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Serum biomarker tests are useful in delineating between patients with gastric atrophy and normal, healthy stomach

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Abstract

AIM: To study the value of serum biomarker tests to differentiate between patients with healthy or diseased stomach mucosa: i.e. those with *Helicobacter pylori (H pylori)* gastritis or atrophic gastritis, who have a high risk of gastric cancer or peptic ulcer diseases.

METHODS: Among 162 Japanese outpatients, pepsinogen Ⅰ (Pg Ⅰ) and Ⅱ (Pg Ⅱ) were measured using a conventional Japanese technique, and the European GastroPanel examination (Pg Ⅰ and Pg Ⅱ, gastrin-17 and *H pylori* antibodies). Gastroscopy with gastric biopsies was performed to classify the patients into those with healthy stomach mucosa, *H pylori* non-atrophic gastritis or atrophic gastritis.

RESULTS: Pg Ⅰ and Pg Ⅱ assays with the GastroPanel and the Japanese method showed a highly significant correlation. For methodological reasons, however, serum Pg Ⅰ, but not Pg Ⅱ, was twice as high with the GastroPanel test as with the Japanese test. The biomarker assays revealed that 5% of subjects had advanced atrophic corpus gastritis which was also verified by endoscopic biopsies. GastroPanel examination revealed an additional seven patients who had either advanced atrophic gastritis limited to the antrum or antrum-predominant *H pylori* gastritis. When compared to the endoscopic biopsy findings, the GastroPanel examination classified the patients into groups with "healthy" or "diseased" stomach mucosa with 94% accuracy, 95% sensitivity and 93% specificity.

CONCLUSION: Serum biomarker tests can be used to differentiate between subjects with healthy and diseased gastric mucosa with high accuracy.

Key words: Gastric atrophy; *Helicobacter pylori*; Serum gastrin-17; Serum pepsinogen

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INTRODUCTION

In 1994, the International Agency on Research for Cancer (IARC) considered *Helicobacter pylori (H pylori)* infection to be a class I carcinogen[1]. *H pylori* infection results in chronic gastritis that will develop into atrophic gastritis of some grade or type in half of infected subjects during their lifetime[2,3]. *H pylori* itself is not carcinogenic but the gastritis it causes, particularly atrophic gastritis, and the subsequent hypochlorhydric

stomach are carcinogenic[1,4-9]. On the other hand, subjects with normal, healthy stomach mucosa have no significant cancer risk, and are also not at risk for peptic ulcer diseases except those who use aspirin or NSAIDs[10]. Therefore, the differentiation between patients with healthy (no *H pylori*, gastritis or atrophic gastritis) and diseased gastric mucosa is clinically relevant. From the viewpoint of cost-effectiveness, this differentiation may be helpful in clinical decision-making and in rationalizing and optimizing diagnostic, therapeutic and screening procedures[11-15].

In the diagnosis of atrophic gastritis, and in the differentiation between healthy and diseased stomach mucosa, two options are available. The first option is gastroscopy and microscopic examination of endoscopic biopsy from the gastric antrum and corpus. The second non-invasive option, is the examination of gastric biomarkers from serum or plasma. Serum levels of pepsinogen (Pg) have been used for decades to diagnose atrophic corpus gastritis non-invasively[16-21]. In particular, in Japan, a country known to have a high prevalence of *H pylori* infection accompanied by gastric atrophy, the usefulness of the serum test to diagnose gastric atrophy has been extensively investigated[22-26], and there has been some success in screening subjects with a high risk of gastric cancer by determining the serum Pg I and Pg I / II ratio[8,27]. Recently, a European biomarker examination, GastroPanel (Biohit Plc, Helsinki, Finland), which not only assays Pg levels but also measures serum or plasma levels of gastrin-17 (G-17) and *H pylori* antibodies (HpAb) of both IgG and IgA class from the same sample using the ELISA technique has been validated[28-30]. In addition to corpus atrophy, the GastroPanel examination also allows exploration of the structure and function of the antrum mucosa, and can indicate the presence of intragastric acidity[31-34].

The aim of this study was to examine, in a Japanese population, how well the European GastroPanel examination delineates patients with atrophic gastritis, and, in particular, how well these examinations differentiate between patients with healthy and diseased gastric mucosa. A second aim was to examine how the conventional Japanese Pg assays fit with those in the European GastroPanel examination.

