

Helicobacter pylori chronic gastritis on patients with premalignant conditions: OLGA and OLGIM evaluation and serum biomarkers performance

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ABSTRACT – Background – *H. pylori* chronic atrophic gastritis is a premalignant lesion, and its staging, according to OLGA and OLGIM systems aims to identify patients at increased risk of developing gastric cancer and optimize their follow-up. GastroPanel[®], serum biomarkers panel including pepsinogen I (PGI), pepsinogen II (PGII), Gastrin 17 (G17) and anti-*H. pylori* antibodies is a noninvasive test for adenocarcinoma risk assessment in chronic *H. pylori* gastritis patients. **Objective** – Prospective study to evaluate the concordance between OLGA and OLGIM grading systems, as well as to evaluate GastroPanel's performance in patients with premalignant lesions secondary to *H. pylori* chronic gastritis in Brazil. **Methods** – Patients with *H. pylori* chronic gastritis with premalignant lesions confirmed by histology were recruited from the gastrointestinal clinic of a University Hospital. All participants underwent endoscopic examination with biopsies which were reported according to updated Sydney system and premalignant lesions grading systems (OLGA and OLGIM). Blood samples were collected for biomarkers serological analysis (GastroPanel[®], Biohit, Helsinki, Finland). The cut off values used to define high risk patients were those recommended by the manufacturer: PGI ≤ 30 $\mu\text{m/L}$ and PGI/PGII ≤ 3 . **Results** – 41 patients were recruited: 28 women, 13 men, mean age 67.3 (47-89, SD: 9.6) years. By OLGA system, were obtained: OLGA 0 (n=1), OLGA I (n=7), OLGA II (n=17), OLGA III (n=9), and OLGA IV (n=7). By OLGIM system, were obtained: OLGIM 0 (n=14), OLGIM I (n=5), OLGIM II (n=10), OLGIM III (n=10), and OLGIM IV (n=2). Regarding histological staging among patients staged as low risk (OLGA/OLGIM 0, I and II) and high risk (OLGA/OLGIM III and IV) for gastric cancer development, the concordance rate found between both classifications was 85.4%. Considering high risk patients, those patients thus included in at least one of the systems the final distribution of our sample considered 24 low-risk and 17 high-risk patients for the development of gastric cancer. To determine by GastroPanel[®] whether the patient would be at low or high risk of developing gastric cancer, PGI showed a sensitivity, specificity and accuracy of 0.47 (95%CI: 0.26–0.69), 0.67 (95%CI: 0.47–0.82), and 0.58 (95%CI: 0.43–0.72), respectively, while PGI/PGII showed sensitivity, specificity and accuracy of 0.06 (95%CI: 0.01–0.27), 0.83 (95%CI: 0.64–0.93) and 0.51 (95%CI: 0.36–0.66), respectively. **Conclusion** – The histological classifications OLGA and OLGIM presented a substantial concordance rate among themselves. Simultaneous use of both histological classification systems increased the identification's rate of high-risk patients. Biomarker analysis was not effective to distinguish low to high risk patients in the studied population. Further studies are needed to validate its use in clinical practice in Brazil. **HEADINGS** – Atrophic gastritis, diagnosis. *Helicobacter pylori*. Severity of illness index. Biomarkers. Algorithms.

INTRODUCTION

Helicobacter pylori infection is already recognized as the main etiological factor of chronic gastritis, with an evolutionary potential for the development of peptic ulcer and gastric neoplasms (adenocarcinoma and MALT lymphoma)^(1,2). Although its presence evokes a local and systemic immune response, *H. pylori* infection, once acquired, persists indefinitely until it is properly treated. The accurate diagnosis of gastritis associated with *H. pylori* is confirmed by histopathological examination⁽³⁾.

The sequence *H. pylori* infection → chronic gastritis → glandular atrophy → intestinal metaplasia is a set of associated changes that are

very frequently observed. The risk of gastric adenocarcinoma is four to five times higher in patients with severe body atrophy compared to healthy patients. Among patients with severe atrophy of the antrum, there is an 18 times greater risk for development of gastric cancer, reaching 90 times in those with severe atrophy of body and antrum (pangastritis) when compared to healthy people⁽⁴⁻⁹⁾.

Populational studies have been carried out to quantify the risk of this neoplasia in patients with premalignant gastric lesions in western world. In 2008, a cohort conducted in the Netherlands with 92,250 people with premalignant lesions estimated the following risks for developing gastric cancer, within a period of ten years after the initial diagnosis: 0.8% for people with atrophic gastritis; 1.8% for

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patients with intestinal metaplasia; 3.9% for patients with mild to moderate dysplasia and 32.7% for those with high-grade dysplasia⁽¹⁰⁾. In 2015, a cohort conducted in Sweden analyzed 405,172 individuals who underwent gastric biopsy for non-malignant indications from 1979 to 2011. The findings obtained allowed to predict that 1/256 patients with normal gastric mucosa, 1/85 with chronic gastritis, 1/50 with atrophic gastritis, 1/39 with intestinal metaplasia and 1/19 with dysplasia will develop gastric cancer within 20 years after identification of these lesions⁽¹¹⁾. Such findings suggest that endoscopic follow-up implementation in patients with marked premalignant lesions could reduce mortality from gastric cancer if cost-benefit analysis proves favorable for a given population.

