Value of GastroPanel in the diagnosis of atrophic gastritis

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Abstract. Analysis of serum biomarkers for the assessment of atrophic gastritis (AG), considered as precursor of the intestinal type of gastric cancer, is of growing interest. The combination of pepsinogen (PG), gastrin-17 (G17) and anti-Helicobacter pylori (H. pylori) antibody serological assays (panel test) is a non-invasive tool for the diagnosis of atrophic gastritis. However, the diagnostic reliability of this test remains uncertain. The aim of our study was to assess the diagnostic performance of the serum panel test (GastroPanel) for the diagnosis of atrophic gastritis. From dyspeptic patients, endoscopic biopsy samples (two from the gastric corpus and two from the antrum) and blood samples were collected. The determination of sPGI, sPGII, sG17 and IgG antibodies to H. pylori (H.p IgG) was performed using an enzyme-linked immunosorbent assay (GastroPanel; Biohit Oyj). Histopathology results were compared with GastroPanel values. Sixty patients were included: 35 (58.3%) females and 25 (41.66%) males; mean age 67.63±9.36 years; 45% H. pylori-positive. A total of 65% of patients had atrophic gastritis. There were no significant differences between the levels of biomarkers and localization of atrophy. The ratio PG1/PG2 was lower in patients with multifocal atrophy; the difference being close to the threshold of statistical significance. In cases of intestinal metaplasia the values of G17, PG1, PG2, H.p IgG were not statistically altered compared to those without intestinal metaplasia; only the ratio PG1/PG2 was lower in intestinal metaplasia; the difference being almost of statistical significance. Our results revealed that, GastroPanel values did not differ depending on the severity of the atrophy. Biomarkers used by GastroPanel do not have enough accuracy for use in the diagnosis of atrophy in the population studied. A low accuracy only for the ratio PG1/PG2 in patients with multifocal atrophy was found. However, our data revealed a correlation in detecting intestinal metaplasia.

Introduction

Atrophic gastritis (AG) is the highest known independent risk factor (risk condition) for distal, noncardial gastric cancer (1-3). Gastric carcinogenesis is a long and multistep process, known as the ‘Correa's Cascade’. In this model of gastric carcinogenesis, gastric cancer is preceded by gastric precancerous lesions: Atrophic gastritis (AG), intestinal metaplasia (IM), low-grade dysplasia, and high-grade dysplasia, developed successively following chronic infection with Helicobacter pylori (H. pylori) (4,5). Each of these lesions is associated with an increased risk of gastric cancer which correlates with the severity of the lesions, but AG and IM are the most common and the most widely studied (6-9).

For the early detection of gastric cancer and to reduce mortality, international guidelines recommend endoscopic follow-up and gastric biopsies for subjects with atrophic gastritis, even after H. pylori eradication (10,11).

A non-invasive tool able to easily identify individuals with atrophic gastritis, is essential for improving the early diagnosis of gastric cancer. To avoid numerous gastroscopies and increase patient adhesion to surveillance several strategies have been developed. Among them, serological markers are of growing interest to assess the presence of gastric atrophy (12).

Numerous and potential serological biomarkers such as serum pepsinogen 1 and 2 (PG1 and PG2, respectively), gastrin-17 (G17), antiparietal cell antibodies, IgG anti-H. pylori antibodies (H.p Ab), have been used, separately or combined, to predict gastric mucosa status (12).

PG1 is secreted only by oxintic glands of the corpus, PG2 is secreted by pyloric glands and proximal duodenal mucosa and G17 is only secreted by the G cells of the antral mucosa (13). Serum PG1 levels and/or the PG1/PG2 ratio appear to be lower in patients with corpus atrophic gastritis, and low G17 serum level, in combination with positive anti-H. pylori antibodies (H.p Ab), would indicate the presence of antrum atrophic gastritis (13).

Some studies have tested this serologic panel (GastroPanel) for the noninvasive diagnosis of atrophic gastritis and have obtained encouraging results (14-19); however, other studies do not support its usefulness (20-22).