MATERIALS AND METHODS

Patient series

A total of 162 subjects (95 men) with a mean age of 55 years (range, 22-79 years) who visited the Tohoku University outpatient clinic for upper GI endoscopy were prospectively enrolled in this study from July 2006 to January 2008. The reasons for endoscopic examination were as follow: dyspeptic symptoms in 42 subjects, screening purposes in 54 asymptomatic subjects, annual endoscopic check-up in 38, and positive results during mass screening with barium meal examinations in 28. When enrolling the participants, individuals with a history of gastric surgery, prior *H pylori* eradication therapy, serious systemic disease, and those taking anti-secretory or anti-coagulant drugs were excluded. A fasting blood sample was obtained from each patient before endoscopy, and the serum was separated and stored in a dichotomous fashion at -20℃. An aliquot of each serum sample was subjected to both Pg assay using the Japanese technique and the GastroPanel examination as described below.

Endoscopy and biopsy

Diagnostic upper GI endoscopy was performed in all patients. Endoscopic examination revealed duodenal ulcer scar in 11 subjects, gastric ulcer or gastric ulcer scar in 10, reflux eosophagitis in six, duodenal adenoma in one, gastric adenoma in one, and no abnormal findings or gastritis alone in the others. Endoscopic biopsies were taken from the antrum and corpus, all along the greater curvature (one biopsy from both sites). Biopsy specimens were routinely fixed in neutral formalin and processed in paraffin. Tissue sections were stained with HE, Alcian blue and modified Giemsa (*H pylori* stain) methods.

Classification of patients

Based on histological appearances of the antral and corpus biopsies, the patients were classified into five categories. These categories were:

Atrophic gastritis in corpus alone (C): moderate or severe atrophy (40%-100% loss of normal oxyntic glands with the appearance of intestinal metaplasia and chronic inflammation in varying degree in the available corpus biopsy, in association with normal appearance of the antrum biopsy).

Atrophic gastritis in antrum and corpus (AC): moderate or severe atrophy (40%-100% loss of normal oxyntic and antral (pyloric) glands with the appearance of intestinal metaplasia and chronic inflammation in varying degree in the available antral and corpus biopsies).

Atrophic gastritis in antrum alone (A): moderate or severe atrophy (40%-100% loss of normal antral (pyloric) glands with the appearance of intestinal metaplasia and chronic inflammation in varying degree in the available antral biopsy, in association with normal appearance of the corpus biopsy).

Non-atrophic ("superficial") chronic gastritis (S): no atrophic or metaplastic changes, but the presence of chronic inflammation of varying degree and activity, and with varying grades of *H pylori* in the antrum and/or corpus biopsies.

Normal stomach mucosa (N): mucosa normal in both antrum and corpus biopsy. No atrophy, metaplasia or inflammation.

Categories C, AC and A represented patients with advanced (moderate or severe) atrophic gastritis (AG). Category N represented patients with healthy and normal stomach mucosa. The category of patients with "diseased" gastric mucosa included all those in categories S, A, AC and C.

The biopsy specimens were interpreted by an experienced pathologist (Professor Pentti Sipponen,

Helsinki University Hospital, Helsinki, Finland) without knowledge of the clinical data or results from the biomarker analyses.

Pg Ⅰ and Ⅱ assays with the Japanese technique

Serum levels of Pg were measured by chemiluminescent enzyme immunoassay using commercial kits (Lumipulse pepsinogen Ⅰ & Ⅱ, Fujirebio Inc., Tokyo, Japan)[35]. For the diagnosis of atrophic corpus gastritis, three different criteria were used as follows[22,36,37]: "Mild" criteria: Pg Ⅰ ≤ 70 μg/L and Pg Ⅰ/Ⅱ ≤ 3.0; "Moderate" criteria: Pg Ⅰ ≤ 50 μg/L and Pg Ⅰ/Ⅱ ≤ 3.0; "Strict" criteria: Pg Ⅰ ≤ μg/L and Pg Ⅰ/Ⅱ ≤ 2.0; For each group of criteria, both cut-offs for Pg Ⅰ and Pg Ⅰ/Ⅱ were required to be fulfilled at the same time.