In order to provide prognostic/therapeutic useful information in premalignant gastric lesions patients management, histological systems have been developed for staging gastritis in this situation. In 2007, the Operative Link for Gastritis Assessment (OLGA) system was developed based on presence, extension and topography (antrum and/or gastric body) of atrophic changes⁽¹²⁾. Patients classified as stage III or IV are considered to be at high risk. The Operative link for Gastric Intestinal Metaplasia (OLGIM) Assessment system is also based on the same concept, but only considers the presence, extension and topography of lesions related to intestinal metaplasia⁽¹³⁾. The prognostic value of both systems has been documented in different studies, with different samples and populations, and its adoption is recommended by different consensus and guidelines meetings in different regions of the world⁽¹⁴⁻¹⁸⁾.

To avoid excessive performance of invasive and costly procedures such as upper digestive endoscopy, there is a need for searching new non-invasive diagnostic methods, capable of detecting patients at risk of developing gastric cancer, such as patients with different phenotypes chronic gastritis, especially those associated with *H. pylori* infection. This is particularly relevant in countries with a high prevalence and incidence of *H. pylori* infection and gastric cancer in the population.

Pepsinogens, pro-enzymes of pepsin, are classified according to their biochemical and immunological properties into two types: pepsinogen I (PGI) and pepsinogen II (PGII). Both are produced by the gastric mucosa but in different locations. While PGI is produced exclusively by the chief cells and mucous cells of the gastric body, PGII is produced by these cells and also by mucous cells in the cardiac region, pyloric glands, and Brunner glands in the duodenal mucosa. Both pro-enzymes are excreted mainly into the gastric lumen, but a minimal portion (around 1%) diffuses into the bloodstream and can be measured^(19,20). PGI and PGII are increased in patients with *H. pylori* chronic gastritis. However, as atrophy of the body's mucosa occurs, due to the reduction of oxyntic glands, there is a more significant reduction in PGI than in PGII in mild atrophy phase, since this is also produced in other regions of the stomach. Sometimes the mucosa's inflammation associated with *H. pylori* infection is so severe that, even in the presence of atrophy, the levels of PGI and PGII may be elevated⁽²¹⁾. To overcome this limitation, the PGI/PGII (RPG) ratio is used, and today is considered the best serological marker for gastric atrophy and already used as a tool for gastric cancer risk screening in Japan and, incipiently, in other countries⁽²²⁻²⁷⁾. To improve the accuracy of non-invasive diagnosis of gastric atrophy, the addition of other biomarkers to pepsinogens has been suggested. By associating anti-*H. pylori* antibodies to pepsinogens dosage (ABCD method), Asian researchers have shown that the method has the potential to stratify healthy adults from those at increased risk

of developing gastric cancer⁽²⁸⁾. Another association of biomarkers recently described (GastroPanel[®], Biohit, Helsinki, Finland), involves, in addition to the determination of pepsinogens and anti-*H. pylori* antibodies, the determination of gastrin-17 (G17), all of them through the collection of a single blood sample. Two recent meta-analyses have evaluated the performance of GastroPanel[®]: Syrjänen K⁽²⁹⁾ analyzed the results of 8,654 patients from different countries, having found sensitivity of 70.2% and specificity of 93.9% in the diagnosis of body's atrophic gastritis and sensitivity of 53.8% and specificity of 84.1% in the diagnosis of antrum atrophic gastritis. Zagari RM, et al.⁽³⁰⁾ analyzed 20 studies involving 4,241 participants, finding similar sensitivity (70.4%) for the diagnosis of body's atrophic gastritis and sensitivity of 65.4% for the diagnosis of antrum atrophic gastritis.

There are still few studies that relate levels of pepsinogens to the diagnosis of gastric atrophy in Latin America countries^(31,32). The aim of this study was to perform a prospective study to evaluate the concordance between OLGA and OLGIM systems, as well as GastroPanel[®] performance in patients with premalignant lesions secondary to *H. pylori* chronic gastritis in Brazil.

METHODS

A consecutive series of adult patients of both sexes, with *H. pylori* chronic gastritis with associated premalignant conditions on histology, was recruited from November/2016 to April/2019 at the upper gastrointestinal outpatient clinic of University Hospital. Patients were excluded if they had coagulation disorders that should avoid gastric biopsies or if they had acute illnesses and indication for surgery or urgent treatment to control their symptoms. Were also excluded patients who used antibiotics on the 30 days preceding upper digestive endoscopy, proton pump inhibitor (PPI), and histamine H2 receptor antagonist on the 10 days preceding upper digestive endoscopy, and patients with chronic atrophic gastritis from proven autoimmune etiology.

All patients included in the study answered a pre-established clinical questionnaire and, after agreeing to participate in the study and signing the informed consent form, were submitted to blood collection for the serological panel and upper digestive endoscopy.

Serological panel (GastroPanel[®])

Immediately before endoscopic examination, a cubital vein blood sample (4 mL) was collected, and after centrifugation, the plasma was immediately stored into a -80°C freezer. All samples were processed for ELISA readings using Sprinter XL equipment (Euroimmun, Germany). Each marker was analyzed on an individual microplate, and the device's software was programmed according to the manufacturer's instructions, who provided the following reference values: pepsinogen I: 30–160 µm/L; pepsinogen II: 3–15 µm/L; gastrin 17: 1–7 pmol/L; *Helicobacter pylori* IgG ELISA: <30 EUI = negative. For the classification of patients into low and high risks for the development of gastric cancer, the following values were considered: PGI ≤30: high-risk patient; PGI >30: low-risk patient; PGI/PG II ≤3: high-risk patient; PGI/PGII > 3: low-risk patient.

