico familiar de câncer gástrico e tratamento prévio para *H. pylori*. As amostras foram avaliadas para presença de atrofia glandular, metaplasia intestinal, displasia e também de infecção pelo *H. pylor*i.

RESULTADOS: Foram avaliados 1.549 prontuários e relatórios de pacientes, sendo 945 elegíveis, a média de idade foi de 52,2 (± 14,3) anos e a maioria dos pacientes (73,3%) era do sexo feminino. A prevalência de infecção por *H. pylori* foi de 47,5% (n = 449) e o maior percentual foi entre 30-39 anos (58,7%). Entre os pacientes com *H. pylori* positivo (+) que desenvolveram metaplasia intestinal, há mais risco de ter metaplasia incompleta do que completa (OR: 4,34; 1,1–17,1; 95%CI). Pacientes que fumam têm maior risco de desenvolver atrofia glandular (OR: 1,91; 1,09–3,33; 95%CI) e metaplasia intestinal (OR: 1,93; 0,72 – 5,11; 95%CI).

CONCLUSÃO: O estudo reforça os fatores de risco como tabagismo e infecção por *H. pylori* como precursores para desenvolvendo de lesões pré-neoplásicas em uma

população da região sul do Brasil, ressaltando a importância da cessação do tabagismo e prevenção da infecção por *H. pylori* e o tratamento de pacientes infectados.

DESCRITORES: Metaplasia; *Helicobacter pylori*; Atrofia; Câncer gástrico

INTRODUCTION

Adenocarcinomas are the predominant type of gastric cancer, corresponding to 95% of these neoplasms. In general, patients seek medical care when they have more evident symptoms, which indicate more advanced stages of the disease and this is the main reason for the high mortality rate of this cancer(1).

The main factors that predispose to gastric cancer are the patient's history and lifestyle. About habits, smoking and type of diet are the most important. A high intake of poorly preserved foods or a large amount of nitrate predisposes to the onset of the disease. In addition, the scarce consumption of vitamins A and C, antioxidant substances present in several fruits and proteins, are also risk factors for gastric adenocarcinoma(2,3).

As for the antecedents, the main risk factor is infection by *Helicobacter pylori*, which increases up to six times the risk of gastric cancer, through gastritis, atrophy, and hypochlorhydria, consequences of infection. Another disease that can facilitate the appearance of adenocarcinoma is pernicious anemia, an autoimmune disease that produces an anti-intrinsic factor or anti-parietal cell antibody, this when blocked no longer produces acid, leading to hypochlorhydria. Atrophic gastritis (AG), whichever is also in the hypochlorhydria stage, can progress to intestinal metaplasia (IM). This gastritis resulting from these two risk factors predisposes to persistent gastric ulcer, in this way can also make the patient more willing to develop cancer(1,3,4).

Helicobacter pylori is a bacterium that prefers to colonize in the antrum and cardia, but it also frequently colonizes the fundus and the body of the stomach. This gram-negative bacillus can survive under the acidic conditions of the stomach, creating resistance through synthesized enzymes, such as phospholipases and proteases that degrade mucus, who protects the gastric epithelium, as well as neutralizes the pH of the stomach that surrounds the bacteria. The characteristic of being a spiral and flagellate bacillus allows greater

motility to adhere to the parietal cells of the gastric mucosa, causing a process of inflammation and release of toxins that reduce the integrity of the mucosa. This inflammation becomes chronic and the cells are damaged, giving rise to carcinogenesis through various stages. These stages start with chronic non-atrophic gastritis that progress with loss of the gastric glands, followed by intestinal metaplasia, occuring when there is a replacement of the glandular, superficial, and foveolar epithelium in the oxyntic or antral mucosa by the intestinal epithelium, and finally dysplasia that transforms into a gastric adenocarcinoma(1, 5, 6).