GastroPanel examination

Pg Ⅰ and Ⅱ, amidated gastrin-17, and IgG and IgA class antibodies to *H pylori* were determined using specific ELISA tests (Biohit Plc, Helsinki, Finland) and were performed in batches of 40 samples on a micro-well plate, according to the manufacturer's instructions. All EIA techniques were based on the measurement of absorbance after the peroxidation reaction at 450 nm. Between the reaction steps the plates were washed using a BW50 Microplate Strip Washer (Biohit Plc, Helsinki, Finland). Absorbances were measured using a micro-well plate reader (BP800 Microplate Reader, Biohit Plc, Helsinki, Finland). To determine PgI and gastrin-17 values, second order fits on standard concentrations were used to interpolate/extrapolate from unknown sample concentrations automatically with the help of the BP800 in-built software (Biohit Plc, Helsinki, Finland).

H pylori antibodies were expressed as enzyme immuno units (EIU) according to the formula included in the test kit: Sample EIU = [X (A_{Sample})-X (A_{Blank})]/[X ($A_{Calibrator}$)-X (A_{Blank})]. EIU levels ≥ 30 were considered *H pylori* positive. In the GastroPanel examination, normal ranges for serum/plasma Pg Ⅰ, Pg Ⅱ, Pg Ⅰ/Ⅱ ratio and amidated gastrin-17 were determined by the manufacturer as 30-165 micro/L, 3-15 micro/L, 3-20, and 1-10 pool/L, respectively (www.gastropanel.net).

According to available validations of the GastroPanel examination against endoscopic histology, advanced (moderate or severe) atrophic gastritis was observed with high accuracy ("strict" criteria) if the serum/plasma Pg Ⅰ was < 30 μg/L and/or Pg Ⅰ/Pg Ⅱ ratio < 3[28,29]. Advanced (moderate or severe) antral atrophy or antral predominant *H pylori* gastritis was observed if the HpAb test was positive and fasting serum G-17 < 1 pmol/L.

Classification of patients into different gastritis categories by the GastroPanel examination

Classification of patients using the GastroPanel examination into categories C, AC, A, S or N was carried out using cut-offs for the test parameters as provided by the manufacturer and by using the GastroSoft® computer program (Biohit Plc, Helsinki, Finland). This computer program is based on extensive background material obtained endoscopically and histologically, the program calculates the probabilities for all diagnostic categories from this database. Finally, the GastroSoft program automatically provides the most likely alternative diagnosis. Classification of patients using the GastroPanel examination was done without knowledge of endoscopy and histology results.

Statistical analysis

For the GastroPanel examination and the conventional Japanese Pg assay, the accuracy, sensitivity, and specificity were estimated and compared with histological assessment of the antrum and corpus biopsies. These statistical parameters for the diagnosis of atrophic gastritis were calculated from the serological tests to discriminate histological C, AC, and A from S and N. In the differentiation analysis between patients with healthy and diseased stomach mucosa, these parameters were calculated and used to discriminate C, AC, A, and S from N. The correlations in serum Pg levels between the GastroPanel examination and the conventional Japanese assay were assessed using linear regression analysis, and Pearson correlation coefficients (r) were estimated for each analysis. The study was approved by Tohoku University School of Medicine Ethics Committee and each subject gave written informed consent.

RESULTS

Serum levels of Pg

Serum levels of Pg Ⅰ and Pg Ⅱ correlated significantly and very well ($r = 0.97$, $P < 0.001$ and $r = 0.98$, $P < 0.001$, respectively) between the Japanese assays and the GastroPanel methods in the same serum samples (Figure 1A and B). A technical and methodological difference did exist, however, in that the Pg Ⅰ test in the GastroPanel examination gave exactly twice the Pg Ⅰ level to that in the Japanese assays. No differences were observed between the Pg Ⅱ tests. Accordingly, the Pg Ⅰ/Pg Ⅱ ratio in the GastroPanel examination was exactly twice the ratio in the conventional Japanese tests, even though the correlation between the Pg ratios was highly significant and very good (Figure 1C; $r = 0.96$, $P < 0.001$).

Atrophic gastritis

GastroPanel: Using the "strict" criteria for advanced atrophic gastritis (moderate or severe in grade; see Materials and Methods), Table 1 shows the distribution of patients into the different gastritis categories. When compared to endoscopic histology, the accuracy of the GastroPanel examination to diagnose atrophic gastritis was 87%, the sensitivity was 40% and the specificity 94%.