Upper digestive endoscopy with gastric biopsies

During endoscopy, six gastric biopsies were collected (two biopsies from gastric antrum, one biopsy from angular notch and three from gastric body). All biopsies were fixed in 10%

formaldehyde and included in paraffin blocks separately and reported according to the Updated Sydney System for Gastritis Classification⁽³³⁾. The histological study of the gastric mucosa was performed in histological sections of 4 µm thick by a single gastrointestinal pathologist. The histological stains used were hematoxylin-eosin (HE) for histopathological analysis and Giemsa for *H. pylori* infection presence. All patients had their histological findings staged according to the OLGA⁽³⁴⁾ and OLGIM⁽¹³⁾ systems.

Statistics

Descriptive statistics techniques were used. Continuous variables were compared using Student's *t*-test, Mann-Whitney test (non-parametric data), and the chi-square test was used to quantitatively assess the relationship between results obtained. Considering the histological results of the OLGA-OLGIM set as the gold standard, sensitivity, specificity, positive predictive value, negative predictive value, accuracy and 95% confidence interval (CI) were calculated for the results obtained through serological biomarkers. Kappa values and 95%CI were determined to concordance analysis between OLGA and OLGIM systems. The Confidence Interval Analysis (CIA) program was used to calculate the confidence intervals using Wilson's method. Statistical significance was recognized for values of $P < 0.05$. All statistical analyzes were performed using the MINITAB statistical package (Minitab Inc., USA) version 16, Excel (Office 10). The study was approved by the *Universidade Federal de Minas Gerais* Research Ethics Committee. For sampling, the number of subjects required as low risk to develop gastric cancer (OLGA and OLGIM I or II) and high risk (OLGA or OLGIM III or IV) was calculated based on studies showing expected values for GastroPanel[®] reported in previous studies⁽²⁹⁾. It was estimated with 80% power, 172 and 61 patients from low risk and high risk, respectively. As the amount of patients needed would take too long to be recruited, it was adopted a convenience, not probabilistic sample composed by the number of patients suitable for this preliminary study included during the two years and six months study period.

RESULTS

Initially, 46 patients were recruited and five patients were excluded: one by using oral anticoagulant, two due to thrombocytopenia, one due to erroneous inclusion (proven autoimmune gastritis), and one patient for refusing to participate in the study. Thus, a total of 41 patients participated in the study, and their demographic characteristics can be seen in TABLE 1.

Histological findings

TABLE 2 shows the observed distribution of all patients according to the histological staging of gastritis OLGA and OLGIM. FIGURE 1 shows concordance's rate between both histological systems regarding the staging of patients as low and high risk of the development gastric cancer. It can be seen that, among the 41 patients in the study, 24 were classified as low risk by both systems, 11 were classified as high risk by both systems and six patients presented discordant classifications, thus conferring 0.678 (95%CI: 0.440–0.916) kappa value and 85.4% concordance rate. Considering high-risk patients those patients thus included in at least one the histological staging systems, the final distribution of our sample considered 24 patients at low risk and 17 as high risk for the development of gastric cancer. Based on this distribution,

TABLE 1. Demographic characteristics of the 41 patients in the study.

Sex: male/female	13/28
Mean age (years): (SD)	67.3 (9.6)
Mean BMI (kg/m ²): (SD)	26.8 (5.1)
Alcoholism: n (%)	6 (15)
Smoking: n (%)	8 (20)
Education: n (%)	
Elementary School	19 (46.3)
High School	19 (46.3)
Higher Education	3 (7.4)
Comorbidities: n (%)	
None	1 (2.4)
Hypertension	29 (70.7)
Diabetes mellitus	13 (31.7)
NSAIDs: n (%)	3 (7.3)
Dyspepsia: n (%)	22 (53.7)
Family history of gastric cancer: n (%)	5 (12.2)

SD: standard deviation; BMI: body mass index; NSAIDs: nonsteroidal anti-inflammatory drugs.

TABLE 2. Distribution of patients according to OLGA and OLGIM histological grading systems (n=41).

	OLGA 0	OLGA I	OLGA II	OLGA III	OLGA IV
	1	7	17	9	7
Number of patients	OLGIM 0	OLGIM I	OLGIM II	OLGIM III	OLGIM IV
	14	5	10	10	2

OLGA: Operative Link for Gastritis Assessment; OLGIM: Operative link for Gastric Intestinal Metaplasia.

