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Original Article

Value of Serological Biomarker Panel in Diagnosis of Atrophic Gastritis and *Helicobacter pylori* Infection

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Abstract

Background: Gastric cancer is one of the most common types of cancer worldwide. *Helicobacter pylori* infection is clearly correlated with gastric carcinogenesis. Therefore, the use of a new non-invasive test, known as the GastroPanel test, can be very helpful to identify patients at a high risk, including those with atrophic gastritis, intestinal metaplasia, and dysplasia. This study aimed to compare the results of GastroPanel test with the pathological findings of patients with gastric atrophy to find a safe and simple alternative for endoscopy and biopsy as invasive methods.

Methods: This cross-sectional study was performed on patients with indigestion, who were referred to Motahari Clinic and Shahid Faghihi Hospital of Shiraz, Iran, since April 2017 until August 2017 for endoscopy of the upper gastrointestinal tract. The serum levels of gastrin-17 (G17), pepsinogen I (PGI), and pepsinogen II (PGII), as well as *H. pylori* antibody IgG, were determined by ELISA assays. Two biopsy specimens from the antrum and gastric body were taken for standard histological analyses and rapid urease test. A pathologist examined the biopsy specimens of patients blindly.

Results: A total of 153 patients with indigestion (62.7% female; mean age, 63.7 years; 37.3% male; mean age, 64.9 years) were included in this study. The G17 levels significantly increased in patients with chronic atrophic gastritis (CAG) of the body (9.7 vs. 32.8 pmol/L; $P=0.04$) and reduced in patients with antral CAG (1.8 vs. 29.1 pmol/L; $P=0.01$). The results were acceptable for all three types of CAG, including the antral, body, and multifocal CAG (AUCs of 97%, 91%, and 88% for body, antral, and multifocal CAG, respectively). The difference in PGII level was not significant. Also, the PGI and PGI/PGII ratio did not show a significant difference (unacceptably low AUCs for all). The *H. pylori* antibody levels were higher in patients infected with *H. pylori* (251 EIU vs. 109 EIU, AUC=70, $P=0.01$). There was a significant relationship between antibody tests and histopathology.

Conclusion: Contrary to Biohit's claims, the GastroPanel kit is not accurate enough to detect CAG; therefore, it cannot be used for establishing a clinical diagnosis.

Keywords: Serologic diagnosis, Pepsinogen II, Pepsinogen I, Gastrin-17, Chronic atrophic gastritis, *Helicobacter pylori*

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Introduction

Chronic gastritis caused by *Heliobacter pylori* infection is one of the most important precancerous lesions of the stomach.[1] Correa first discussed the importance of these lesions as a starting point for gastric mucosal changes that can lead to intestinal-type gastric adenocarcinoma.[2] Chronic *H. pylori* infection, by stimulating the host immune response, causes chronic active inflammation and mucosal damage, resulting in multifocal atrophic gastritis, intestinal metaplasia, glandular dysplasia, and adenocarcinoma.[3,4] As these changes do not occur in all infected individuals, the possible effects of other environmental and genetic factors should be considered.[5,6]

Most studies on the carcinogenesis of chronic gastritis have focused on antrum and fundus gastric tumors, besides the topography of gastritis due to the relatively high prevalence of these tumors in the distal and middle gastric region. Evidence also suggests the greater severity and extent of gastritis in the anterior part of the body.[7,8] It seems that inflammation due to the presence of *H. pylori* in some areas of the gastric mucosa is a risk factor for gastric adenocarcinoma.

Some studies consider gastritis to be more severe in the fundus compared to the antrum, to be a risk factor for gastric adenocarcinoma.[8,9] However, with the increasing number of cancers in the gastric cardia, the accuracy of this index is questionable. Therefore, further topographic study of the severity, grade, and activity of chronic gastritis is needed in different areas of the stomach.[10] The GastroPanel test is recommended for patients with chronic inflammation in the upper respiratory tract and elderly patients with chronic respiratory or

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cardiovascular diseases who cannot undergo endoscopy to diagnose gastrointestinal problems. The GastroPanel test is recognized as a simple, non-invasive, comfortable and safe option for patients.

Today, the role of *H. pylori* as one of the main causes of chronic gastritis is no longer disputed. Gastritis caused by *H. pylori* has been identified as type B gastritis or chronic atrophic gastritis (CAG) , according to the International Classification of Gastritis.[11] On the one hand, *H. pylori* is part of the natural bacterial flora of the gastrointestinal tract, and it is not always necessary to remove the gastric mucosa for sampling, as almost half of the world's population is infected with this bacterium. On the other hand, approximately 3% of people infected with *H. pylori* develop atrophic gastritis, which leads to gastric cancer in most cases and to gastric ulcer in 50% of cases. Overall, eradication of *H. pylori* infection can treat atrophic gastritis; therefore, the risk of diseases associated with atrophic gastritis is reduced or eliminated.[12]

Currently, there are no clear criteria for the treatment of *H. pylori,* and in a large proportion of patients, treatment is prescribed irrationally. This can lead to the emergence of bacterial resistance to antibiotics, with negative consequences for patients with *H. pylori* infection due to unnecessary treatments. Commonly, when a patient complains of indigestion, endoscopy is immediately prescribed for diagnostic purposes. However, this method is aggressive and poses a great risk to the patient.