Finally, experience with GastroPanel is limited; no study has been carried out in a Romanian population.

Materials and methods

Patients. This was a prospective study, carried out at a single tertiary center, namely the Second Medical Department
and the Endoscopy Laboratory, Emergency Clinical County Hospital (Cluj-Napoca, Romania). Patient recruitment was from July 2017 to August 2018. A total of 60 patients were included in our study: 35 (58.3%) females and 25 (41.66%) males. The mean age of the patients was 67.63±9.36 years (range, 50-87 years). Inclusion criteria were as follows: Patients older than 50 years, with dyspepsia. After fulfilling this inclusion criteria, upper gastrointestinal endoscopy was performed.

Exclusion criteria were as follows: Hepatic, lung, renal, endocrine, metabolic, hematological or malignant diseases; history of chemotherapy or gastric surgery, history of H. pylori eradication; history of alcohol or drug abuse; pregnancy. A demographic questionnaire was completed including socio-demographic data and medical history. The Ethics Committee of Emergency Clinical County Hospital approved the study following European and local regulations. All admitted patients signed an informed consent.

Investigations. Upper gastrointestinal endoscopy was performed by gastroenterologists to all patients and biopsies were obtained (two from the gastric corpus and two from the antrum). Pathological examinations of biopsy samples were conducted by one single expert pathologist and the results were reported according to the updated Sydney system (23). Blood samples were obtained from all patients after 10 h of fasting. Two weeks before blood extraction, patients had ceased receiving proton pump inhibitors (PPIs). EDTA tubes were centrifuged at 2,000 x g, for 10-15 min, at 20-25°C. Blood was stored at -20°C until the assay was performed.

The determination of sPGI, sPGII, sG17 and IgG antibody to H. pylori (H.p IgG) was performed using an enzyme-linked immunosorbent assay (ELISA) (cat. no. 601 020.02 for PGII; cat. no. 601 035 for G17; cat. no. 601 010.01 for PG1; cat. no. 601 040.02 for H.p IgG; GastroPanel ELISA; Biohit Oyj). Recommended cut-off points for GastroPanel were (as reported by the manufacturer): sPGI: 30-120 mg/l, sPGII: 2-10 mg/l, sG17: 2-10 pmol/l and H.p IgG titre: -30 EU. Accordingly, a value of 30 mg/l for sPGI was assumed as a biomarker of atrophic corpus gastritis, and a value of 2 pmol/l for sG17 was assumed to be a biomarker of antral atrophic gastritis, in the absence of hyperchlorhydria (22). All tests were performed at the centralized laboratory Bioclinica, Cluj Napoca, Romania. According to the pathological examination, subjects were classified into four groups: non-atrophic gastritis, corpus atrophy, antral atrophy, multifocal atrophy. Histopathology results were compared with GastroPanel values.

Statistical analysis. The distribution of parameters was evaluated using Kurtosis and Skewness. The normal distributed data were expressed as the mean ± standard deviation, and abnormal distributed data were expressed as median and 25 and 75th percentiles. Comparison between groups was performed using the Mann-Whitney U-test and Wilcoxon W-test for continuous and discrete variables, respectively. The comparisons between histologic features and sPGI, sPGII and sG17 were performed using Kruskal-Wallis test. P<0.05 was considered to indicate a statistically significant difference.

Receiver operating characteristic (ROC) curves were used to calculate the overall diagnostic performance of G17, PG1, PG2, and the PG1/PG2 ratio for the diagnosis of gastric atrophy. If the area under the ROC curve (AUC) was acceptable (0.70), the optimal cut-off points were assessed, and then sensitivity analysis was calculated. The accuracy of the algorithm of GastroPanel was assessed against histology (gold standard); sensitivity, specificity, and positive and negative predictive values were also calculated.

Results

A total of 60 patients were included in our study; 35 (58.3%) females and 25 (41.66%) males. (Table I). There were no significant differences between biomarker values depending on sex: G17 (P=0.969), PG1 (P=0.708), PG2 (P=0.263) or PG1/PG2 (P=0.472) (Table II).