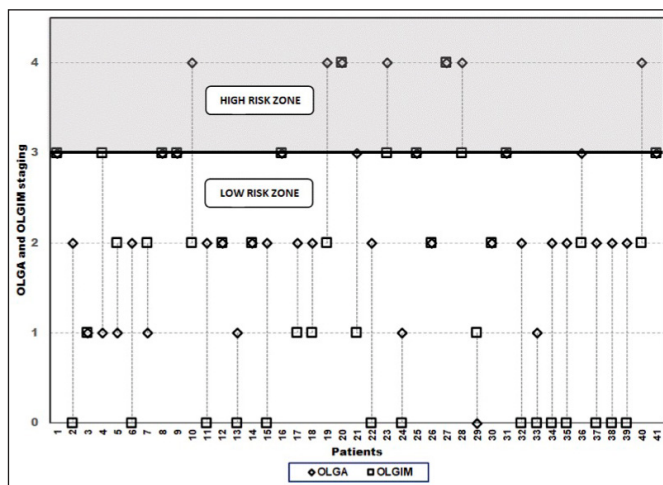


FIGURE 1. OLGA and OLGIM staging systems in 41 patients of the study.

TABLE 3 shows that the two groups do not present statistically significant differences on demographic variables, except for gender variable, with the female gender being predominant in high-risk group ($P=0.02$).

TABLE 3. Comparison of demographic characteristics in the 41 patients classified by the OLGA and OLGIM gastritis grading systems, as low and high risk for developing gastric cancer.

Variables	OLGA or OLGIM Low risk (n=24)	OLGA and/or OLGIM High risk (n=17)	P-value
Mean age (years): SD	65.7 (10.1)	69.6 (8.6)	0.36*
Mean BMI (kg/m ²): SD	26.7 (4.4)	26.8 (6.1)	0.75*
Sex: male/female	11/13	2/15	0.02**
Education: ES/H	12/12	7/10	0.58**
Smoking: no/yes	19/5	14/3	0.80**
Alcoholism: no/yes	21/3	14/3	0.65**
Family history of gastric cancer: no/yes	22/2	14/3	0.37**
NSAIDs: no/yes	22/2	16/1	0.80**
Previous <i>H. pylori</i> treatment: no/yes	2/22	4/13	0.17**
<i>H. pylori</i> at histology: no/yes	18/6	16/1	0.11**
Dyspepsia: no/yes	12/12	7/10	0.58**

SD: standard deviation; OLGA: Operative Link for Gastritis Assessment; OLGIM: Operative link for Gastric Intestinal Metaplasia; ES: Elementary School; H: High School or Higher Education. *Mann Whitney test; **chi-square test.

Serological biomarkers

TABLE 4 shows PGI, PGI/PGII, and Gastrin-17 values obtained in patients with low and high risks for the development of gastric cancer by OLGA system, OLGIM system, and by OLGA-OLGIM set. No statistically significant differences were found in any of comparative analyses performed.

TABLE 5 shows the accuracy determinations of PGI biomarker and PGI / PGII ratio to determine whether the patient would be at low or high risk for developing gastric cancer. The PGI showed a sensitivity of 0.50, 0.42, and 0.47 for the OLGA, OLGIM and OLGA-OLGIM set, respectively. The observed specificity was 0.68, 0.62, and 0.67 for the OLGA, OLGIM and OLGA-OLGIM set, respectively and accuracy of 0.61, 0.56, and 0.58 for the OLGA, OLGIM, and OLGA-OLGIM set, respectively. The PGI / PGII showed sensitivity of 0.06, 0.00 and 0.06 for the OLGA, OLGIM, and OLGA-OLGIM set, respectively. The observed specificity was 0.84, 0.83, and 0.83 for the OLGA, OLGIM, and OLGA-OLGIM set, respectively, and accuracy of 0.49, 0.58 and 0.51 for the OLGA, OLGIM, and OLGA-OLGIM set, respectively.

Helicobacter pylori

FIGURE 2 shows previous *H. pylori* infection treatment information and histology and serology results. Only one patient had no informed previous infection's treatment and tested negative both by histology and serology.

TABLE 4. Comparative analysis of PGI levels, PGI / PGII, and Gastrin-17 observed in patients classified according to the risk of developing gastric cancer by the OLGA, OLGIM and by the OLGA and OLGIM set.

Variable	OLGA Low risk (n=25)	OLGA High risk (n=16)	P-value*
PG I (µg/L): mean (SD)	64.2 (67.6)	57.8 (64.9)	0.640
PGI/PGII: mean (SD)	17.9 (13.6)	17.8 (7.2)	0.659
Gastrin-17 (pmol/L) mean (SD)	12.4 (11.8)	29.5 (28.9)	0.317
Variable	OLGIM Low risk (n=29)	OLGIM High risk (n=12)	P-value
PG I (µg/L): mean (SD)	64.2 (73.0)	50.1 (44.3)	0.808
PGI/PGII: mean (SD)	17.4 (13.4)	18.8 (4.1)	0.398
Gastrin-17 (pmol/L) mean (SD)	14.7 (18.4)	9.4 (19.3)	0.086
Variable	OLGA and OLGIM Low risk (n=24)	OLGA and/or OLGIM High risk (n=17)	P-value
PG I (µg/L): mean (SD)	65.4 (68.8)	56.4 (63.1)	0.624
PGI/PGII: mean (SD)	17.9 (13.9)	17.8 (6.9)	0.701
Gastrin-17 (pmol/L) mean (SD)	9.3 (10.6)	18.6 (25.5)	0.317

OLGA: Operative Link for Gastritis Assessment; OLGIM: Operative link for Gastric Intestinal Metaplasia; SD: standard deviation. *Mann Whitney test.

TABLE 5. Accuracy measures of the PGI and PGI/PGII considering the OLGA, OLGIM gastritis grading systems and by the OLGA and OLGIM set.