Gastric atrophy and intestinal metaplasia are considered gastric cancer malignant precursor lesions. This cancer is considered the fifth most common type of cancer in the world and the 3rd cause of death from cancer(1). Two of the classifications of types of gastric cancer are the most frequent, diffuse and intestinal, being the intestinal-type adenocarcinoma responsible for most cases and the most common site of involvement is in the antrum and body of the stomach. (6, 7).

The prognosis of gastric cancer is generally poor; this is probably due to its late diagnosis. Due to this factor, added to the knowledge of the development of the disease, it is pertinent to investigate the risk factors for premalignant lesions so that the diagnosis can be established early, with chances of increasing the life expectancy of patients(1,3).

From this review, the purpose of this paper was to evaluate the prevalence of malignant precursor lesions and their associated factors in patients who underwent an upper digestive endoscopy exam and who had gastric biopsy analyzed at two reference laboratories in Guarapuava City, Parará State.

METHODS

This descriptive, observational, individualized cross-sectional study was performed based on results from upper digestive endoscopies with biopsy collected between January, 2019 and January, 2021, in two pathology laboratories in the city of Guarapuava, which are also integrated into the Unified Health System. The clinical data of these patients were evaluated regarding sex,

age, smoking status and the presence of positive family history in a first-degree relative for gastric cancer.

The smoking status was considered positive when there was an active smoking during the exam or at least one year previous the exam.

Patients over 18 years of age who sought the secondary care service and who were submitted to upper endoscopy with samples of gastric antrum and/or body and for whom *H. pylori* were investigated by specific staining were included in the study. For patients with more than one endoscopic exam with biopsies, only the samples corresponding to the first exam in the study period were considered. Patients under 18 years of age, those undergoing control endoscopy after treatment for H. pylori, who presented a different pattern in the sample, previous gastrectomy, also with biopsy compatible with gastric neoplasia, and those whose medical records were incomplete were excluded. As for the biopsy samples, the antrum and body samples were included simultaneously and separately.

The slides were stained by the GIEMSA method which shows satisfactory sensitivity, specificity, positive predictive value and accuracy for bacillus identification(8).

Samples were evaluated for the presence of *H. pylori* in the antrum and/or gastric body (present or absent) and according to two morphologic variants: intestinal metaplasia and glandular atrophy, with these variables classified as absent or present, and when present ranked as mild, moderate and severe for glandular atrophy and complete or incomplete for intestinal metaplasia.

The Campo Real Ethics Committee approved this study and the report CAAE number is 38557620.0.0000.8947.

Statistical analysis

The Excell Microsoft Office Professional Plus 2013 program was used for data input and data analyses was performed with IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. For statistical analysis, nominal data will be presented in frequencies with percentages and numerical data in mean with standard deviation. The differences in the distribution of variables were

evaluated by the chi-square test and those with a P-value < 0.05 were considered statistically significant.

RESULTS

A total of 1,549 medical records and patient reports were analyzed and 945 met de inclusion criteria. Regarding the patients excluded from the sample, 30 were minors, 139 had post-treatment endoscopy for *H. pylori*, 69 the sample was of another pattern, 12 had already undergone previous gastrectomy and 354 the medical record was incomplete (Figure 1). The average age of those included was 52.2 (±14.3) years old; the majority of them were women (n=695; 73.5%). As shown in Table 1, the prevalence of *H. pylori* infection in this population was 47.5% (n=449). The highest percentage of infection by *H. pylori* was between 30-39 years (58.7%), while the smallest percentage was detected among patients higher than 60 years (39.2%), a decrease was detected between 40-49 years of age followed by an increase between the patients with 50-59 years ($p<0.01$). The frequency of infection was higher among women (49.8%), however, there was no statistical significance ($p=0.47$).