The mean age of patients was 67.63±9.36 years (range, 50-87 years), with 32 (51.61%) patients between 50 and 59 years, 13 (20.96%) patients between 60 and 69 years, and 15 (24.19%) patients older than 70 years (Table III).

There were no significant differences between biomarker values and age groups: G17 (P=0.121), PG1 (P=0.533), PG2 (P=0.259), PG1/PG2 (P=0.578) and ac H.p IgG (P=0.635) (Table IV).

There were no significant differences between levels of biomarkers and localization of atrophy: G17 (P=0.599), PG1 (P=0.270), PG2 (P=0.813), PG1/PG2 (P=0.175) and ac H.p IgG (P=0.782) (Tables V and VI).

GastroPanel values were not significantly altered in patients with antral atrophy or corpus atrophy compared to those without atrophy (Tables VII and VIII).

In addition, in cases of multifocal atrophy the values of G17, PG1, PG2, H.p IgG were not statistically altered compared to those without atrophy: G17 (P=0.894), PG1 (P=0.370), PG2 (P=0.415), PG1/PG2 (P=0.060) and ac H.p IgG (P=0.139). However, the ratio PG1/PG2 was lower in patients with multifocal atrophy; the difference being close to the threshold of statistical significance 6.2 (3.1; 10.4) vs. 10.2 (6.8; 29.6) P=0.060 (Table IX).

Table I. Levels of biomarkers depending on sex.

| Biomarkers | Sex  | Median (IQ: 25-75%) |
|------------|------|---------------------|
| PG1        | M    | 84.8 (36.1-136)     |
| F          | 64.3 (44.6-111.4) |
| PG2        | M    | 9.4 (3.6-18.25)     |
| F          | 8.4 (1.6-10.7) |
| PG1/PG2    | M    | 8.3 (5.49-14.1)     |
| F          | 9.7 (6.1-28.1) |
| G17        | M    | 5.5 (1-26.45)       |
| F          | 5.3 (1-28.9) |
| Ac. H.p IgG | M | 61.8 (18.1-96.65) |
| F          | 42.7 (15-85.5)  |

IQ: 25-75%, interquartile range between 25 and 75th percentiles; PG1, pepsinogen 1; PG2, pepsinogen 2; G17, gastrin-17; Ac. H.p IgG, anti-Helicobacter pylori immunoglobulin G antibodies.
A cut-off value for PG1/PG2 of <6.59 was calculated to differentiate multifocal atrophy patients from the other patients [AUC 0.672; Se 61.5% (95% CI 31.6-86.1), Sp 76% (95% CI 61.2-87.4); P=0.04] (Table IX and Fig. 1).

Furthermore in cases of intestinal metaplasia the values of G17, PG1, PG2, H.p IgG were not statistically altered compared to those without intestinal metaplasia: G17 (P=0.791), PG1 (P=0.532), PG2 (P=0.962), PG1/PG2 (P=0.083) an ac H.p IgG (P=0.806); only the ratio PG1/PG2 was lower in intestinal metaplasia; the difference being almost statistically significant [7.4 (4.4; 12.4) vs. 11 (6.4; 29.6); P=0.083] (Tables X and XI).

A cut-off value for PG1/PG2 of <8.8 was calculated to differentiate intestinal metaplasia patients from the other patients [AUC 0.637; Se 66.6% (95% CI 43.0-85.4), Sp 60.5% (95% CI 43.4-76.0); P=0.07] (Table XI and Fig. 2).
Patients included in the study were divided into 2 groups: patients without gastric atrophy (n=21) 35%; and patients with gastric atrophy (n=39) 65%. Those with atrophy (n=39) were divided into 2 subgroups with mild atrophy (n=26) and moderate atrophy (n=13). No patients with severe atrophy were found. In the non-atrophic group there were patients with spotty gastritis and erosive gastritis. *H. pylori* infection was found in 45% of patients (n=27).