Accuracy measures	Gastritis grading systems			
	OLGA	OLGIM	OLGA and OLGIM	
PGI	Sensitivity (95% CI)	0.50 (0.28–0.72)	0.42 (0.19–0.68)	0.47 (0.26–0.69)
	Specificity (95% CI)	0.68 (0.48–0.83)	0.62 (0.44–0.77)	0.67 (0.47–0.82)
	PPV (95% CI)	0.50 (0.28–0.72)	0.31 (0.14–0.56)	0.50 (0.28–0.72)
	NPV (95% CI)	0.68 (0.48–0.83)	0.72 (0.52–0.86)	0.64 (0.44–0.80)
	Accuracy (95% CI)	0.61 (0.46–0.74)	0.56 (0.41–0.70)	0.58 (0.43–0.72)
	PGI/PGII	Sensitivity (95% CI)	0.06 (0.01–0.28)	0.00 (0.00–0.24)
Specificity (95% CI)		0.84 (0.65–0.94)	0.83 (0.65–0.92)	0.83 (0.64–0.93)
PPV (95% CI)		0.20 (0.04–0.62)	0.00 (0.00–0.43)	0.20 (0.04–0.62)
NPV (95% CI)		0.58 (0.42–0.73)	0.68 (0.50–0.80)	0.56 (0.40–0.70)
Accuracy (95% CI)		0.49 (0.34–0.63)	0.58 (0.43–0.72)	0.51 (0.36–0.66)

OLGA: Operative Link for Gastritis Assessment; OLGIM: Operative link for Gastric Intestinal Metaplasia; PGI: pepsinogen I; PGII: pepsinogen II; PPV: positive predictive value; NPV: negative predictive value.

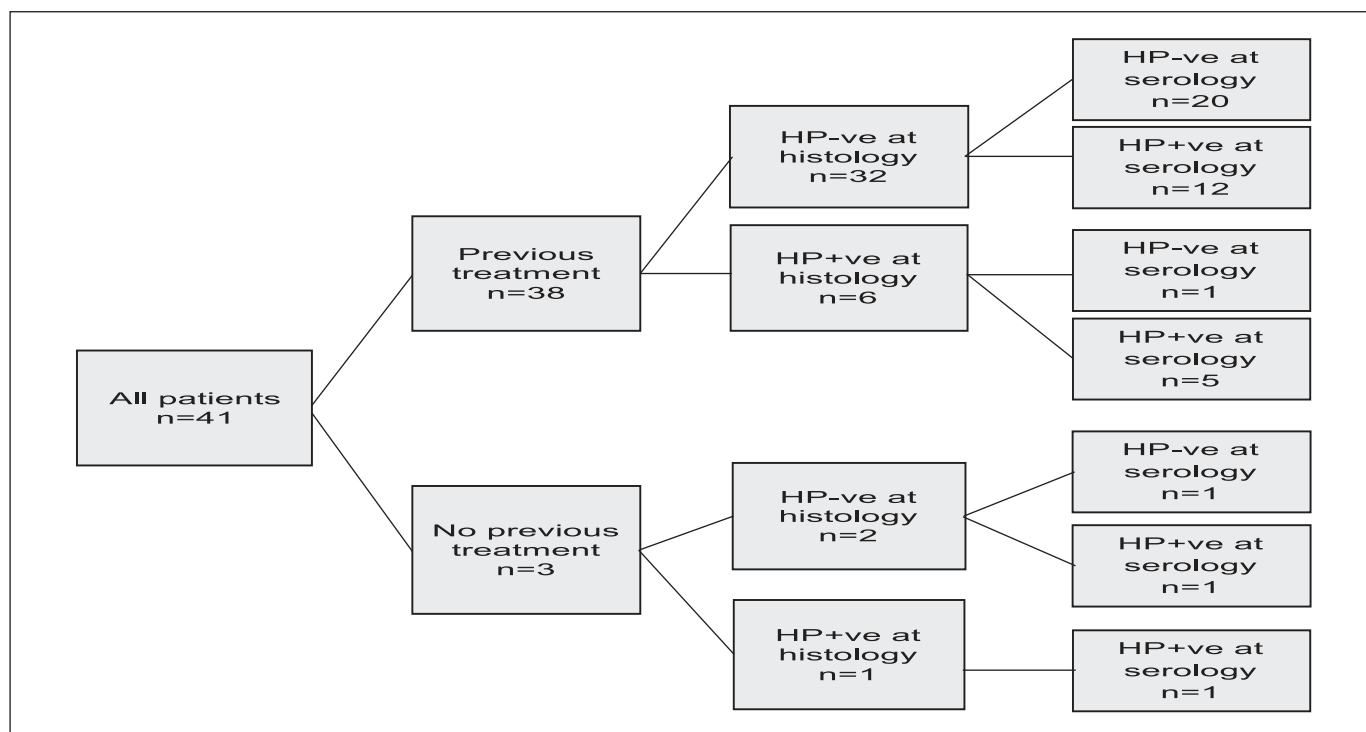


FIGURE 2. Findings regarding *H. pylori* infection (n=41) on previous treatment of the infection, the search for bacteria during histological examination and the serological findings of the presence of anti-*H. pylori* antibodies.

