

# Pepsinogen Test for the Evaluation of Precancerous Changes in Gastric Mucosa: a Population-Based Study

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## ABSTRACT

**Aims:** The aim of the study was to evaluate the rationale of blood pepsinogen (PG) testing in population based screening settings.

**Methods:** Participants from a cross-sectional population-based study of cardiovascular risk factors in Latvia were invited to participate in the current study. Pepsinogen I and II were measured in blood samples taken during the initial study and at follow-up; upper gastrointestinal endoscopy was performed. There were three groups of patients: with moderately decreased (PG I < 70 ng/ml and PG I/PG II ratio < 3), with strongly decreased (PG I < 30 ng/ml and PG I/PG II ratio < 2), and with normal PG level. Biopsy with *H. pylori* detection was performed (updated Sydney system).

**Results:** Results from 259 patients were analyzed. Pepsinogens were decreased in 133 (51.4%), *H. pylori* was positive in 177 (66.0%) cases. Mean age was significantly lower in patients with normal compared to strongly decreased PG level group (52.8 vs. 64.1 years,  $p < 0.001$ ). Prevalence of severe corpus atrophy was higher in the strongly decreased compared to the normal PG test group: 7.0% vs. 0%; the same tendency was noted in the distribution of OLGA stages III-IV - 10.5% and 0.0%, OLGIM stages III-IV - 3.5% and 0%, and low-grade dysplasia - 15.8% and 2.4% ( $p < 0.05$ ). Two cases of gastric cancer were found; both presented decreased PG levels. A strong association between *H. pylori* eradication and PG ratio dynamics was found ( $p < 0.05$ ).

**Conclusions:** All high-risk lesions were found in the decreased PG test groups; two cancer cases were revealed. However, PG demonstrated low specificity and low value of repeated testing. The value of PG as a sole test for gastric cancer risk is limited.

**Key words:** pepsinogens – screening – atrophy – gastric cancer – follow-up – *H. pylori*.

**Abbreviations:** EDTA: ethylenediaminetetraacetic acid; ELISA: enzyme-linked immunosorbent assay; GA: gastric atrophy; GC: gastric cancer; IM: intestinal metaplasia; OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative link on intestinal metaplasia assessment; PG: pepsinogen.

## INTRODUCTION

Gastric cancer (GC) is the fourth prevailing cancer and the second dominant cause of cancer death in the world [1]. In Latvia, GC takes the fifth place in cancer incidence after prostate, lung, colorectal and breast cancers. The mortality is even higher: according to GLOBOCAN 2012, GC is the second leading cause of cancer-related deaths in Latvia (8.1%). Latvia takes the fifth place in Europe in incidence and mortality from

GC [2]. The most common type of GC, the intestinal type, is a consequence of a prolonged precancerous cascade in the gastric mucosa [3, 4], involving a multistep process from chronic gastritis through gastric atrophy (GA), intestinal metaplasia (IM) and dysplasia to the GC [3-5]. However, the first specific recognizable step in the precancerous process is GA, defined as the loss of normal glandular tissue [3, 5]. In addition, GA is the endpoint of chronic processes, such as chronic gastritis associated with *Helicobacter pylori* (*H. pylori*) infection, autoimmunity directed against gastric glandular cells and influence of some other environmental factors [3, 5, 6]. Although in most developed countries *H. pylori* now infects less than 20% of adults and 5% of children [7], it has been estimated that GA may still develop in 40–50% of *H. pylori*-infected individuals, while 1–2% of infected individuals will develop GC during their lifetime [8].

At present, the gold standard for diagnosis of gastric mucosal changes is the biopsy performed during an upper gastrointestinal endoscopy followed by histological examination [3, 6]. Evaluation of the histological status of the mucosa can be performed using the updated Sydney System, the Operative Link on Gastritis Assessment (OLGA) and the Operative Link for Gastric Intestinal Metaplasia assessment (OLGIM) systems. The OLGA system was developed to improve the histological staging system for GA, using the histological grading system recommended by the updated Sydney System [3, 9]. According to the protocol, GA in gastric antrum and corpus is classified in grades 0 to 3, while the OLGA stages I-IV depend on GA grades, found in both the corpus and antrum [3, 5]. Similarly to OLGA, OLGIM staging is based on histological findings and consists of stages I-IV, which depend on the severity of IM in the gastric antrum and corpus [5, 10].