To accurately diagnose and treat *H. pylori* gastritis, it is necessary to provide accurate and non-invasive methods that can be confidently used to assess the gastric mucosa and *H. pylori* infection. After years of basic medical research in Finland, the Biohit GastroPanel test was developed based on the enzyme-linked immunosorbent assay (ELISA). Overall, by using blood tests, the functional activity of the entire gastric mucosa can be determined. The GastroPanel algorithm for the diagnosis of CAG involves the evaluation of the aforementioned biomarkers. This algorithm offers a final diagnosis and risk assessment, as shown in Figure 1.

Objectives

As the use of GastroPanel for identifying patients with atrophic gastritis, intestinal metaplasia, and dysplasia is under debate, the present study aimed to investigate the efficacy of this diagnostic biomarker.

Materials and Methods

This cross-sectional study (a diagnostic test accuracy study) was performed in Shiraz, Iran, during 2017-2019. The GastroPanel test measures four indicators: IgG antibodies against *H. pylori,* pepsinogen I (PGI) level, pepsinogen II (PGII) level, and gastrin-17 (G17) level. The presence of all these parameters indicates *H. pylori* infection, as well as atrophy. A total of 153 patients (62.7% female; mean age, 63.7 years; 37.3% male; mean age, 64.9 years) were referred to Motahari Clinic and Shahid Faghihi Hospital of Shiraz for endoscopy of the upper gastrointestinal tract.

The inclusion criteria were patients over 50 years with clinical signs of indigestion. The exclusion criteria were as follows: malignant diseases of the liver, kidneys, lungs, endocrine, metabolism, or blood; previous treatment for *H. pylori*; history of alcohol or drug abuse; and pregnancy. Proton pump inhibitor (PPI) therapy was not considered as an exclusion criterion in this study because most

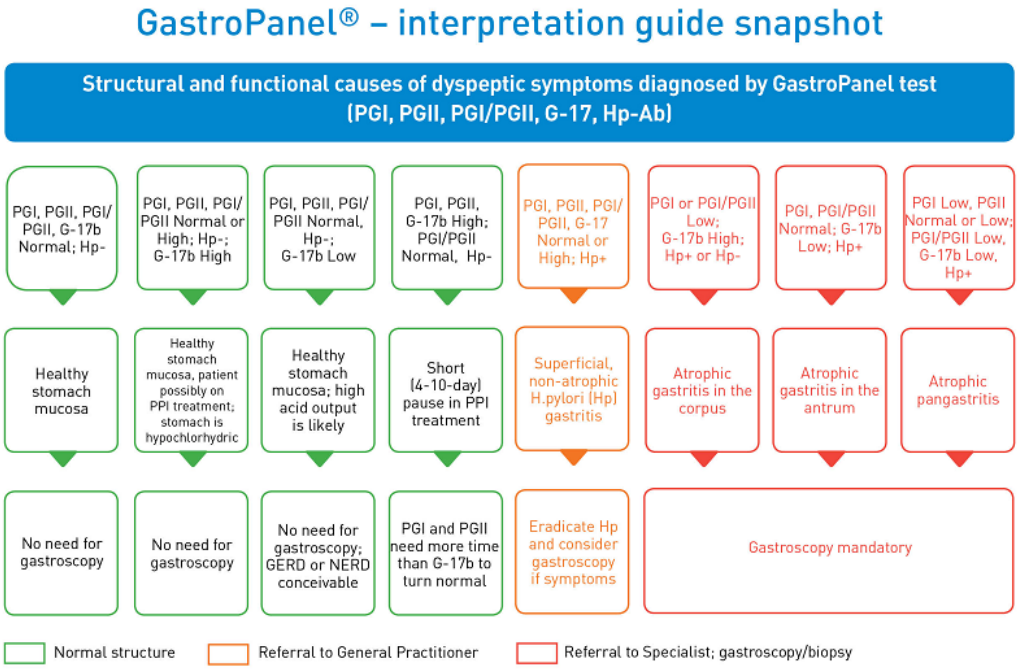

Figure 1. GastroPanel algorithm for the diagnosis of CAG

patients undergoing upper gastrointestinal endoscopy had previously used these drugs.

Biochemical Tests

The serum levels of G17, PGI, and PGII and baseline *H. pylori* were measured using a commercial ELISA kit (Biohit plc, Helsinki, Finland). Fasting blood samples were taken from all the patients. The patients did not receive gastric acid secretion inhibitor drugs, including PPIs, for two weeks before sampling. The EDTA tubes were centrifuged for 15 minutes. Next, 50 µL of G17 stabilizer was added to the plasma. The blood samples were stored at -20°C until further tests. All the tests were performed in the laboratory of the gastroenterology research center of Shiraz University of Medical Sciences, Shiraz, Iran.