DISCUSSION

Our study's findings, obtained from 41 patients with *H. pylori* chronic gastritis and premalignant lesions, showed that 41.4% were high risk histologically classified. Although a recent systematic review about the prevalence of advanced gastric premalignant lesions in countries with low/moderate gastric cancer incidence (like Brazil), estimate 7.3% incidence (95%CI: 5.6–9.05) for atrophic gastritis and 7.7% (95%CI: 3.2–12.1) for intestinal metaplasia⁽³⁵⁾, these findings can be justified by origin bias, since our patients were recruited from a tertiary service, specialized on assisting patients with chronic esophageal-gastric-duodenal diseases. Besides the high mean age of patients, 67.3 (SD: 9.6) years, is another contributory factor, considering that premalignant lesions prevalence is three times higher in individuals over 40 when compared with those younger than 40 years old⁽³⁵⁾.

The analysis of OLGA and/ or OLGIM systems performance as a protocol to obtain gastric biopsies capable of increasing the premalignant lesion's detection yield has shown promising results. In 2018, Yue H, et al.⁽³⁶⁾, carried out a systematic review and meta-analysis assessing the association between OLGA and OLGIM systems and the risk of gastric cancer, as well as the strength of this association. 2,700 patients included in six case-control studies (OLGA system used in all and OLGIM system in three) and two cohorts (one including OLGA system and another OLGIM system) were analyzed. Regarding the OLGA system, the analysis of cohort studies revealed that individuals staged as high risk had a 27.7 times greater risk of developing gastric cancer compared to their counterparts. The analysis of the only cohort analyzing the OLGIM system showed that patients classified as high-risk had

RR 16.67 (95%CI: 0.80–327.53) for the development of gastric cancer or gastric dysplasia. The authors conclude that close and frequent monitoring of patients classified as high risk in OLGA or OLGIM systems is necessary to facilitate early diagnosis of gastric cancer.

Two recent cohorts have also analyzed the role of OLGA and OLGIM systems in assessing the concordance between intensity of pre-neoplastic lesions and gastric cancer development risk. Rugge M, et al.⁽³⁷⁾, in 2018, in Italy, followed 7,436 patients who underwent upper digestive endoscopy due to dyspeptic complaints. Histological evaluation was performed according to the OLGA system (OLGA 0: 80%, OLGA I: 12.6%, OLGA II: 4.3%, OLGA III: 2.0% and OLGA IV: 0.3%) and patients were followed for a median period of 6.6 years. 28 out of 7,436 patients included in the study developed neoplastic lesions: 17 patients with low-grade dysplasia, four with high-grade dysplasia, and seven with gastric cancer. According to OLGA staging at the time of study inclusion, 1/28 cases of gastric neoplasia were classified as OLGA 0, 2/28 patients as OLGA I, 3/28 patients as OLGA II, 17/28 patients as OLGA III and 5 / 28 as OLGA IV. Multivariate analysis of the study including gender, age, *H. pylori* presence and OLGA system determined upon admission to the study revealed, among these variables, only OLGA system as a predictor of neoplastic progression: being OLGA III: HR: 712.4 (95%CI: 92.543–5484.5) and OLGA IV: HR: 1450.7 (95%CI: 166.7–12626.0). In 2019, Den Hollander WJ et al.⁽³⁸⁾, prospectively analyzed 279 Dutch and Norwegian patients included in the study due to histological evidence of atrophic gastritis, intestinal metaplasia and/or dysplasia of the gastric mucosa at gastroscopy and staged according to the OLGIM system. After an average follow-up period of 57 months,

4/279 (1.4%) patients developed high-grade adenoma/dysplasia or gastric cancer. The progression to neoplasia occurred in one patient in low-risk group according to OLGIM system and in two patients in high-risk group ($P=0.11$). The authors conclude that, even in regions with a low incidence of gastric cancer, follow-up programs are able to detect gastric cancer in potentially curable stages, with a risk of neoplastic progression of 0.3% per year.

In our study, the two histological staging systems, OLGA and OLGIM, were concordant in 85.4% (kappa value: 0.678) and disagreement in 14.6% ($n=6$). The simultaneous use of both histological classification systems allowed 17 patients to be identified as high risk, 11 through identification by both systems, with five additional patients classified as high risk only by the OLGA system and one additional patient classified as high risk only by the OLGIM system. These findings coincide with those observed in a recent study and meta-analysis^(36,37) suggesting that, although the OLGIM system provides easier identification of intestinal metaplasia and better interobserver reproducibility, it fails to identify an appreciable number of high-risk patients. Therefore, it is suggested that, for an accurate prediction of gastric cancer risk, both systems should be used simultaneously in daily pathological practice.