To reduce the prevalence of GC, it is important to identify and manage the high risk group patients with precancerous lesions [11]. Therefore, it would be a challenge to diagnose gastric precancerous changes in an asymptomatic population, using a non-invasive technique [11]. One of the most promising non-invasive tests for diagnosis of GA is the detection of pepsinogen (PG) levels in blood [12, 13]. Human PGs (classified into PG I and PG II) are inactive pro-enzymes of pepsin, originating from the gastric mucosa [3-5]. Pepsinogen I is secreted by the chief cells in the fundus and corpus; PG II is also secreted by the pyloric glands in the antrum and Brunner's glands in the proximal duodenum [3, 14]. Pepsinogen I and PG II are secreted into the gastric lumen, and only 1% leak into circulating blood [4]. It has been estimated that PG I, secreted by oxyntic glands, mostly reflects the degree of potential atrophy. However, the ratio of PG I/ PG II is considered to be a more sensitive indicator of atrophic changes, especially if *H. pylori* infection is present, which stimulates the secretion of PG II due to inflammation and cellular proliferation [3, 15, 16].

It is assumed and also found in several studies [15], that PG test results directly correlate with *H. pylori* status in patients, based on the fact that *H. pylori* is the main etiological factor for atrophic changes in the gastric mucosa [5, 8, 17, 18].

We aimed to evaluate the rationale of using the PG test for screening of gastric mucosa high-risk lesions and malignancies, and further, to analyze the long-term dynamics of PG test results in patients with different states of gastric mucosa and *H. pylori* status.

## METHODS

### Study design

The study was part of a larger cross-sectional study for the determination of cardiovascular risk factors performed in 2009, during which blood samples were collected from randomly selected general adult population in Latvia [19]. At the baseline PG I, PG II and PG I/PG II ratio levels were assessed in blood samples. Further, at follow-up (during years 2013 to 2015) a written invitation was sent to all participants, asking them to take part in the current study. In addition, they were asked to fill out a questionnaire about previous *H. pylori* eradication therapy, to donate a blood sample for repeated

analysis of PG I, PG II and PG I/ PG II level and to perform upper gastrointestinal endoscopy with histological evaluation of gastric mucosa and detection of *H. pylori* status.

The mean PG I, PG II and PG I/ PG II ratio levels at baseline and follow-up were compared in groups of patients with normal/low risk histological gastric mucosal status and high risk mucosal histological status (corpus atrophy, OLGA stage III-IV, OLGIM stage III-IV, low-grade dysplasia, GC).

### Patients

The initial sample of randomly selected individuals from the Latvian Population Registry during a cross-sectional study included data of 3,807 individuals (aged 25-74 years). All individuals with available contact information (n=1,748) were invited to participate in this study.

Participants were classified into three groups according to the level of PG in the blood sample: patients with normal PG test (PG I  $\geq$  70 ng/ml and/or PG I/ PG II  $\geq$  3); with moderately decreased (PG I < 70 ng/ml and PG I/ PG II < 3) and with a strongly decreased PG test (PG I < 30 ng/ml and PG I/ PG II < 2), which was a subgroup within the moderately decreased PG test group.

### Pepsinogen detection

Blood samples were collected in EDTA vials; the samples were centrifuged for 30 minutes, the plasma separated, and the samples immediately frozen. Plasma samples remained frozen until tested (up to 1 week at -20°C, but for a longer period at -80°C). Transportation of all samples was arranged on dry ice. The analysis was performed at a certified laboratory according to the instructions of the manufacturer.

PG I and PG II levels were detected by the Eiken test system (Eiken Chemical Co., Tokyo, Japan). According to the manufacturer, the PG I level was considered moderately decreased if PG I was < 70 ng/ml and strongly decreased, if PG I was < 30 ng/ml. The PG I/ PG II ratio was considered moderately decreased if < 3, and strongly decreased if it was < 2.

### Upper endoscopy and histology

The histological assessment was based on biopsy samples from antrum, corpus and incisura angularis according to the updated Sydney system; assessment of *H. pylori* was based on modified Giemsa staining [19, 20]. Biopsies were analysed independently by two expert gastrointestinal pathologists and histological consensus was achieved.

Corpus atrophy, OLGA stages III-IV, OLGIM stages III-IV and low-grade dysplasia were considered as high-risk histological lesions of gastric mucosa.