Histopathological Analysis

For sampling, one sample was taken from the antrum and two samples from the gastric body. After transferring the samples to the laboratory, they were processed using standard methods and molded in paraffin. Next, 5-micron sections were prepared from the molds, stained by hematoxylin and eosin (H&E) method, and studied by pathologists for different histopathological variables. The second pathologist of the medical team examined all the slides with important findings, such as cancer, dysplasia, and metaplasia. In case of diagnostic disagreement, the slides were re-examined with the participation of both pathologists. Out of every 10 slides studied, one slide was randomly selected for re-examination by the second pathologist. Diagnostic indicators for gastritis were taken from the updated Sydney Classification of Gastritis.

Several variables were examined in this study. Generally, gastritis refers to the presence of inflammatory cells of any kind in the lamina propria of the gastric mucosa. However, the presence of several lymphocytes and plasma cells in the normal antral and cardia mucosa was not considered as gastritis. The rate of lymphocyte and plasma cell infiltration was considered as the grade, and the rate of neutrophil infiltration was considered as gastritis activity.[13] Besides, intensity and activity were classified from zero to three, and the average values were included in all calculations. *H. pylori* infection was confirmed when both rapid urease test and histology were positive, whereas the result was considered negative when both tests were negative (Table 1).

Statistical Methods

The standard deviation (SD) and mean indexes were calculated for quantitative variables, and 95% confidence interval (CI) was measured for qualitative variables. To compare the mean values of quantitative variables, *t* test or Wilcoxon test was used, depending on the normal distribution of data. For comparing the mean values of more than two groups, one-way analysis of variance (ANOVA) was used by measuring R squared (R^2) and partial eta squared (η^2) for linear evaluations. Besides, percentages were compared using χ^2 test. A P value less than 0.05 was considered statistically significant.

Moreover, a receiver operating characteristic (ROC) curve was used to calculate the overall diagnostic performance of G17, PGI, PGII, and PGI/PGII ratio for the detection of CAG, as well as *H. pylori* antibodies for the detection of *H. pylori* infection. If the area under the ROC curve (AUC) was acceptable (0.70), the best cutoff point was measured, and then the sensitivity of analysis and probability ratios were calculated. Besides, the accuracy of the GastroPanel algorithm was evaluated against histology (gold standard). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios were also calculated. All statistical analyses were performed in SPSS for Windows version 24.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 20.23 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

Gastrin-17

The mean G17 levels significantly increased in patients with body CAG (9.7 vs. 32.8 pmol/L; mean = 19.5 pmol/L, SD: 5.3 pmol/L, $P = 0.04$). Nevertheless, it reduced in patients with antrum CAG (1.8 vs. 29.1 pmol/L; mean = 9.05 pmol/L, SD = 6.7 pmol/L, $P < 0.01$). Moreover, the AUC for G17 was calculated to detect antral CAG (0.91), body CAG (0.97), and multifocal CAG (0.88). The cutoff point for antral CAG was 6.0 pmol/L, with sensitivity, specificity, PPV, and NPV of 71.4% (95% CI: 59.4–81.6%), 98.8% (95% CI: 93.4–99.8%), 17.2%, and 92.7%, respectively; the positive and negative likelihood ratios were 59.2 and 0.29, respectively.

The best cutoff point for diagnosing body CAG was 16.5 pmol/L, with sensitivity, specificity, PPV, and NPV of 88.2% (95% CI: 76.7–100%), 86.3% (95% CI: 79.5–91.6%), 23.5% (95% CI: 11–35%), and 95.5% (95% CI: 91–

Table 1. Levels of biomarkers depending on the histological diagnosis

	Body atrophy		Antral atrophy		Non-atrophic gastritis		Multifocal atrophy	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gastrin (pmol/L)	24.22	4.9	5.33	3.95	9.88	2.47	17.44	3.47
PG I (µg/L)	105.9	54.9	110.8	53.3	110.0	54.2	122.0	52.7
PG II (µg/L)	17.04	11.61	16.49	11.41	14.58	8.88	18.07	10.99
PG I/PG II	7.62	4.39	9.13	8.6	9.37	6.06	10.38	11.4
H. pylori Ab (EIU)	33.61	15.51			16.11	11.89	95.36	34.1

100%), respectively; the positive and negative likelihood ratios were also 7.32 and 0.0, respectively. Moreover, the best cutoff point for diagnosing multifocal atrophy was 13.0 pmol/L, with sensitivity, specificity, PPV, and NPV of 96.8% (95% CI: 83.2–99.5%), 81.1% (95% CI: 73.1–87.7%), 56.6%, and 99%, respectively; the positive and negative likelihood ratios were 5.13 and 0.04, respectively (Figure 2).

Pepsinogen I

In terms of the serum PG level, the difference between patients with and without body atrophy was not significant (117 vs. 110.5 µg/L). Also, comparison of the serum PG level between patients with and without antral atrophy showed no significant difference (114.2 vs. 108.9 µg/L). The AUCs for antral and body atrophy were calculated to be 0.513 and 0.551, respectively. The AUC was also determined for each condition, which was unacceptably low. Due to poor results, the cutoff point was not calculated (Figure 3).