Studies have been performed to evaluate the concordance between OLGA and OLGIM systems in the staging of premalignant gastric lesions and their progression to gastric cancer. Both were developed from the Sydney System for classification and grading of gastritis⁽³³⁾, which is dependent on the histopathological findings from endoscopic biopsies. One limitation attributed to the OLGA system is related to the fact that its main parameter is the intensity and extent of atrophic gastritis, with studies by North American⁽³⁹⁾ and European⁽⁴⁰⁾ pathologists showing that interobserver agreement is low, even when using a visual analog scale. On the other hand, the OLGIM system, when proposing the use of intestinal metaplasia, the next step of the Pelayo Correa cascade for the development of gastric cancer⁽⁴⁾, offers a more easily identifiable marker in the gastric mucosa and, consequently, with greater interobserver agreement^(33,41). Isajevs S, et al.⁽⁴²⁾, in 2014, compared the interobserver agreement between general pathologists and gastrointestinal specialized pathologists in the staging of gastritis by OLGA and OLGIM systems in 835 patients. The OLGIM system provided the highest interobserver agreement, however it was observed that a substantial proportion of high-risk individuals would not be detected if only the OLGIM system was adopted. In 2018, Mera RM, et al.⁽⁴³⁾, in a follow-up study for up to 16 years of 795 patients with pre-neoplastic gastric lesions, demonstrated that the probability of progression to gastric cancer among patients classified as high and low risk by the OLGIM system was twice as high as that observed in patients classified as high and low risk by the OLGA system.

In our study, the analysis of the demographic variables of patients classified in OLGA and OLGIM systems together as high and low risks showed statistical significance only for the gender variable, with the female gender being predominant in the high-risk population ($P=0.02$). The small sample of this study turns difficult to make greater inferences, requiring studies with greater sample power.

Our findings related to *H. pylori* infection showed that 38/41 (92.7%) patients underwent eradication treatment, with 6/38 (15.7%) still harboring the bacteria. The findings of 84.2% cure rate are consistent with *H. pylori* eradication rates obtained from

the Brazilian and Latin American populations, in different studies⁽⁴⁴⁾. A single patient in the study who denied previous anti-*H. pylori* treatment and whose histological and serological studies were negative showed a histological pattern of atrophic gastritis classified as OLGA IV. It is interesting to note that this situation has been described by ABCD Japanese serological classification, as being in group D, with a high risk for gastric cancer in which atrophy is so intense that it would turn gastric mucosa uninhabitable for *H. pylori*.⁽⁴⁵⁾

For the prediction of premalignant changes identified by histology the analysis of PGI biomarkers and PGI/PGII ratio, based on OLGA-OLGIM set, showed 47% sensitivity for PGI (95%CI: 26–69) and 67% specificity (95%CI: 47–82), and for PGI/PGII ratio, the sensitivity was 6% (95%CI: 1–27) and 83% specificity (95%CI: 64–93). Regarding G-17 determination, based on OLGA-OLGIM set, the mean values obtained in patients classified as low and high risk had no statistically significant difference from each other opposing a previous meta-analysis, with 13 studies, which described a 82% accuracy of G17 in identifying patients with chronic atrophic gastritis⁽⁴⁶⁾. The values obtained here, unsatisfactory as discriminating patients with low and high risk of developing gastric cancer have also been observed in other studies. A prospective, multicenter, Spanish study analyzed 91 dyspeptic patients with the same serological panel used here. The values of PGI and PGI/PGII ratio did not show statistically significant differences when compared to histology, with 50% sensitivity (95%CI: 39–61) and 80% specificity (95%CI: 71–88)⁽⁴⁷⁾. In Peru, Calarossi A, et al.⁽⁴⁸⁾ found sensitivity of 54% and specificity of 68% of serological panel to identify chronic atrophic gastritis. Recent meta-analysis analyzed the performance of the GastroPanel® in 20 studies including 4,241 patients and observed sensitivity of 74.7% (95%CI: 62–84.3) and specificity of 95.6% (95%CI: 92.6–97.4) of the serological panel to identify patients with chronic atrophic gastritis⁽³⁰⁾. Another systematic review and meta-analysis study for the accuracy analysis of serological panel, including 27 studies, identified a sensitivity of 53.8% and specificity of 84.1% of the method to identify chronic atrophic gastritis⁽²⁹⁾.

Our results showed that GastroPanel® was not effective in identifying patients with pre-neoplastic lesions, and one of the factors that may have interfered on results is the mean age (67.3 years) of our studied population. In a review article Miki K⁽²⁵⁾, in 2006, considers sex, age, *H. pylori* infection, smoking and alcohol consumption as factors capable of influencing serum levels of pepsinogens and suggests that lower levels of pepsinogen tests found in the elderly population can be attributed to atrophic changes in the gastric mucosa and not exactly to the age itself. A recent Japanese guideline on the management of *Helicobacter pylori* infection also highlights the possibility that patients with gastric atrophy, mainly over 65 years of age, with an ongoing or past infection, often yield false-negative results on pepsinogen tests⁽⁴⁹⁾. In this context, we assessed the presence of an association between advanced age (≥ 65 years) and higher levels of PGI and failed to find any statistically significant difference between the compared groups.

The present study has limitations that deserve consideration. Initially, although the study covered all patients with *H. pylori* chronic gastritis and associated pre-malignant lesions seen in a specialized outpatient clinic at university hospital for the period of the study, the small size hinders extrapolation of data obtained for the Brazilian population. The histopathological examination

performed by a single professional, although specialized in gastrointestinal pathology, became unable the determination of inter-observer concordance rates in the staging of OLGA and OLGIM systems. However, this preliminary study allows an approximate assessment of what is observed in real life. The use of endoscopic examinations with white light devices used on all our patients mimics the reality of endoscopic practice, not only in Brazil but also in countless countries around the world. However, it is undisputed to recognize the progressively increasing role of technological advances in endoscopic examinations as optical filters use (NBI®, narrow-band imaging) for image magnification of pre-malignant gastric lesions, with its use already recommended in recent guidelines in the area⁽⁴⁹⁻⁵¹⁾. The serological evaluation of gastric atrophy presence through the use of biomarkers, in this study, restricted to a higher age group also constitute limitations of the present study and require future investigations.