### Statistical analysis

For statistical analysis and data storage Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, Washington, USA) and IBM SPSS program 20.0 were used. Demographic data were analysed by descriptive statistical methods. Age groups were analyzed in 10-year cohorts.

The paired *t*-test was used to compare mean values of PG among study groups; chi-square test (P for trend) and Z test were used to evaluate data on PG I, PG II and PG I/PG II ratio

dynamics in age groups from baseline to follow-up. P value <0.05 was considered as significant.

### Ethical considerations

The project was conducted in accordance with the Helsinki Declaration; the study protocol was approved by the Ethics Committee of the Research Institute of Cardiology, University of Latvia. All patients signed consent forms before enrolment.

## RESULTS

### Characteristics of the final patient sample

Overall, 271 people came for the follow-up (response rate 15.4%), whereas all data were available for 259 participants. Out of them, 82/259 (31.7%) were men.

The mean age of the patients was 56.5 years (SD  $\pm$  12.5), median of age 58.0, range between 22 and 87 years. Based on the age at enrolment, the largest patient group was between 61 to 70 years of age (30.1%).

### Demographic data of participants in relation to PG test at baseline and follow-up

Demographic data of participants in relation to the PG test at baseline are shown in Table I. The percentage of individuals with moderately and strongly decreased PG test did not differ between men and women. The mean age of patients was significantly higher among patients with a moderately and strongly decreased PG test ( $p < 0.001$ ,  $\chi^2 = 36.0$ ).

**Table I.** Demographic data of participants in relation with pepsinogen test at baseline

	Pepsinogen test at baseline		
	Normal N=98 (37.8%)	Moderately decreased N=161 (62.2%)	Strongly decreased N=55 (21.2%)
Age, years; mean (median)	52.8 (61)	59.9 (64)	64.1 (56)
Women; N (%)	69 (38.9)	108 (61.1)	36 (20.3)
Men; N (%)	29 (35.4)	53 (64.6)	19 (23.2)

A significant correlation between PG test results and age was observed ( $p < 0.01$ ).

The mean PGI / PG II ratio levels were significantly higher in patients below 50 years of age compared to patients older than 50 years (4.3 and 2.4, respectively,  $p = 0.004$ ).

Similarly, in the age group <50 years there was a significantly larger proportion of individuals with normal PG

levels compared to the age group 61-70 years and >70 years. Significantly more patients with moderately and strongly decreased PG test were found in the age groups 61-70 and >70 years (Table II).

**Table II.** Pepsinogen test results in different age groups

Age groups, years	PG test normal, N (%)	PG test moderately decreased, N (%)	PG test strongly decreased, N (%)
<41	23 (76.7)*	7 (23.3)	3 (10.0)
41-50	34 (64.2)*	19 (35.8)	6 (11.3)
51-60	30 (50.0)	30 (50.0)	11 (18.3)
61-70	27 (34.6)	51 (65.4)*	17 (21.8)
> 70	12 (31.6)	26 (68.4)*	21 (55.3)*

\*p for trend <0.05

At follow-up, 126 (48.7%) individuals with normal PG test were identified, 133 (51.4%) with decreased PG test; 57 (22.0%) of them showed strongly decreased PG test results.

### PG test dynamics

Negative dynamics of PG I was noted among patients with moderately decreased PG test in all age groups: the median of PG I decreased from 32.5 to 30.6 ( $p > 0.05$ ).

The median of PGI / PGII ratio significantly decreased in the age group 41-50 ( $p < 0.001$ ) and significantly increased in groups 51-60 and >70 years ( $p < 0.05$  and  $p < 0.05$ , respectively).

### Histology in relation to age at follow-up

The proportion of individuals with higher OLGA and OLGIM stages increased with age. Nevertheless, there was an atypical distribution of dysplasia with peak prevalence in the age group below 60 years (Table III).

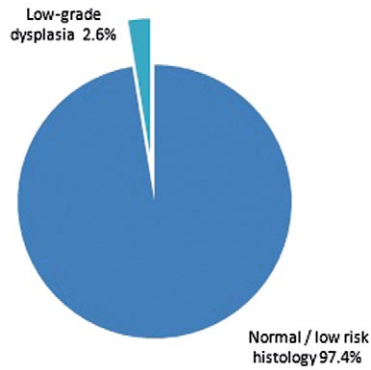
### PG test and histology at follow-up

A higher prevalence of individuals with dysplasia and severe corpus atrophy, as well as high-grade OLGA and OLGIM stage was noted in the group of patients with a strongly decreased PG test, compared to patients with moderately decreased and normal PG test ( $p = 0.038$ ) (Figs. 1-3).