Pepsinogen II

There was no significant difference in the level of PGII between the groups. The characteristic ROC curve was drawn to detect atrophy in the antrum and body. The AUCs were 0.507, 0.555, and 0.554, respectively, which were not acceptable. The best cutoff point for diagnosing body atrophy was 30.28 µg/L, with sensitivity of 28.6% (95% CI: 8.6–58.1%), specificity of 93.5% (95% CI: 88.1–97.0%), PPV of 19% (95% CI: 10–28%), and NPV of 94.2% (95% CI: 88–100%); the positive likelihood ratio was 4.41, and the negative likelihood ratio was 0.76 (Figure 4).

PGI/PGII Ratio

There was no significant difference in the PGI/PGII ratio index in different atrophied gastric areas. The AUC for the subsurface level was unacceptable for diagnosis of atrophy in all cases: antral atrophy, 0.54; body atrophy, 0.544; and multifocal atrophy, 0.51 (Figure 5).

Helicobacter pylori Antibodies

To diagnose *H. pylori* infection, the patients' antibody levels were measured by the ELISA method. The mean level of antibodies was significantly different between infected and non-infected patients (65.8 vs. 18.6 EIU, $P=0.01$). The AUC for infection diagnosis was 0.97. The best cutoff point was 36.9 EIU. The accuracy of the cutoff point was as follows: sensitivity, 93.8% (95% CI: 87.0–97.7%); specificity, 94.6% (95% CI: 85.1–98.8%); PPV, 96.8%; NPV, 89.8%; positive likelihood ratio, 17.51; and negative likelihood ratio, 0.07 (Figure 6).

Discussion

This study aimed to compare the GastroPanel test results with pathological findings in patients with signs and symptoms of gastritis, presenting to hospitals in Shiraz, Iran. In some previous studies, based on Biohit's claims,

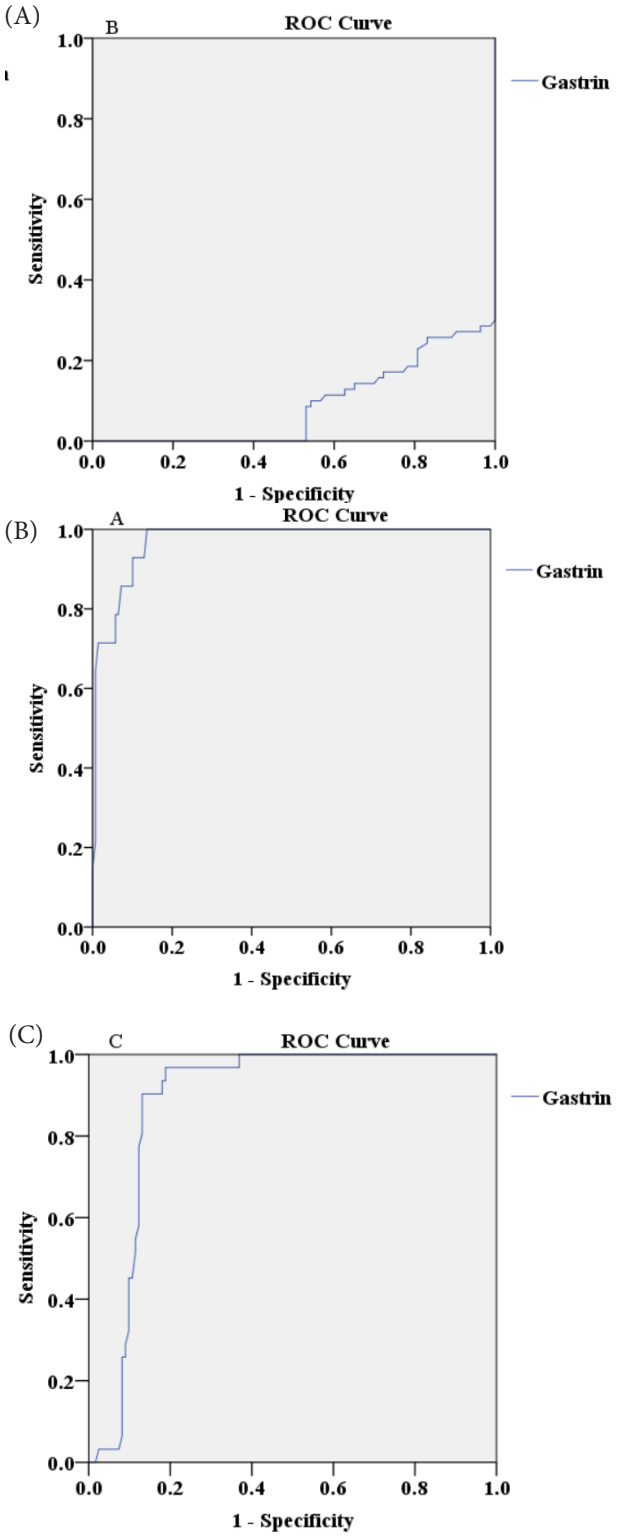

Figure 2. Gastrin-17: area under the ROC curve (AUC) for the diagnosis of (A) Antral atrophy; (B) Body atrophy; and (C) Multifocal atrophy. ROC: receiver operating characteristic

the GastroPanel kit has been proposed as a non-invasive method for diagnosing gastric atrophy, as well as various degrees of atrophy.[10,14-16] Nevertheless, there is some controversy about this issue,[17] and the results of the present study did not confirm this assumption.