Of all the samples analyzed, 105 (11.2%) patients had some degree of intestinal metaplasia, 93 (9.8%) of them with complete metaplasia, and 12 (1.4%) with incomplete. Regarding glandular atrophy, 73 (7.8%) patients had some degree, with 45 (4.8%) mild atrophy, 25 (2.6%) moderate, and 3 (0.4%) severe. Of these patients, 24 (2.5%) had both metaplasia and atrophy in their sample. Regarding the risk factors surveyed during the study, 37 (3.9%) patients had a positive family history of gastric cancer and 100 (10.6%) patients were smokers.

When *H. pylori* was evaluated as a risk factor for the development of intestinal metaplasia, no statistical significance was found in the sample, with the odds ratio for the occurrence of metaplasia associated with *H. pylori* infection was 0.88 (0.58 – 1.32; 95%CI) not allowing association as a risk factor (Table 2). Patients with *H. pylori* infection who had developed intestinal metaplasia have a 3.4-fold increased risk of having incomplete than complete metaplasia (OR: 4.34; 1.1–17.1; 95%CI) (Table 3). When evaluating *H. pylori* as a risk factor for patients

with glandular atrophy, there was no statistical significance in the sample, the odds ratio was 1.42, with a variance between 0.97 and 2.06 (Table 4).

Regarding smoking, when evaluated as a risk factor for the development of intestinal metaplasia, smoking patients have a 91% increased risk of developing metaplasia (OR: 1.91; 1.09–3.33; 95%CI) (Table 5). Similarly, when evaluated in relation to glandular atrophy, smoking patients have a 1.39-fold increase in the chance of developing atrophy (OR: 2.39; 1.3–4.4; 95%CI) (Table 6).

The risk of patients with a positive family history for gastric cancer to develop intestinal metaplasia, it did not obtain statistical significance to make this statement (OR: 1.92; 0.92 – 4.5; 95%CI) (Table 7). Similarly, when compared to the risk of developing glandular atrophy, there was also no statistical significance (OR: 1.93; 0.72 – 5.11; 95%CI) (Table 8).

In addition, the coexistence of intestinal metaplasia, glandular atrophy and positive and negative *H pylori* was also evaluated (Figure 2). It was observed that among patients with *H. pylori* (+), 6 (0.6%) had at least one type of precursor lesion, 398 (42.1%) had no metaplasia or atrophy and 24 (2.5%) had an *H. pylori* infection, atrophy, and metaplasia simultaneously. Among patients with *H. pylori* (-), 17 (1.8%) had a precursor lesion, 43 (4.5%) had both precursor lesions present, and the majority (n=436; 42.1%) did not show metaplasia or atrophy.

DISCUSSION

In the present study, our objective was to demonstrate the epidemiological profile of the population in question and the risk factors that contribute to the development of pre-neoplastic lesions.

H. pylori is considered an important risk factor for the development of intestinal atrophy and metaplasia(10,11,12). In developing countries, infection by *H. pylori* is very common, and about 50% of the world population is infected by this bacterium, that has a prevalence in Brazil of up to 71%(13,14). In the current study, the prevalence of infection by H. pylori was 47.5%, being higher than in a previous study by Rodrigues et al. which was 31.7% in a different region of Brazil.

This difference is probably due to the profile of the population studied (private x public health system).

When analyzing the epidemiological profile of the studied population, we observed a similar profile regarding gender and age to other studies such as Rodrigues et al., in addition to conferring a higher percentage of *H. pylori* infection between 30-39 years. In our study, the lowest percentage of *H. pylori* was in patients older than 60 years, unlike the study mentioned, in which the lowest percentage was in patients younger than 30 years. This difference can be explained by the sample size of the studies.

Regarding gastric atrophy and intestinal metaplasia, studies show that they are precursor lesions of gastric cancer(3,9,11). A systematic review and meta-analysis analyzed the prevalence of intestinal atrophy and metaplasia in the general population, including 107 original articles comparing countries with high versus low to moderate incidence of gastric cancer(12). In the cited review, there was a higher prevalence of atrophy in the general population than intestinal metaplasia. When compared countries with a high incidence of this neoplasm, the prevalence of atrophy was 41.7%, while in countries with a low to moderate incidence it was 22.8%. Regarding metaplasia, 21.7% presented in countries with low to the moderate incidence of gastric cancer and 28.1% in countries with high incidence, with no significant difference between these countries.