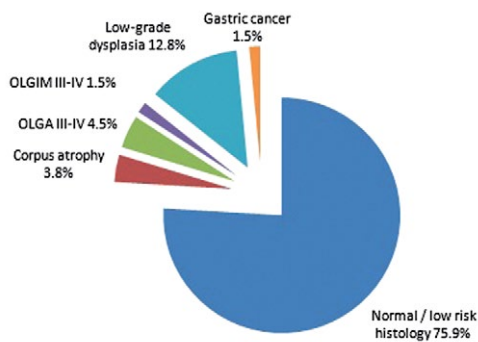
Among the 20 patients with low-grade dysplasia, 3 (2.4%) were with normal PG test and 17 (12.8%) with moderately decreased PG test. Overall, 9 (15.8%) participants with low-grade dysplasia had strongly decreased PG test. There were 5 cases of simultaneous IM in those with low-grade dysplasia. Four cases were in patients with strongly decreased PG levels,

**Table III.** Prevalence of atrophic changes in age groups at follow-up

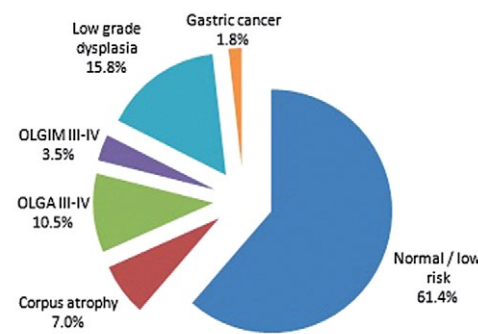
Age (years)	OLGA I-II N (%)	OLGA III-IV N (%)	OLGIM I-II N (%)	OLGIM III-IV N (%)	Corpus atrophy N (%)	Dysplasia N (%)	Gastric cancer N (%)	Total N
<41	16 (53.3)	0 (0.0)	4 (13.3)	0 (0.0)	4 (13.3)	5 (16.7)	0 (0.0)	30
41-50	26 (49.06)	0 (0.00)	9 (16.98)	0 (0.00)	7 (13.21)	5 (9.43)	0 (0.00)	53
51-60	46 (76.7)	2 (3.3)	16 (26.7)	1 (1.7)	19 (31.7)	9 (15.0)	0 (0.0)	60
61-70	54 (69.2)	3 (3.9)	33 (42.3)	1 (1.3)	32 (41.0)	2 (2.6)	0 (0.0)	78
>70	29 (76.3)	1 (2.6)	19 (50.0)	0 (0.0)	17 (44.7)	0 (0.0)	2 (100.0)	38
Total	171 (66.0)	6 (2.3)	81 (31.3)	2 (0.8)	79 (30.5)	21 (8.1)	2 (0.8)	



**Fig. 1.** Histological status in the group of patients with normal pepsinogen test at follow-up. Normal PG test: PG I  $\geq$  70 ng/ml and/or PG I/PG II ratio  $\geq$  3.



**Fig. 2.** Histological status in the group of patients with moderately decreased pepsinogen test at follow-up. Moderately decreased PG test: PG I < 70 ng/ml and PG I/PG II ratio < 3.



**Fig. 3.** Histological status in the group of patients with strongly decreased pepsinogen test at follow-up. Strongly decreased PG test: PG I < 30 ng/ml and PG I/PG II ratio < 2.

and one case in the moderately decreased PG group. Moreover, all five patients also had corpus atrophic lesions.

Among individuals with corpus atrophy, a significant negative dynamics of PG II was found: the mean levels of PG II significantly decreased from 16.6 ng/ml to 13.2 ng/ml ( $p=0.042$ ). In other high-risk histology groups (OLGA III-IV, OLGIM III-IV, low-grade dysplasia), the mean PG I, PG II and PG I/ PG II levels were only non-significantly decreased at follow-up ( $p$  for trend = 0.065).

Two cases of GC were found during the study and both were diagnosed at the age >70 years. Both patients had decreased PG test and *H. pylori* infection without self-reported eradication (Table IV).