In the present study, there was a decrease in the G17 level of patients with antral atrophy and an increase in

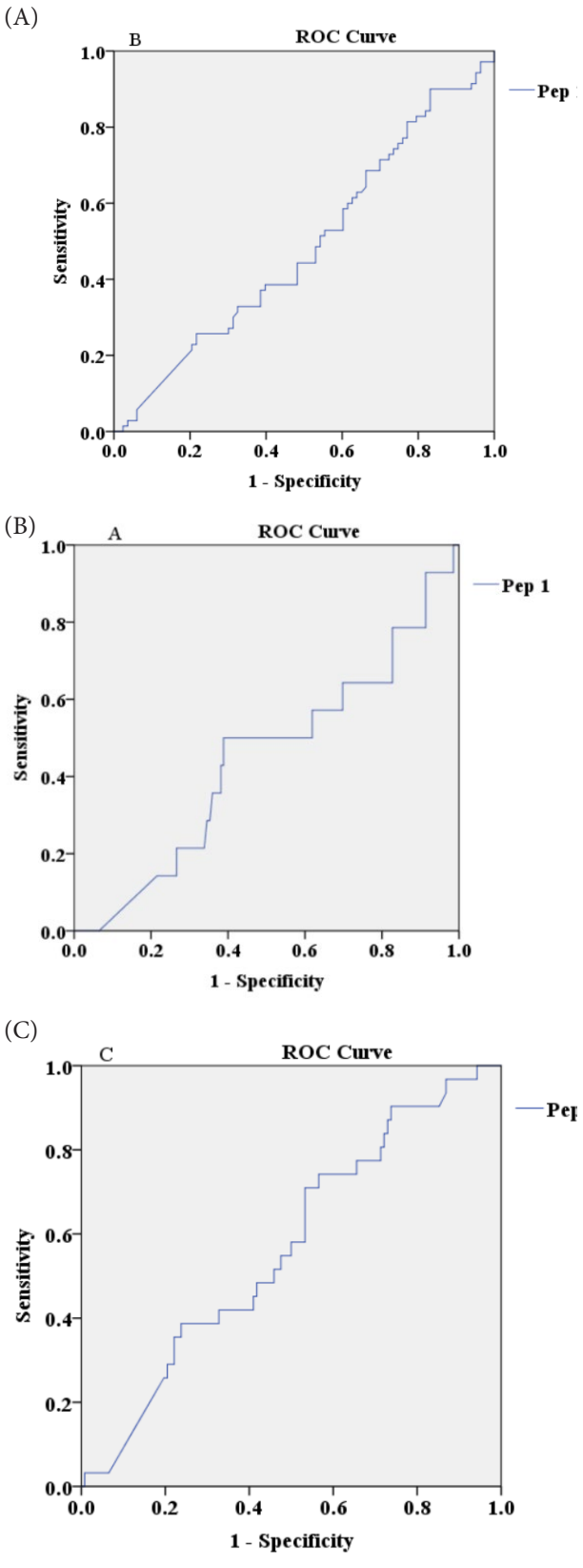

Figure 3. Pepsinogen I: area under the ROC curve (AUC) for the diagnosis of (A) Antral atrophy; (B) Body atrophy; and (C) Multifocal atrophy. ROC: receiver operating characteristic