GastroPanel values did not differ depending on the severity of the atrophy: G17 (P=0.599), PG1 (P=0.270), PG2 (P=0.813), PG1/PG2 (P=0.175) and ac H.p IgG (P=0.782) (Tables VI and XII).

### Discussion

Several authors have suggested a non-invasive test defined as a ‘serological biopsy’, aimed at providing a gastric function serum profile, especially of gastric atrophy (17,19,24,25).

The results of a recent meta-analysis suggest that the combination of pepsinogen, G17, gastrin-17, Ac. H.p IgG, anti-*Helicobacter pylori* immunoglobulin G antibodies was a reliable tool for the diagnosis of the presence and site of atrophic gastritis (26).

Thus, GastroPanel could be a useful noninvasive method to reduce unnecessary gastroscopies. The results of our study did not support this theory.
In our study it was demonstrated that GastroPanel values (biomarkers G17, PG1, PG2) were not significantly altered in patients with antral atrophy or corpus atrophy compared to those without atrophy. The measurement of G17 and PG2 for the diagnosis of antral atrophy had an unacceptably low accuracy.

In addition, in cases of multifocal atrophy the values of G17, PG1, PG2, H. pylori IgG were not statistically altered compared to those without atrophy: However, the ratio PG1/PG2 was lower in patients with multifocal atrophy; the difference being close to the threshold of statistical significance.

In the cases of multifocal atrophy, a sensitivity of 61.5% and specificity of 76% were determined (P=0.04). In this regard, our results are supported by another study, which found discouraging results. The study revealed that PG1 differences between patients with or without corpus atrophy were not significant (112 vs. 117 µg/l), and no statistically significant differences for PG1/PG2 for the localization of the atrophy were reported; but, compared to our results, they found that the mean levels of G17 were significantly reduced in patients with atrophy in the antrum (5 vs. 13 pmol/l; P<0.01) (27).

The ratio PG1/PG2 (in our study) was lower in patients with intestinal metaplasia; the difference being almost statistically significant (P=0.083) with a sensitivity of 66.6% and a specificity of 60.5% (P=0.07).
According to our findings, PG and G17 were not valid enough to differentiate between patients with or without atrophic gastritis. Nasrollahzadeh et al similarly reported a relatively low validity for PG and G17 to distinguish non-atrophic gastritis (28).

The suboptimal accuracy of GastroPanel (and the individual biomarkers) may be negatively affected by some other variables, but these unknown altering variables (such as a possible spotty gastritis with ‘normal function’) arise from real clinical practice experience.

The main limitation of the present study is that we did not find patients with severe atrophy in the study population. This theory is supported by a group of French researchers who claim that GastroPanel has an insufficient diagnostic performance in case of mild gastric atrophy. However, it can be useful in selected groups of patients at high risk for gastric cancer, in particular to detect severe atrophy and corpus atrophy (29).

In conclusion, our study indicated that biomarkers used by GastroPanel do not have enough accuracy for use in the diagnosis of atrophy in the population studied.

An association was only revealed for the ratio PG1/PG2 which was lower in patients with multifocal atrophy. However,
our present data exhibited low accuracy in detecting intestinal metaplasia. These results suggest that the serological approach may not be the best method to screen for gastric mild atrophy or gastric cancer in people from low prevalence areas, such as Romania. The present results are contrary to expectations and contrary to some authors who claim that GastroPanel is ‘even more reliable than a histology biopsy’ (30).

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
CG, EG and AP performed the literature search for relevant publications on the topic. CG and SG performed endoscopies with biopsy. CG and SG collected the data. EG and AP analyzed the data. CG and SG were responsible for original draft preparation. DD conceived this study, surveyed its progress and contributed to the writing. All the authors read, verified and approved the final version of the manuscript.

Ethics approval and consent to participate
The Ethics Committee of Emergency Clinical Hospital Cluj County approved the study following European and local regulations. Emergency Clinical Hospital Cluj County is a University hospital and all admitted patients signed an informed consent by which they agree that their data are available from the corresponding author on reasonable request.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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