**PG test and *H. pylori* prevalence**

Prevalence of *H. pylori* did not differ significantly among patients with normal PG test, moderately decreased and strongly decreased PG test: 60.3% (76/126), 64.7% (86/133) and 65.0% (37/57), respectively.

However, the proportion of patients with decreased PG test was significantly higher among patients with active *H. pylori* infection without history of *H. pylori* eradication compared to *H. pylori* negative individuals without self-reported eradication and *H. pylori* negative individuals with a history of eradication therapy: 59.6% (96/161) vs. 44.4% (36/81) and 32.0% (8/25), respectively;  $p=0.017$ .

Among *H. pylori* positive patients without self-reported eradication, a significant decrease of PG I/ PG II ratio was observed ( $\Delta -0.033$ ;  $p<0.05$ ). On the other hand, a significant increase of PG I/ PG II ratio was observed in patients with self-reported *H. pylori* eradication ( $\Delta +0.079$ ;  $p<0.05$ ).

**DISCUSSION**

In our study for the evaluation of the PG level, the Eiken test system (Japan) was used. However, most studies on this topic in Europe have been conducted with the Biohit test (Finland). According to recent research in this field, the commercial assays for pepsinogen have a good relative agreement, as PG levels highly correlate among the assays [21]. Moreover, the opinion of the physicians is that the latex agglutination assay from Eiken is easier and more convenient to apply in comparison with the ELISA assay.

According to the results of the present population-based follow-up study all high-risk gastric precancerous lesions at follow-up were observed in patients with moderately and strongly decreased PG test at baseline, supporting the opinion that the test could predict atrophic changes (especially if used in combination with *H. pylori* positivity), demonstrated in

**Table IV.** Characteristics of the patients with gastric cancer

	Baseline		Follow-up		PG test group	HP	HP eradication	Age years	Sex
	PG I (ng/ml)	PG I/II	PG I (ng/ml)	PG I/II					
Patient 1	6.3	0.4	5.3	0.7	strongly decreased	+	-	71	Female
Patient 2	64.0	2.0	47.5	1.7	moderately decreased	+	-	73	Male

HP: *H.pylori*

some previous studies [3, 5, 22, 23]. However, occurrence of all high-risk gastric mucosa lesions in the groups with a decreased PG level could also be explained by selection bias - response rate might have been higher among those with any previous complaints or changes of PGs at baseline. Higher prevalence of dysplasia among younger patients is controversial and could be explained by overdiagnosis in the selected group.

On the other hand, the prevalence of individuals with normal gastric mucosa was high in all groups of patients, even in the group with a severely decreased PG level; 61% of patients were without high-risk lesions, indicating a low specificity of the test. However, the high proportion of false-positive test results could be also explained by other causes that could affect PG levels indicated in other studies [3, 5, 23, 24, 25]. Nevertheless, the low specificity of the test should be kept in mind while interpreting patients' data.

Although in our patient sample the mean PG I and PG II levels as well as PG I/PG II ratio had a tendency to decrease in patients with more advanced atrophic lesions, thus indicating progression of precancerous lesions to GC development as described in the Correa cascade [3], the dynamics of the PG test decrease was not significant.

Overall, our results support the introduction of the screening with the PG test to reveal high-risk groups in the general population, as the absolute majority of the high-risk lesions were found in groups with moderately/strongly decreased PGs. These data are in agreement with the Maastricht V statement regarding PG serology being the most useful non-invasive method to explore gastric mucosa status [26], but the results of the screening might be strengthened by additional serological markers such as anti-*H. pylori* antibodies and gastrin 17 [26, 27].

Moreover, both individuals with GC in our study were in the group with the decreased PG test results. Although the small number of GC cases does not allow drawing a conclusion regarding the accuracy of the PG test as a non-invasive method for the detection of GC, this finding matches several other studies in the field [12, 28, 29].

A similar study was performed by McNicholl et al. to evaluate the accuracy of serological tests (PG I, PG II, gastrin 17 and anti-*H. pylori* antibodies) in the diagnosis of atrophic gastritis. In their study, there were no statistically significant differences in the level of PGs in the groups with and without corpus atrophy. Only in the case of PG II was found a borderline significant difference [30]. Concerning the corpus atrophy, we noted changes in PG II: the mean levels of PG II significantly decreased in these patients in dynamics. Therefore, PG II could be a useful marker for corpus atrophy screening. However, according to Venerito et al., *H. pylori*-positivity might have a proper influence on the results, so the diagnostic performance of a serological test could be limited [31].