Conventional Japanese Pg assay: Using the "strict" criteria for cut-offs of Pg levels (Pg Ⅰ ≤ 30 μg/L and Pg Ⅰ/Ⅱ ≤ 2.0) in the Japanese assay, Table 2 shows the distribution of patients into positive and negative groups regarding atrophic gastritis. When compared to endoscopic histology, the accuracy, sensitivity and specificity of the test were 88%, 45% and 96%,

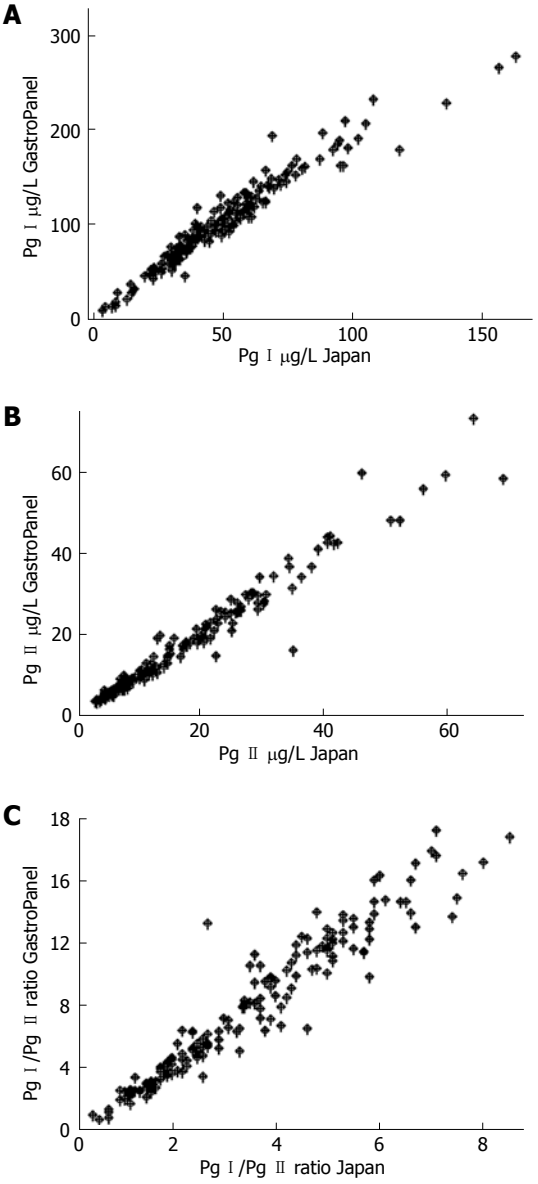

Figure 1 Serum levels of Pg using the GastroPanel examination and the Japanese Pg test in the same serum samples. A: Serum Pg Ⅰ; B: Serum Pg Ⅱ; C: Serum Pg Ⅰ/Ⅱ ratio.

respectively, which corresponded well with those from the GastroPanel examination. If the pepsinogen criteria were lowered to "moderate" (Pg Ⅰ ≤ 50 μg/L and Pg Ⅰ/Ⅱ ≤ 3.0) or "mild" (Pg Ⅰ ≤ 30 μg/L and Pg Ⅰ/Ⅱ ≤ 2.0), the sensitivity of the examination increased but the specificity decreased (Table 3).

Differentiation between patients with healthy and diseased stomach mucosa

The GastroPanel examination, but not Pg testing alone, enabled the differentiation of patients into those with healthy or diseased mucosa (presence of *H pylori* gastritis or atrophic gastritis which may be *H pylori* positive or negative). The GastroPanel test included assays of Pg Ⅰ and Pg Ⅱ as biomarkers for atrophic gastritis in corpus mucosa but also included an amidated G-17 assay as a biomarker of structure and function of the gastric antrum, and assays for the presence or absence of *H pylori* antibodies as a biomarker of on-going *Helicobacter* infection and gastritis. If all biomarkers in the GastroPanel examination were normal, the stomach mucosa was considered normal and healthy. If any of the biomarkers were abnormal, the patient was considered to have *H pylori* gastritis or atrophic gastritis. Using this delineation (see Materials and Methods), Table 4 shows the distribution of the patients into two subgroups (i.e. those with healthy and normal stomach versus those with *H pylori* gastritis or atrophic gastritis). In this setting, the findings from biopsy histology were compared between the two delineated subgroups. In this analysis, the accuracy, sensitivity and specificity of the GastroPanel test to diagnose healthy stomach mucosa were 94%, 95% and 93%, respectively.