In the present study, the prevalence of metaplasia was 11.2% and of atrophy was 7.8%, being lower than expected for countries with a low incidence of gastric cancer. However, these numbers follow the same direction as some studies already carried out in Brazil and were in agreement with a retrospective study carried out in the southeast region of Brazil, in which the prevalence of intestinal metaplasia and atrophy was, respectively, 14.7% and 10.3%(6).

Some studies show that the risk of gastric cancer may be greater in patients with incomplete-type metaplasia than in those with the complete-type, in addition to increasing the risk in patients with a family history of gastric cancer in a first-degree relative(16-19). A meta-analysis of seven studies demonstrated that having incomplete versus complete metaplasia is associated with a three-fold increased risk for developing gastric cancer (over 3 to 13 years follow-up; relative risk [RR] 3.3, 95%CI, 1.9 -5.6)(20). When evaluating the prevalence of intestinal atrophy and metaplasia in relation to infection by *H. pylori*, there was no

statistical significance in our study, but patients who had *H. pylori* infection and metaplasia had a higher risk of developing incomplete than complete metaplasia.

When evaluating the prevalence of pre-neoplastic lesions in relation to smoking, we saw that patients who smoke are at increased risk for the development of atrophy (OR: 2.39; 1.3–4.4; 95%CI) and metaplasia (OR: 1.91; 1.09–3.33; 95%CI), thus increasing the chance of developing gastric cancer, since smoking is an important risk factor for this condition(15).

A family history of gastric cancer is also considered a risk factor for cancer (15,17), but in the present study, it was not possible to associate this factor with the development of pre-neoplastic lesions.

Smoking cessation and *H. pylori* eradication are measures that decrease the risk of gastric cancer, although eradication of the infection does not completely regress metaplasia and atrophy, it can delay the development of these lesions and progression to gastric cancer(10, 21, 22).

We considered the study's limiting factors, the low replicability of the sample, as it was limited to only one city in the southern region of Brazil, another limitation is the sample only from the gastric body or only from the antrum.

CONCLUSION

The present study contributes to a better understanding of the risk factors associated with the development of pre-neoplastic lesions in a population in southern Brazil, which include smoking and *H. pylori* infection. We also conclude that there is an increased risk of developing incomplete-type metaplasia in this population, further increasing the chance of gastric cancer. Thus, we reinforced measures such as smoking cessation and the prevention of *H. pylori* infection, as well as the treatment of infected patients.

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ATTACHMENTS

TABLE 1

Table 1. Prevalence of *H. pylori* infection according to age and sex.

Variable	***H. pylori* negative** n (%)	***H. pylori* positive** n (%)	**Total**	**P-value**
	496 (52.4%)	449 (47.5%)	945	
Age				< 0.01
< 30 yrs	37 (46.2%)	42 (53.8%)	79	
30 - 39 yrs	45 (41.3%)	64 (58.7%)	109	
40 - 49 yrs	94 (53.7%)	81 (46.3%)	175	
50 - 59 yrs	130 (48.5%)	138 (51.5%)	268	
> 60 yrs	191 (60.8%)	123 (39.2%)	314	
Sex				0.47
Female	348 (50.1%)	346 (49.8%)	694	
Male	148 (59%)	103 (41%)	251	

TABLE 2

Table 2. Prevalence of intestinal metaplasia according to *H. pylori* infection status.