Discussion about the point-of-no-return continues in respect to the importance of *H. pylori* eradication therapy in individuals with on-going *H. pylori* infection. Our results support eradication therapy, since negative PG test dynamics was observed in *H. pylori* positive individuals without eradication therapy. Moreover, PG test results improved significantly in patients who reported eradication of *H. pylori*, thus indirectly suggesting the effectiveness of

eradication and importance of *H. pylori* as the initiator of the atrophic changes in gastric mucosa. *H. pylori* positive subjects have lower PG I/II ratio than those without *H. pylori* which is explained by the fact that the production of PG I is considerably reduced, and, by contrast, PG II increases when the gastric mucosa is infiltrated by neutrophils and mononuclear cells in the antrum as it occurs during *H. pylori* infection [32]. However, previous studies have shown controversial results. Only some of the studies reported a correlation between the PG test and *H. pylori* eradication status or improvement or even healing of corpus atrophy [32-35]. In contrast, the reliability of PG I and PG I/PGII results is questioned because changes of PGII level are observed earlier than changes of PG I level [33, 36].

Association between serum PG level and *H. pylori* was also described by Parsonnet et al. [37] and many other authors [16, 38, 39]. Zhang et al. [29] concluded that patients with decreased PG and negative *H. pylori* infection have an especially high risk of GC.

From this point of view, *H. pylori* presence influences the results of the PG test and, consequently, increases the rate of false positive preneoplastic changes, and could be eradicated to eliminate the impact and to get more reliable data [36, 40]. Moreover, according to Maastricht V recommendations, in high-risk regions mass eradication of *H. pylori* is advised [26]. However, *H. pylori* is not the sole agent involved in gastric carcinogenesis. Additionally, a mass eradication program may fail frequently because of resistance to antibiotics and proton pump inhibitors (PPIs), risk of re-infection and other causes [41]. Even if *H. pylori* has been eradicated, PG screening should be performed to determine possible point-of-no-return mucosal lesions. A better decision could become the wider use of the ABCD screening method using two different cut-off values according to the *H. pylori* antibody status [42].

Several studies have demonstrated an association of atrophic changes in gastric mucosa with aging, which might explain the progressive decrease of PG level in older age groups [43]. Moreover, the prevalence of *H. pylori* increases with age [6, 14, 25, 43]. Our results also showed a further decrease of PG I at the follow-up in groups with already decreased PG I level at baseline, mostly in age groups > 70 years, thus signaling the continuous progression of mucosal changes.

According to previous research on GC epidemiology, women are less affected than men with the proportion 1.5:2.5 [1, 3, 14, 43]. In our study sample, 68.3% of the participants were women, which could be explained by a higher response rate among women (possibly due to more concern about their health) described in other studies as well [12, 18]. Nevertheless, the majority of the men had decreased PG levels in comparison to women, similar with previous data [18, 29, 44].

## CONCLUSIONS

In the studied population-based patient sample all high-risk gastric precancerous lesions at follow-up were observed in patients with moderately and strongly decreased PG test at baseline. It supports the opinion that this test could predict atrophic changes, especially if used in combination with *H. pylori* positivity.

However, only a minority of individuals with moderately and strongly decreased PG test had advanced gastric mucosal lesions, thus indicating a rather low specificity of the test in population-based settings. Therefore, the value for PGs as a single test for GC diagnosis and precancerous lesions in population-based settings is limited; it could be however used for choosing further diagnostic tests or a follow-up strategy.

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**Authors' contribution:** O.S. performed data statistical analysis, literature review, manuscript composition, discussion. J.P., I.D., L.T. and I.P. participated in data statistical analysis, methodology, research design and language corrections. P.J., A.V., I.K., D.S. and D.R. performed data collection and systematization. I.K. and I.T. contributed with performing endoscopies. I.L.-K. and S. I. contributed with histology evaluation. V.P., J.P., V.D. and A.E. conducted the primary research, provided patient information for the current research. M.L. is the head of current research, provided manuscript organization and corrections, as well as discussion. All authors read and approved the final version of the manuscript.

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