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RAPID COMMUNICATION

Non-invasive diagnosis of gastric mucosal atrophy in an asymptomatic population with high prevalence of gastric cancer

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Abstract

AIM: To validate a non-invasive method to detect gastric mucosal atrophy in a Chilean population with high prevalence of gastric cancer and a poor survival rate.

METHODS: We first determined the optimal cut-off level of serum pepsinogen (PG)-1, PG-1/PG-2 ratio and 17-gastrin in 31 voluntary symptomatic patients (mean age: 66.1 years), of them 61% had histologically confirmed gastric atrophy. Then, in a population-based sample of 536 healthy individuals (209 residents in counties with higher relative risk and 327 residents in counties with lower relative risk for gastric cancer), we measured serum anti-*H pylori* antibodies, PG and 17-gastrin and estimated their risk of gastric cancer.

RESULTS: We found that serum PG-1 < 61.5 μg/L, PG-1/PG-2 ratio < 2.2 and 17-gastrin > 13.3 pmol/L had a high specificity (91%-100%) and a fair sensitivity (56%-78%) to detect corpus-predominant atrophy. Based on low serum PG-1 and PG-1/PG-2 ratio together as diagnostic criteria, 12.5% of the asymptomatic subjects had corpus-predominant atrophy (0% of those under 25 years and 20.2% over 65 years old). The frequency of gastric atrophy was similar (12% *vs* 13%) but *H pylori* infection rate was slightly higher (77% *vs* 71%) in the high-risk compared to the low-risk counties. Based on their estimated gastric cancer risk, individuals were classified as: low-risk group (no *H pylori* infection and no atrophy; *n* = 115; 21.4%); moderate-risk group (*H pylori* infection but no atrophy; *n* = 354, 66.0%); and high-risk group (gastric atrophy, with or without *H pylori* infection; *n* = 67, 12.5%). The high-risk group was significantly older (mean age: 61.9 ± 13.3 years), more frequently men and less educated as compared with the low-risk group.

CONCLUSION: We propose to concentrate on an upper gastrointestinal endoscopy for detection of early gastric cancer in the high-risk group. This intervention model could improve the poor prognosis of gastric cancer in Chile.

Key words: Gastric cancer; *H pylori*; Gastric atrophy; Non-invasive diagnosis; Pepsinogen; Gastrin

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INTRODUCTION

Gastric cancer (GC) is still highly prevalent in Chile and the world[1]. With the exception of Japan, which has implemented early detection strategies through the population screening, the diagnosis of GC is usually late and its prognosis is very poor. In Chile, a study showed that a global survival rate at 5 years after diagnosis was less than 15%, although it surpassed 90% when early stage tumors were treated with curative resection[2].

In spite of the identification of *H pylori* infection as a relevant etiological factor, this has not yet led to significant changes in the diagnostic or therapeutic strategy. The initial pathogenic role of *H pylori* infection is currently undisputed, explaining between 70% and 90% of GC risk in a given population[3,4]. As first postulated by Correa[5], *H pylori* produces an inflammation of the gastric mucosa (gastritis) that, evolving asymptomatically through many years, progresses in a decreasing proportion to gastric atrophy (GA), intestinal metaplasia, dysplasia, and finally to well differentiated adenocarcinoma. Other diverse environmental and genetic factors modulate this chain of

events. Atrophy and intestinal metaplasia of the gastric mucosa are doubtfully reversible lesions that determine a significant increase in the risk of developing GC[5,6].

The "gold standard" for the diagnosis of gastric atrophy is the histological study of biopsies obtained during an upper gastrointestinal (GI) endoscopy, an invasive method hardly suitable for population screening. Non-invasive strategies, applicable to an asymptomatic population, would allow having better knowledge of the frequency and natural history of gastric mucosal atrophy, testing prevention strategies and diagnosing more effectively the progression to (early) gastric cancer.

The possibility to detect gastric atrophy by means of some serum markers, such as pepsinogen (PG)-1, PG-1/PG-2 ratio and 17-gastrin, has recently been described[7-9]. However, the apparent geographic or even racial variability in the diagnostic performance of these tests precludes its simple extrapolation to our milieu.