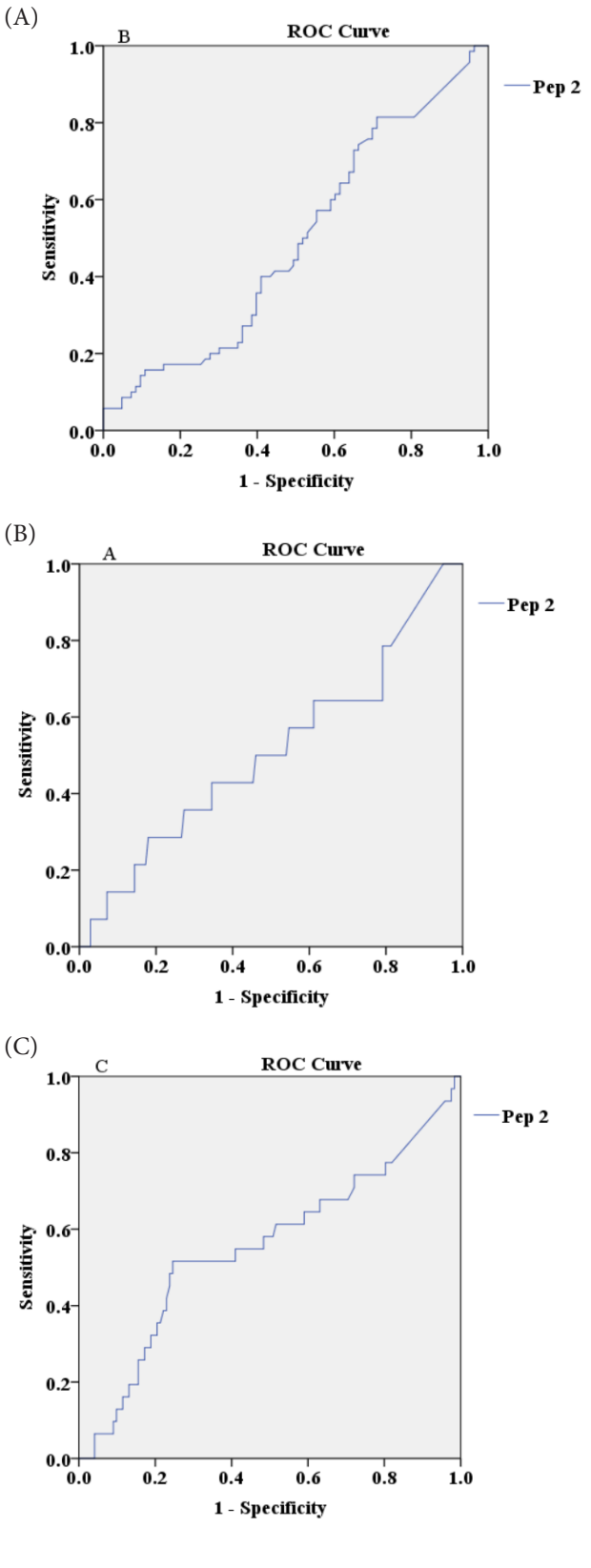

Figure 4. Pepsinogen II: area under the ROC curve (AUC) for the diagnosis of (A) Antral atrophy; (B) Body atrophy; (C) Multifocal atrophy. ROC: receiver operating characteristic.

increase in PGI in patients with antral atrophy, there was a downward trend in PGI levels. Based on our findings, PGI and gastric atrophy are not significantly related.

Although there is evidence suggesting a significant relationship between pepsinogen and atrophic gastritis,

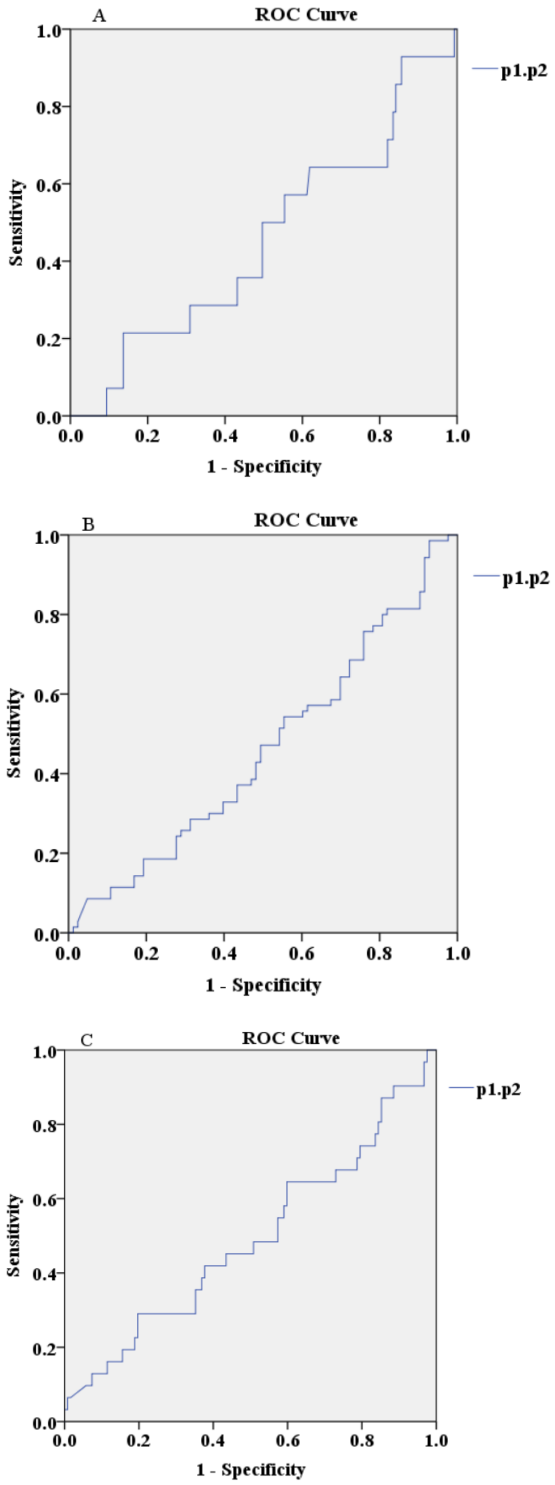

Figure 5. Pepsinogens I/II: area under the ROC curve (AUC) for the diagnosis of (A) Antral atrophy; (B) Body atrophy; (C) Multifocal atrophy. ROC: receiver operating characteristic