Table 1 Prevalence of patients in different gastritis categories. Comparison between GastroPanel examination and biopsy histology

GastroPanel	Histology					
	C	AC	A	S	N	Total
C	3	0	0	4	0	7
AC	1	2	0	0	0	3
A	0	1	1	5	0	7
S	3	1	5	73	3	85
N	0	2	1	4	53	60
Total	7	6	7	86	56	162

Accuracy: 87%; sensitivity: 40%; specificity: 94%; C, AC, A: Moderate or severe atrophic gastritis in corpus alone, in antrum and corpus simultaneously, and in antrum alone, respectively; S: Non-atrophic *H pylori* gastritis; N: Normal and healthy stomach mucosa.

Table 2 Prevalence of patients in corpus atrophy positive (AG+) and negative (AG-) categories if "strict" criteria for cut-off of positive Pg test (Pg test+ versus Pg test-) are used. Comparison between Japanese Pepsinogen test and biopsy histology

	AG+	AG-	Total
Pg test+	9	6	15
Pg test-	11	136	147
Total	20	142	162

AG: Atrophic corpus gastritis present (+) or absent (-). Pg: Pepsinogen test positive (+) or negative (-) for atrophic corpus gastritis.

Table 3 Sensitivity and specificity of the Japanese pepsinogen test and GastroPanel examination in atrophic gastritis if the cut-offs (criteria) for the positive pepsinogen test result are set to be mild, moderate or strict (%)

Pepsinogen test criteria	Sensitivity	Specificity
Japanese-mild	75	69
Japanese-moderate	65	77
Japanese-strict	45	96
Gastropanel-strict	40	94

DISCUSSION

The present analysis showed that non-invasive serum Pg assays accurately diagnosed Japanese patients with atrophic corpus gastritis. Similar findings were also obtained

Table 4 Prevalence of patients in categories of "healthy" or "diseased" gastric mucosa. Comparison between GastroPanel examination and biopsy histology

GastroPanel	Histology		
	Healthy stomach mucosa	Diseased stomach mucosa	Total
Healthy stomach mucosa	53	7	60
Diseased stomach mucosa	3	99	102
Total	56	106	162

Accuracy: 94%; sensitivity: 95%; specificity: 93%.

using both the conventional Japanese Pg tests and the Pg assays of the novel European GastroPanel examination in which, in addition to Pg, the serum/plasma levels of amidated gastrin-17 (G-17) and *H pylori* antibodies (IgG and IgA) were also measured. The diagnostic accuracy of both the Japanese test and the GastroPanel test was more than 80% when compared with endoscopic biopsy histology. In addition, it is noteworthy that, since both the Japanese and the European (GastroPanel) Pg tests seemed to fit without any exceptions, no racial differences could be demonstrated in Pg antigens by the present study-both the Japanese and European assays gave very similar results.

The GastroPanel test included assays of amidated G-17 and *H pylori* antibodies in addition to the Pg assays. The rationale for this is that the serum level of amidated G-17 is a biomarker of the function and structure of the gastric antral mucosa. Serum levels of G-17 were high in subjects with atrophic gastritis limited to corpus mucosa alone but normal and low in those in whom atrophic gastritis was present in both the antrum and corpus (multifocal atrophic gastritis of Correa - highest risk condition for gastric cancer known so far). The rationale for the serological *H pylori* test, on the other hand, is that the presence or absence of *H pylori* antibodies in serum is the most reliable biomarker of an on-going *H pylori* infection. When compared with the ^{13}C urea breath-test (UBT) or stool antigen test, the serological test avoids false-negative results which appear in more than half of patients with atrophic corpus gastritis (hypochlorhydric stomach) or PPI use when analyzed using the UBT or stool antigen test. In this sense, the GastroPanel biomarker examination provides a most reliable tool for delineating between patients with healthy stomach and those with *H pylori* non-atrophic gastritis or atrophic gastritis.

In the present study, the biomarker tests were compared with endoscopic biopsy histology. Endoscopic biopsy histology is, however, not a reliable gold standard. Biopsy results are commonly biased by several factors, including such confounders as biopsy sampling, number of biopsies available from each stomach compartment, laboratory processing of the specimens, and interpretation of the biopsy by pathologists. In the present study, the biopsy analysis was based on only one biopsy from both the antrum and corpus, and so the study protocol did not strictly follow the guidelines of the Sydney System (the guidelines indicate at least two biopsies from each compartment). Interpretation of the biopsy findings by pathologists may, therefore, easily fail, particularly in antral biopsies, in which the interobserver agreement, even between "expert" pathologists, is known to be imperfect and may require practice or even the application of morphometry[38-40].