The general objective of this study was to validate a non-invasive diagnostic tool for gastric mucosal atrophy and then to apply it to an asymptomatic population in order to identify the population groups at greater risk for developing GC. The specific objectives were: (1) to determine the diagnostic performance of PG-1, PG-1/PG-2 and 17-gastrin in serum for the diagnosis of gastric atrophy in a sample of symptomatic patients, compared to the histology as a gold standard; (2) to determine serologically the frequency of gastric atrophy in a sample of asymptomatic subjects residing in counties with different risks of developing GC; and (3) to non-invasively categorize the estimated risk of developing GC in the same sample.

MATERIALS AND METHODS

Subjects

For the diagnostic validation study, we included voluntary patients older than 40 years old, with clinical indications for upper GI endoscopy. Exclusion criteria were: use of proton pump inhibitors within the last month, gastric cancer, active peptic ulcer or previous gastric resection. The Ethics Committee of our institution approved the study.

For the population study, we used the sera of 536 subjects selected from the 3600 subjects that constituted a random Chilean population sample in which a National Health Survey was performed[10]. This sub-sample was obtained by ordering the subjects from the original sample according to mortality risk for GC in their county of residence (described below) and then selecting subjects from the extreme counties on the list (those with greater and lower relative risk of GC, respectively) until reaching the number of available determinations.

Diagnostic validation study

After obtaining informed consent from the patients, an upper GI endoscopy was performed. Two sets of biopsies from the gastric corpus and the antrum (both the gastric wall and greater curve) were sent separately for histological analysis. An additional antral biopsy was destined to a rapid urease test (ProntoDry®, Medical Instrument Corp, Brignais, France). Serum from a 10-mL blood sample was separated and stored at -20℃ until processing.

Population study

Blood samples were obtained from all over the country during the 2003 National Health Survey, sent to regional hospitals and then to our center, where the sera were stored at -80℃ until processing. The categorization of relative risk (RR) of GC for each subject was calculated according to the mortality rates for GC registered in his/her county of residence during 1985-2002, corrected for age, sex and population size, and adjusted through a hierarchical Poisson regression model, considering the extra-Poisson structural variability, estimated by Bayesian analysis[11,12]. The counties with a RR of mortality for GC > 1 were considered high-risk counties.

Analytical determinations

For anti-*H pylori* serology, the commercial bioelisa assay HELICOBACTER IgG (BioKit®, Barcelona, Spain) was used. In previous studies, we determined that the most appropriate cut-off level for the diagnosis of *H pylori* infection in the Chilean adult population was 72.8 arbitrary units (AU)/mL.

Determination of serum levels of PG-1, PG-2 and 17-gastrin was performed using a commercial ELISA assay (Gastropanel®; (BioKit®, Helsinki, Finland), following the manufacturer's instructions.

Histological study

The formalin-fixed and paraffin-embedded samples were cut into thin sections and stained with hematoxylin-eosin (H&E). The modified Sydney classification[13] was used to classify the histological findings in the gastric corpus and the antrum separately. We used previously described criteria for histological categorization[14]. Non-atrophic chronic gastritis was defined as the presence of chronic inflammation (score $\geqslant$ 1), with or without acute inflammation, with no atrophy (score = 0) in the corpus or the antrum. Chronic atrophic gastritis was diagnosed in the presence of atrophy (Sydney score $\geqslant$ 1), with or without intestinal metaplasia, associated with chronic inflammation (score $\geqslant$ 1). The patients with atrophic gastritis were classified as antrum predominant when the atrophy score was greater in the antrum than in the corpus, corpus predominant when the score was greater in the corpus and multifocal when the score was the same in the both sites.

Statistical analysis

The Student's *t* test, ANOVA or Kruskal-Wallis test were used for univariate analysis of the discrete variables (age and serum levels of PG-1, PG-1/PG-2, 17-gastrin) and the chi-square test or the Fisher exact test for categorical variables (sex, endoscopy variables and levels of PG-1, PG-1/PG-2 and 17-gastrin above or below the respective cut-off levels) associated with the presence of histological atrophy. Through ROC (receiving operator characteristic) curves, the best cut-off levels were determined for the serum levels of PG-1, PG-1/PG-2 and 17-gastrin for the detection of the antrum and corpus atrophy (Table 1). To evaluate the diagnostic performance of the serologic

Table 1 Correlation between the serum levels of pepsinogen and gastrin with the type and topography of histological gastritis (median)

	Chronic non-atrophic gastritis (n = 10)	Antrum-predominant atrophic gastritis (n = 10)	Corpus-predominant atrophic gastritis[1] (n = 9)
PG-1 (μg/L)[a]	115.6	103.3	40.9
PG-1/PG-2[a]	4.39	5.62	2.22
17-gastrin[b] (pmol/L)	6.2	3.7	36.8

[1]Including 1 patient with multifocal atrophic gastritis; [a]$P < 0.05$ or [b]$P < 0.01$ between the three groups (Kruskal-Wallis Test).