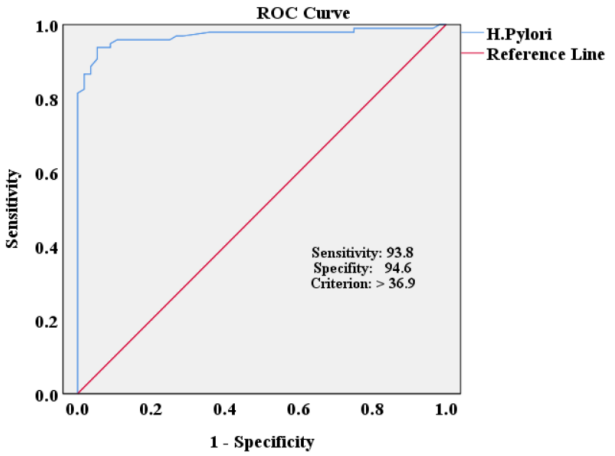

Figure 6. *Helicobacter pylori*; Area under the ROC curve (AUC) for infection diagnosis

no significant relationship was found in the present study, even considering the presence of atrophy in different areas of the stomach.[12,19,20] Since PGII is secreted in all areas of the stomach, a decrease in PGII levels is expected in CAG, besides body atrophy 4-6, 8, 15. In patients with body atrophy, there is a significant increase in PGII levels. In the GastroPanel system, the PGI/PGII ratio is relevant for diagnosing body atrophy; however, in the present study, it showed no practical value. The accuracy of antibody levels against *H. pylori* for the diagnosis of *H. pylori* infection has been controversial among physicians and researchers for many years.[21,22] Generally, antibody levels against *H. pylori* have many fluctuations in different patients; therefore, they cannot be used alone to definitely diagnose *H. pylori* infection. According to the results of the current study, high levels of antibodies against *H. pylori* can indicate a previous infection with *H. pylori*. Nevertheless, most researchers and physicians believe that *H. pylori* antibody tests cannot be used as reliable methods to diagnose an active infection.[23,24]

As claimed by the designers of the GastroPanel test, this kit is a non-invasive method not only for diagnosing high-risk cases of gastric cancer, but also for the early differentiation of gastric mucosal lesions from non-atrophic gastritis and gastric cancer. Various unknown variables can affect the accuracy of this kit or any tests in this kit. Endoscopy allows physicians to observe the gastrointestinal wall more efficiently and accurately and detect the smallest intestinal problems; therefore, there is a possibility of bias by using this kit. The GastroPanel test uses special algorithms that are probably based on the cutoff combinations of all tests. Comparison of the results with the gold standard (pathological examination) in this study showed the very low accuracy of the GastroPanel test, which could not detect almost half of atrophies (sensitivity, 50%).

One of the limitations of this study was the low prevalence of atrophy in the population, which increased the CIs. Therefore, to prevent bias, more attention should be paid to the CIs of sensitivity and specificity.

Conclusion

Based on the current findings, the tests included in the GastroPanel kit lacked sufficient accuracy to diagnose atrophy individually. According to the results, the use of this commercial software cannot be recommended for inpatient diagnosis. Therefore, further studies are needed to produce and present a simple, practical, and non-

invasive method for the diagnosis of gastric diseases, such as atrophic gastritis.

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Authors' Contribution

Critical revision of the manuscript: Gholamreza Sivand Zadeh; study concept and design: Abbas Zahmatkesh; data acquisition, analysis and interpretation of data, and drafting of the manuscript: Saeid Amiri Zadeh Fard; pathological examinations and interpretation of data: Mohammad Hossein Anbardar; supervision of study processes: Kamran Bagheri Lankarani. All the authors contributed to the final revision of this manuscript.

Competing Interests

The authors declare no conflict of interest related to this work.

Data Availability Statement

The data that support the findings of this study are available upon request from the corresponding author.

Ethical Approval

The Ethics Committee of Shiraz University of Medical Sciences approved this study (IR.SUMS.MED.REC.1397.109).

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Informed Consent

Written informed consent was obtained from all participants included in this study.