	Intestinal metaplasia				
Infection Status	**Absent** n (%)	**Present** n (%)	**Total**	**OR**	**P-value**
	840 (88.8%)	105 (11.2%)	945		
H. pylori (-)	438 (88.3%)	58 (11.7%)	496	0.88 (0.58 - 1.32)	0.55
H. pylori (+)	402 (89.5%)	47 (10.5%)	449		

TABLE 3

Table 3. Prevalence of the degree intestinal metaplasia according to *H. pylori* infection status.

	Intestinal metaplasia				
	Incomplete	**Complete**			
Infection Status	n (%)	n (%)	**Total**	**OR**	**P-value**
	12 (12.4%)	93 (88.6%)	105		
H. pylori (-)	3 (88.3%)	55 (11.1%)	58	4.34 (1.1 - 17.1)	< 0.05
H. pylori (+)	9 (19.1%)	38 (80.9%)	47		

TABLE 4

Table 4. Prevalence of glandular atrophy according to *H. pylori* infection status.

	Atrophy				
	Absent	**Present**			
Infection Status	n (%)	n (%)	**Total**	**OR**	**P-value**
	872 (92.2%)	74 (7.8%)	105		
H. pylori (-)	451 (90,9%)	55 (9.1%)	506	1.42 (0.97 - 2.06)	0.06
H. pylori (+)	421 (92.2%)	73 (7.8%)	494		

TABLE 5

Table 5. Prevalence of intestinal metaplasia according to smoking status.

Smoking status	Intestinal metaplasia Absent	Intestinal metaplasia Present	Total	OR	P-value
	n (%)	n (%)			
	840 (88.8%)	105 (11.2%)	945		
Sim	82 (82%)	18 (18%)	100	1.91 (1.09 - 3.33)	< 0.05
Não	758 (89.6%)	87 (10.4%)	845		

TABLE 6

Table 6. Prevalence of glandular atrophy according to smoking status.

Smoking status	Atrophy Absent	Atrophy Present	Total	OR	P-value
	n (%)	n (%)			
	872 (92.2%)	73 (7.8%)	945		
Sim	85 (85%)	15 (15%)	100	2.39 (1.3 - 4.4)	< 0.05
Não	787 (93%)	58 (7%)	845		

TABLE 7

Table 7. Prevalence of intestinal metaplasia according to family history for gastric cancer.

Family history	Intestinal metaplasia Absent	Intestinal metaplasia Present	Total	OR	P-value
	n (%)	n (%)			
	840 (88.8%)	105 (11.2%)	945		
Sim	30 (81.1%)	7 (18.9%)	37	1.92 (0.82 - 4.5)	0.12
Não	810 (89,2%)	98 (10,8%)	908		

TABLE 8

Table 8. Prevalence of glandular atrophy according to family history for gastric cancer.

Family history	Atrophy Absent	Atrophy Present	Total	OR	P-value
	n (%)	n (%)			
	872 (92.2%)	73 (7.8%)	945		0.39
Sim	32 (86.5%)	5 (13.5%)	37	1.93 (0.72 - 5.11)	0.18
Não	840 (92.4%)	68 (7.6%)	908		