Table 2 Diagnostic performance of serology (pepsinogen and 17-gastrin) to diagnose gastric atrophy

	Cut-off level	Sensitivity % (95% CI)	Specificity % (95% CI)	LR[5]+	LR-	Youden's J index
PG-1 (μg/L)[3]	< 25[1]	44 (12-77)	95 (87-100)	8.8	0.59	0.40 ± 0.17
	⩽ 61.5[2]	78 (40-97)	91 (71-99)	8.6	0.24	0.69 ± 0.15
PG-1/PG-2[3]	< 2.5[1] ⩽ 2.2[2]	56 (21-86)	100 (84-100)	∞	0.44	0.56 ± 0.17
17-gastrin (pmol/L)	< 2[1,4]	30 (16-58)	86 (70-100)	2.1	0.81	0.16 ± 0.16
	⩽ 7.5[2,4]	90 (56-98)	52 (30-74)	1.89	0.19	0.42 ± 0.14
	> 13.3[2,3]	67 (30-92)	96 (77-99)	14.7	0.35	0.62 ± 0.16

[1]Suggested by the manufacturer; [2]Determined by ROC curves; [3]To detect corpus-predominant atrophic gastritis; [4]To detect antrum-predominant atrophic gastritis; [5]LR = likelihood ratio.

determinations, we used the likelihood ratio (LR) and Youden's J index[15] (Table 2). Nominal logistic regression was used to perform a multivariate analysis of variables associated to the groups with different estimated risks of GC (Table 3). A P value less than 0.05 was considered statistically significant. The statistical analyses were performed using Epi Info version 3.2 (Epidemiology Program Office, CDC, Atlanta, GA, USA) and SPSS version 14 (SPSS Inc, Chicago, Illinois, USA) computer programs.

RESULTS

Diagnostic validation of the serologic methods

Thirty-one patients (21 women, 68%) with an average age of 66.1 (range: 42-90) years were included. Endoscopy was normal in 12 (39%) patients, compatible with gastric atrophy in 8 (26%) patients, showed erosive esophagitis in 2 (6.45%) patients and erosive antropathy in 1 (3.22%) patient. Using histology, serology and rapid urease test, *H pylori* infection was found in 13/31 (42%) patients. The serum level of PG-1 was significantly greater in the *H pylori*-infected patients (136.7 ± 60.8 μg/L) as compared with the non-infected patients (78 ± 68.2 μg/L) ($P < 0.05$). The serum levels of PG-2 and 17-gastrin and the PG-1/PG-2 ratio were similar in the both groups.

Histological features of the gastric specimens

According to the Sydney classification[13], chronic gastritis was found in 29 (94%) patients, 19 (61%) of them were atrophic. The atrophy was antrum-predominant in 10 (53%) patients, corpus-predominant in 8 (42%) and multifocal in 1 (5%) patient. Glandular atrophy was scored as moderate or severe (score ⩾ 2) in 47% of the cases. The frequency of *H pylori* infection was higher in the patients with chronic non-atrophic or antrum-predominant atrophic gastritis compared to the patients with corpus-predominant atrophic gastritis (60% and 11%, respectively; $P = 0.054$).

Correlation between histology and serum levels of pepsinogen and gastrin

The results are summarized in Table 1. The serum level of PG-1 was significantly lower in the group with the corpus atrophy, and the PG-1/PG-2 ratio was also lower in this group, although without attaining statistical significance. In comparison with non-atrophic gastritis, the average serum level of 17-gastrin was significantly lower in the patients with the antrum atrophy and significantly higher in those with the corpus atrophy. Table 2 shows the diagnostic performance of the different determinations for the detection of the corpus or antrum gastric atrophy, using the cut-off levels recommended by the manufacturer and those determined through ROC curves. The latter slightly improves sensitivity for the diagnosis of the corpus atrophy, conserving high levels of specificity, which determines LR+ in ranges close to those considered clinically useful (> 10)[16] and a slight improvement in the Youden's J index. The diagnosis of the antrum atrophy through the 17-gastrin level was not reliable. In contrast, the 17-gastrin level over 13.3 pmol/L had a diagnostic performance comparable to PG-1 and the PG-1/PG-2 ratio to diagnose the corpus atrophy.