Biomarker examinations from serum or plasma are free of the biases that affect biopsy histology or sampling. The biomarkers give an average view of the structure and function of the stomach mucosa. In addition to the Pg tests, the GastroPanel examination included assays of serum/plasma levels of amidated G-17 and *H pylori* antibodies. This also allows insight into the function and structure of the gastric antrum, confirms Pg assays, and can suggest the presence of intragastric acidity[31-34]. A low fasting level of serum/plasma G-17 indicates subjects with high intragastric acidity (acid inhibits the release of amidated G-17 from antral G cells) or those with atrophy of the antral mucosa (the loss of antral glands also results in loss and disappearance of antral G cells)[28,29]. In the present study population, seven patients were classified into this category according to the GastroPanel examination. These seven patients were anticipated to have an antrum-limited atrophic gastritis or *H pylori* gastritis that was strongly antrum predominant (a phenotype of *H pylori* gastritis that is associated with the risk of peptic ulcer disease (PU), particularly PU of the duodenal ulcer type)[10]. Low fasting levels of serum/plasma G-17 in connection with low Pg I or Pg I /Pg Ⅱ ratio also identifies subjects who have the highest known risk of gastric cancer; i.e. patients with advanced and extensive atrophic gastritis in both the antrum and corpus (advanced multifocal atrophic gastritis)[4,6,17]. In the present study, three patients (2%) were classified into this category using the GastroPanel examination, which was also confirmed by biopsy histology.

Differentiation between patients with healthy and diseased gastric mucosa is one of the key issues in assessing the risks for serious gastric diseases in clinical practice. If the stomach mucosa is healthy, the risks of serious gastric diseases (cancer or peptic ulcer) are extremely low (nil in practice). With high certainty (accuracy 94%, sensitivity 95% and specificity 93%) the GastroPanel examination indicated that 53 of 162 patients (33%) in this study had normal and healthy stomach mucosa.

Biomarker tests are not "cancer tests". However, they can be used in the screening and diagnosis of subjects with a high cancer risk; i.e. subjects with atrophic gastritis in which a careful diagnostic endoscopy (gastroscopy) is mandatory to find possible neoplastic or precancerous lesions at an early and curable stage. In the post hoc analysis, none of these 53 patients with "healthy" stomach had neoplastic lesions or signs of active peptic ulcers on endoscopy (one patient had a duodenal scar and one had a scar in the stomach mucosa). On the other hand, two of the patients with atrophic gastritis had neoplastic gastric or duodenal adenoma. Thus, in the present study population, all neoplastic gastroduodenal

lesions were found in those patients with diseased stomach mucosa using the GastroPanel examination.

The reasons for the differences in serum levels of Pg I between the Japanese and GastroPanel assays are technical and methodological, and are most likely due to differences in the calibrators used in the assay technique. However, due to the excellent correlations between the tests, the results from the conventional Japanese Pg I assay can easily be converted (by doubling the test results) to correspond with those obtained using the GastroPanel Pg I test, or *vice versa*.

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COMMENTS

Background

Reliable non-invasive diagnosis of *Helicobacter pylori (H pylori)* gastritis and atrophic gastritis, and the delineation of patients with healthy stomach mucosa, are clinically important tasks.

Research frontiers

Biomarker tests are potential non-invasive diagnostic tools for assessment of the function and structure of the stomach mucosa.

Innovations and breakthroughs

Available pepsinogen (Pg) tests, both Japanese and European, are excellent in Asian outpatients when compared in a "head-to-head" analysis in the same study population. The addition of assays for serum amidated gastrin-17 and serological *H pylori* tests to the Pg assays increases the clinical applicability of the biomarker tests.

Applications

A comprehensive set of biomarker tests (GastroPanel) is applicable in the reliable diagnosis of *H pylori* gastritis, atrophic gastritis, and also in the delineation of subjects with healthy, normal stomach mucosa.

Peer review

The authors evaluated the predictive value of the detection of a set of serum biomarkers (Pg Ⅰ/Pg Ⅱ, gastrin-17, and antibodies against *H pylori*) using the European GastroPanel examination among 162 Japanese patients. They found that the GastroPanel examination classified the patients into groups with "healthy" or "diseased" stomach mucosa with 94% accuracy, 95% sensitivity and 93% specificity, as compared to endoscopic biopsy findings. It is helpful for readers to understand the usefulness of this examination among Asian gastric patients.

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