In conclusion, the description of histological findings through OLGA and OLGIM staging systems in patients with *H. pylori* chronic gastritis associated with premalignant lesions showed substantial concordance and should be incorporated into daily practice. The simultaneous description of the two systems, OLGA and OLGIM, is more accurate than when described in isolation. The biomarkers PGI, PGI / PGII ratio, and G17, analyzed separately or together, showed low accuracy for diagnosis of premalignant lesions in the studied population. Further studies are needed to validate its use in clinical practice in Brazil.

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Authors' contribution

Coelho MCF, Coelho LGV and Barbosa AJA contributed to the conception and design of the study; Ribeiro HG, Gomes CGO, and Marinho FP contributed to recruit the patients and collection of the samples; Barbosa AJA and Coelho MCF analysed the biopsies; Coelho MCF and Coelho LGV analysed the data and wrote the paper.

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RESUMO – Contexto – Gastrite atrófica crônica por *H. pylori* constitui lesão pré-maligna e seu estadiamento de acordo com os sistemas OLGA e OLGIM, visa identificar pacientes com maior risco de desenvolver câncer gástrico e otimizar seu acompanhamento. GastroPanel® é um teste não invasivo composto por painel de biomarcadores séricos incluindo pepsinogênio I (PGI), pepsinogênio II (PGII), gastrina 17 (G17) e anticorpos anti- *H. pylori* para avaliação de risco de adenocarcinoma gástrico em pacientes com gastrite crônica por *H. pylori*. **Objetivo** – Estudo prospectivo para avaliar a concordância entre os sistemas de classificação OLGA e OLGIM, bem como avaliar o desempenho do GastroPanel® em pacientes com lesões pré-malignas secundárias à gastrite crônica por *H. pylori* no Brasil. **Métodos** – Pacientes com gastrite crônica por *H. pylori* portadores de lesões pré-malignas confirmadas por histologia (gastrite atrófica e metaplasia intestinal) foram recrutados no ambulatório de gastroenterologia de um hospital universitário. Todos os participantes foram submetidos a exame endoscópico com biópsias de antro e corpo gástricos analisadas de acordo com o Sistema Sydney atualizado e estadiadas pelos Sistemas OLGA e OLGIM de classificação das gastrites. Amostras de sangue foram coletadas para análise sorológica de biomarcadores (GastroPanel®, Biohit, Helsinki, Finlândia). Os valores de corte utilizados para definir pacientes de alto risco para desenvolvimento de câncer gástrico foram os recomendados pelo fabricante: PGI ≤ 30 μ m e PGI/PGII ≤ 3 . **Resultados** – Foram recrutados 41 pacientes: 28 mulheres, 13 homens, idade média 67,3 (47–89, DP: 9,6) anos. Pelo sistema OLGA, foram obtidos: OLGA 0 (n=1), OLGA I (n=7), OLGA II (n=17), OLGA III (n=9) e OLGA IV (n=7). Pelo sistema OLGIM, foram obtidos: OLGIM 0 (n=14), OLGIM I (n=5), OLGIM II (n=10), OLGIM III (n=10) e OLGIM IV (n=2). Em relação ao estadiamento histológico entre os pacientes de baixo risco (OLGA/OLGIM 0, I e II) e alto risco (OLGA/OLGIM III e IV) para o desenvolvimento de câncer gástrico, a taxa de concordância encontrada entre as duas classificações foi de 85,4%, com valor kappa=0,678 (IC95%: 0,440–0,916). Considerando como pacientes de alto risco, aqueles assim estadiados em pelo menos um dos sistemas, a distribuição final de nossa amostra encontrou 24 pacientes de baixo risco e 17 de alto risco para o desenvolvimento de câncer gástrico. Na determinação pelo GastroPanel® para classificação do paciente como de baixo ou alto risco para desenvolvimento de câncer gástrico, PGI mostrou sensibilidade, especificidade e acurácia de 0,47 (IC95%: 0,26–0,69), 0,67 (IC95%: 0,47–0,82) e 0,58 (IC95%: 0,43–0,72), respectivamente, enquanto a razão PGI/PGII mostrou sensibilidade, especificidade e acurácia de 0,06 (IC95%: 0,01–0,27), 0,83 (IC95%: 0,64–0,93) e 0,51 (IC95%: 0,36–0,66), respectivamente. **Conclusão** – As classificações histológicas OLGA e OLGIM apresentaram taxa de concordância substancial entre si. O uso simultâneo de ambos os sistemas de classificação histológica aumentou a taxa de identificação de pacientes de alto risco para desenvolvimento de câncer gástrico. Os resultados do GastroPanel® não foram eficazes para distinguir pacientes de baixo e alto risco para desenvolvimento de câncer gástrico na população estudada. Mais estudos são necessários para validar seu uso na prática clínica no Brasil.

DESCRITORES – Gastrite atrófica, diagnóstico. *Helicobacter pylori*. Índice de gravidade de doença. Biomarcadores. Algoritmos.

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