Population study

Of the 536 subjects, 209 resided in counties at high risk for GC (mean RR = 1.25) and 327 in counties at low risk for GC (mean RR = 0.8). The frequency of *H pylori* infection was 72.9% (95% CI: 70%-76%). The frequency

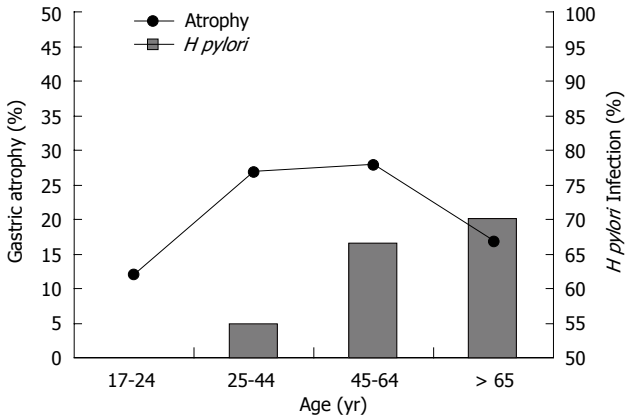

Figure 1 Frequency of gastric atrophy and *H pylori* infection in 536 asymptomatic subjects by age.

of the corpus atrophy was 26.5% when using serum level of PG-1 ⩽ 61.5 μg/L as a diagnostic criterion, and 12.5% when using the more restrictive combination of PG-1 ⩽ 61.5 μg/L and PG-1/PG-2 ⩽ 2.2[17], which was used for the following analyses.

The frequency of *H pylori* infection was higher in the counties with high RR for GC (76.6%) compared to those with low RR (70.6%), although did not reach a statistical significance. The frequency of gastric atrophy was similar between the both groups (11.5% and 13.1%, respectively). The gastric atrophy was significantly correlated with age (Figure 1). No atrophy was detected in the subjects younger than 25 years, while 20.2% of those older than 65 years had PG-1 level and PG-1/PG-2 ratio compatible with the corpus atrophy, which probably explained the reduction in the serological evidence of *H pylori* infection observed in this group.

Using serological data, we divided the samples into three groups: Group A = no *H pylori* infection and no gastric atrophy (low GC risk); Group B = *H pylori* infection but no gastric atrophy (moderate GC risk); and Group C = serological evidence of gastric atrophy, with or without *H pylori* infection (high GC risk). The demographic characteristics and relevant comparisons among the three groups are shown in Table 3. There were significant differences in the distribution of some variables classically related with GC risk, such as age and educational level. Similar to the samples of the symptomatic patients, *H pylori* infection was associated with a significant elevation of PG-1 (87.4 ± 53.2 in non-infected group *vs* 116.6 ± 51.2 μg/L infected group; $P < 0.05$). Similarly, the corpus atrophy was associated with a significant elevation in the serum level of 17-gastrin (Table 3). The proportion of the subjects residing in counties with a high RR of GC was not significantly different among the three groups, although due to the relatively low frequency of gastric atrophy, dispersion of this parameter was wide (95% CI: 25.3%-43.3% for Group A; 36.1%-46.6% for Group B; and 24.5%-48.5% for Group C). In a multivariate analysis, using Group A as a reference, the only variable associated with *H pylori* infection (Group B) was 17-gastrin (OR: 1.05 (95% CI: 1.005-1.10), $P < 0.05$). For the gastric atrophy, the most significant variable was 17-gastrin (OR: 1.13 (95% CI: 1.07-1.18), $P < 0.001$), and also male (OR: 2.08 (95% CI: 1.07-4.04), $P < 0.05$) and older age [OR: 1.02 (95% CI: 1.004-1.05), $P < 0.05$] were significant risk factors, while educational level was a protective factor [OR: 0.9 (95% CI: 0.84-0.99), $P < 0.05$].