FIGURE 1

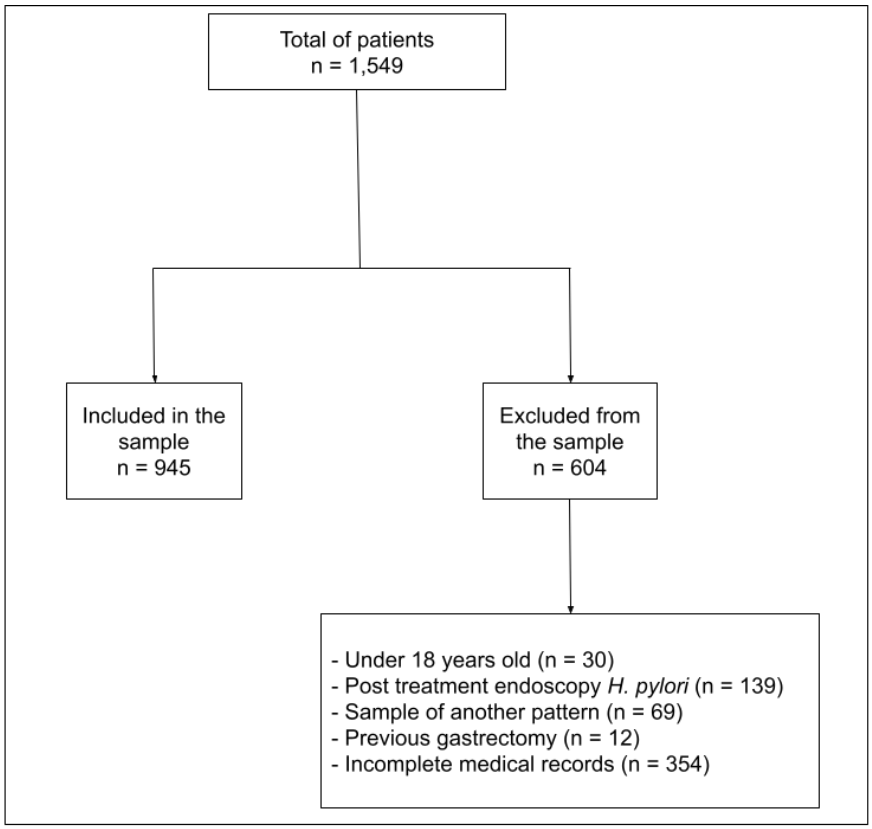

FIGURE 1. Flow diagram of included and excluded patient samples.

FIGURE 2

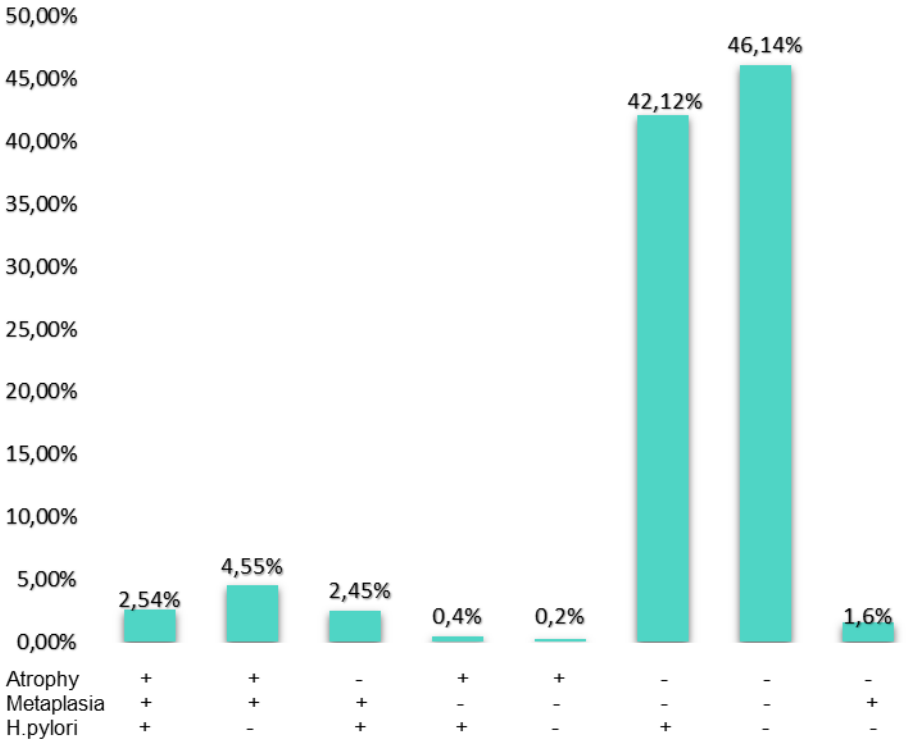

FIGURE 2. Coexistence of glandular atrophy, intestinal metaplasia and H. pylori.