References

1. Schulz C, Schütte K, Koch N, Vilchez-Vargas R, Wos-Oxley ML, Oxley APA, et al. The active bacterial assemblages of the upper GI tract in individuals with and without *Helicobacter* infection. *Gut* 2018;67(2):216-25. doi: 10.1136/gutjnl-2016-312904
2. Shah SC, Gawron AJ, Mustafa RA, Piazuelo MB. Histologic subtyping of gastric intestinal metaplasia: overview and considerations for clinical practice. *Gastroenterology* 2020;158(3):745-50. doi: 10.1053/j.gastro.2019.12.004
3. Shah SC, Gawron AJ, Li D. Surveillance of gastric intestinal metaplasia. *Am J Gastroenterol* 2020;115(5):641-4. doi: 10.14309/ajg.0000000000000540
4. Huang RJ, Choi AY, Truong CD, Yeh MM, Hwang JH. Diagnosis and management of gastric intestinal metaplasia: current status and future directions. *Gut Liver* 2019;13(6):596-603. doi: 10.5009/gnl19181
5. Miller AK, Williams SM. *Helicobacter pylori* infection causes both protective and deleterious effects in human health and disease. *Genes Immun* 2021;22(4):218-26. doi: 10.1038/s41435-021-00146-4
6. Mommersteeg MC, Yu J, Peppelenbosch MP, Fuhler GM. Genetic host factors in *Helicobacter pylori*-induced carcinogenesis: emerging new paradigms. *Biochim Biophys Acta Rev Cancer* 2018;1869(1):42-52. doi: 10.1016/j.bbcan.2017.11.003
7. Curado MP, de Oliveira MM, de Araújo Fagundes M. Prevalence of *Helicobacter pylori* infection in Latin America and the Caribbean populations: a systematic review and meta-analysis. *Cancer Epidemiol* 2019;60:141-8. doi: 10.1016/j.canep.2019.04.003
8. Gupta S, Li D, El Serag HB, Davitkov P, Altayar O, Sultan S, et al. AGA clinical practice guidelines on management of gastric intestinal metaplasia. *Gastroenterology* 2020;158(3):693-702. doi: 10.1053/j.gastro.2019.12.003
9. Nardone G, Rocco A, Staibano S, Mezza E, Autiero G, Compare D, et al. Diagnostic accuracy of the serum profile of gastric mucosa in relation to histological and morphometric diagnosis of atrophy. *Aliment Pharmacol Ther* 2005;22(11-12):1139-46. doi: 10.1111/j.1365-2036.2005.02734.x
10. Zagari RM, Rabitti S, Greenwood DC, Eusebi LH, Vestito A, Bazzoli F. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-*Helicobacter pylori* antibodies serum assays for the diagnosis of atrophic gastritis. *Aliment Pharmacol Ther* 2017;46(7):657-67. doi: 10.1111/apt.14248
11. El-Zimaity H, Choi WT, Lauwers GY, Riddell R. The differential diagnosis of *Helicobacter pylori* negative gastritis. *Virchows Arch* 2018;473(5):533-50. doi: 10.1007/s00428-018-2454-6
12. Lahner E, Carabotti M, Annibale B. Treatment of *Helicobacter pylori* infection in atrophic gastritis. *World J Gastroenterol* 2018;24(22):2373-80. doi: 10.3748/wjg.v24.i22.2373
13. Patil PA, Zhang X. Pathologic manifestations of gastrointestinal and hepatobiliary injury in immune checkpoint inhibitor therapy. *Arch Pathol Lab Med* 2021;145(5):571-82. doi: 10.5858/arpa.2020-0070-RA
14. Makristathis A, Hirschl AM, Mégraud F, Bessède E. Review: diagnosis of *Helicobacter pylori* infection. *Helicobacter* 2019;24 Suppl 1:e12641. doi: 10.1111/hel.12641
15. Loong TH, Soon NC, Nik Mahmud NRK, Naidu J, Rani RA, Abdul Hamid N, et al. Serum pepsinogen and gastrin-17 as potential biomarkers for pre-malignant lesions in the gastric corpus. *Biomed Rep* 2017;7(5):460-8. doi: 10.3892/br.2017.985
16. Tepes B, Seruga M, Vujasinovic M, Urlep D, Ljepovic L, Brglez JN, et al. Premalignant gastric lesions in patients included in national colorectal cancer screening. *Radiol Oncol* 2018;52(1):7-13. doi: 10.1515/raon-2017-0054
17. Grad C, Pop A, Gaborean E, Grad S, Dumitrascu D. Value of GastroPanel in the diagnosis of atrophic gastritis. *Exp Ther Med* 2021;22(5):1347. doi: 10.3892/etm.2021.10782
18. Li Y, Xia R, Zhang B, Li C. Chronic atrophic gastritis: a review. *J Environ Pathol Toxicol Oncol* 2018;37(3):241-59. doi: 10.1615/JEnvironPatholToxicolOncol.2018026839
19. Song JH, Kim YS, Heo NJ, Lim JH, Yang SY, Chung GE, et al. High salt intake is associated with atrophic gastritis with intestinal metaplasia. *Cancer Epidemiol Biomarkers Prev* 2017;26(7):1133-8. doi: 10.1158/1055-9965.epi-16-1024
20. Lahner E, Conti L, Annibale B, Corleto VD. Current perspectives in atrophic gastritis. *Curr Gastroenterol Rep* 2020;22(8):38. doi: 10.1007/s11894-020-00775-1
21. Syrjänen K. A panel of serum biomarkers (GastroPanel®) in non-invasive diagnosis of atrophic gastritis. Systematic review and meta-analysis. *Anticancer Res* 2016;36(10):5133-44. doi: 10.21873/anticanres.11083
22. Paloheimo L, Tiusanen T, Suovaniemi O, SyrjÄnen K. Serological biomarker test (GastroPanel®) in the diagnosis of functional gastric disorders, *Helicobacter pylori* and atrophic gastritis in patients examined for dyspeptic symptoms. *Anticancer Res* 2021;41(2):811-9. doi: 10.21873/anticanres.14833
23. Gisbert JP, Molina-Infante J, Amador J, Bermejo F, Bujanda L, Calvet X, et al. IV Spanish consensus conference on

Helicobacter pylori infection treatment. *Gastroenterol Hepatol* 2016;39(10):697-721. doi: 10.1016/j.gastrohep.2016.05.003

24. El-Serag HB, Kao JY, Kanwal F, Gilger M, LoVecchio F, Moss SF, et al. Houston consensus conference on testing for *Helicobacter pylori* infection in the United States. *Clin Gastroenterol Hepatol* 2018;16(7):992-1002.e6. doi: 10.1016/j.cgh.2018.03.013