Table 3 Characteristics of the asymptomatic population samples according to the estimated gastric cancer risk

Characteristics	Estimated gastric cancer risk			Total (n = 536)
	Low (A) (n = 115)	Medium (B) (n = 354)	High (C) (n = 67)	
Corpus atrophy[1]	Absent	Absent	Present	
H pylori infection[2]	Absent	Present	Present or absent	
Men, *n* (%)	46 (40.0)	168 (47.5)	35 (52.2)	249 (46.5)
Age (yr)[a], (mean ± SD)	49.6 ± 22.2	48.6 ± 18.0	61.9 ± 13.3	50.5 ± 19.0
Educational level (yr)[a], (mean ± SD)	8.8 ± 5.2	8.2 ± 4.3	5.8 ± 4.2	8.0 ± 4.6
Rurality, *n* (%)	27 (23.5)	99 (28.0)	22 (32.8)	148 (27.6)
Living in high-risk counties, *n* (%)	39 (33.9)	146 (41.2)	24 (35.8)	209 (39.0)
17-Gastrin[a] (pmol/L), (mean ± SD)	4.1 ± 6.8	5.6 ± 7.1	14 ± 14.3	6.3 ± 8.8

[1]As determined by serum level of PG-1 ⩽ 61.5 μg/L and PG-1/PG-2 ratio ⩽ 2.2. [2]Serology (+) for *H pylori* (ELISA). [a]Significant variables in the multivariate analysis ($P < 0.05$): B *vs* A: 17-gastrin (OR 1.05); C *vs* A: sex (OR 2.08); age (OR 1.02); education years (OR 0.9); 17-gastrin (OR 1.13).

DISCUSSION

In spite of the advances in the knowledge of gastric carcinogenesis, including the role of *H pylori* infection, early diagnosis and opportune time for surgical intervention will continue to be the basis of effective treatment. Digestive symptoms are late and non-specific events[18] such that in order to diagnose early stage tumors, it is necessary to identify high-risk asymptomatic subjects. This work intends to validate a non-invasive method to advance in this direction.

Even though the detection of *H pylori* infection identifies a group that concentrates virtually all the subjects at risk to develop GC in a population[4], the low incidence of GC in the infected and the generally high frequency of infection in countries with high GC frequency, such as Chile and other Andean countries of South America, determine a limited localizing effect. Additionally, the loss in serological evidence of infection detected in the old-aged group in this population, probably as a consequence of gastric atrophy, would imply missing the group with the highest GC risk. Moreover, the eradication of *H pylori* infection does not seem to prevent the development of GC in subjects that have already developed gastric atrophy or intestinal metaplasia[19].

Gastric atrophy is generally accepted the major risk factor for GC development. A prospective study by Uemura *et al*[4] showed that the patients with severe atrophy had 5 times greater RR than those without atrophy. Other Japanese studies have shown that in *H pylori*- infected subjects, gastric atrophy is associated with up to 90 times greater risk for GC[6,20,21].

The serological diagnosis of gastric atrophy by means of serum PG is based on the fact that a small proportion of the diverse isoforms of this digestive enzyme, produced in the mucosa of the upper digestive tract, enters the blood. The isoforms corresponding to PG-1 are synthesized only in the gastric corpus, while PG-2 isoforms are synthesized in the whole gastric mucosa and even in the proximal duodenum. In the presence of corpus atrophy, the serum level of PG-1 diminishes, while PG-2 is stable or diminishes very slightly. However, published studies are relatively heterogeneous. While most studies seem to validate the diagnostic performance of the method[22-27], other studies show a much less reliable performance[28,29] and even suggest the influence of racial factors[30]. A recent meta-analysis suggested that additional studies are required in diverse populations to determine its real value[17].

Our results showed that in this population, low level of serum PG-1 or low PG-1/PG-2 ratio were able to detect the presence of the corpus atrophy with moderate sensitivity (56%-78%) and high specificity (91%-100%). The latter minimizes the risk of false positives and makes the method especially appropriate to be used in a low prevalence setting, such as expected in an asymptomatic population. The diagnostic performance of low levels of 17-gastrin to detect the antrum atrophy was clearly unsatisfactory in these samples, probably due to the antagonistic effect of concurrent corpus atrophy, which determines a significant elevation of the gastrin level. In contrast, an elevated level of 17-gastrin was highly reliable for the diagnosis of corpus atrophy in the group with confirmed histological diagnosis (Table 1) and also showed a significant correlation with the gastric atrophy in the group with serological diagnosis (Table 3), which supports the validity of this finding. A recent multi-ethnic non-European study, including subjects from Japan, China, Tanzania and the Dominican Republic, and using diagnostic criteria very similar to ours, showed wide variation in serum 17-gastrin levels, related to sex, age and the country of origin, and also demonstrated a significant positive correlation between the level of 17-gastrin and the presence of gastric atrophy[31]. If these results are confirmed through correlation with histology, 17-gastrin may be as useful as PG-1 level to diagnose corpus-predominant gastric atrophy in some populations.

The serum level of PG-1 is also affected by antagonistic influences. Our study and other previous studies[32] confirm that *H pylori* infection, and also the use of proton pump inhibitors[33], raise the level of serum PG-1, which could mask the diminishment determined by gastric atrophy and thereby explain the limited sensitivity of the method.

It is pertinent to ask whether the diagnostic performance demonstrated in the initial sample, constituted of selected, symptomatic, old-aged patients with a high frequency of gastric atrophy (60%) and therefore a relatively low frequency of *H pylori* infection, can be extrapolated to an asymptomatic population sample. To dispel this doubt, it would be necessary to certify histologically the frequency of gastric atrophy in a representative sub-sample of the latter group, which we expect to do soon. In the meantime, we restricted the diagnosis of gastric atrophy only to those subjects who simultaneously had PG-1 levels and PG-1/PG-2 ratios below the previously determined cut-off levels, a more demanding and restrictive diagnostic criterion that has been suggested to minimize the risk of false positive[17]. There is no reliable data with respect to the frequency of gastric atrophy in the Chilean population. A recent study from Japan, a country with which we share an elevated risk for GC, using the same methodology, demonstrated the frequencies of *H pylori* infection and gastric atrophy for the age groups very similar to ours[34].

The demographic analysis of the three proposed risk groups, that were determined serologically, showed that they differed significantly in some variables recognized as associated with GC risk, such as age[35], gender and educational level[36], which indirectly supports the validity of this categorization. Our suggestion is that the group with evidence of gastric atrophy should be followed up and studied preferentially through upper GI endoscopy and biopsies. This non-invasive assessment of GC risk has been evaluated in a recent Japanese study[37], showing that the subjects with serologically detected gastric atrophy, either with or without *H pylori* infection, had annual incidence of gastric cancer significantly higher than those subjects without atrophy. As has been recommended[38], focusing invasive and more expensive diagnostic methods on high-risk groups significantly increases the chance of detecting early GC, that in our country comprised less than 10% of the diagnosed cases[2,39] and merely increased to 15% in the only population-based study performed by Llorens[40] between 1978 and 1986 in non-selected volunteers. As long as the precocity of the diagnosis is not modified, it will not be possible to change the disappointing prognosis of GC in Chile, with a 5-year survival rate after diagnosis, ranging between 3% and 12%[2,39]. In contrast, a recent Japanese population screening study, using serum PG and radiology as diagnostic the methods, detected 88% of early GC with a much lower cost than the conventional screening and concluded that this type of program would be very beneficial for high-risk populations[41].

It is known that Chile has one of the highest mortality rates for GC in the world[42]. Nevertheless, the RR is markedly heterogeneous at the regional and county level, ranging between 0.26 and 2.25. Apparently, the greater part of this difference is explained by the higher frequency of *H pylori* infection, mainly in young people, in high-risk counties (Ferreccio *et al* submitted). The eradication of *H pylori* in this stage, before the development of gastric atrophy, would probably reduce the incidence of GC, as has been demonstrated in a Chinese population[19], although it is a strategy of doubtful practical feasibility given the Chilean population's high frequency of infection (73%). The frequency of gastric atrophy, a late consequence of infection, was expected to be greater in the high-risk counties which could not be confirmed in this study, probably due to an insufficient sample size.

In summary, our results confirmed the diagnostic usefulness of the serum levels of pepsinogen and gastrin for the non-invasive detection of corpus-predominant gastric atrophy in the symptomatic patients, showed its

feasibility in an asymptomatic population and suggested that the method could be useful to identify the groups with higher risks of developing GC, in which preventive and control measures can be focused. It is probable that successive PG and/or 17-gastrin determinations (annually or biannually), confirming low levels or showing a decreasing tendency, would lead to even better diagnostic performance. The incorporation of this method to preventive health examination in a selected population (i.e., men, older than 50, residents in high-risk counties) could probably increase the proportion of GC diagnosed in the early or incipient phase, the only method to improve the prognosis of this serious and frequent disease.

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