Validation of Serum Assays for the Diagnosis of Gastritis

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Title of the study: Validation of Blood Test Finding for the Diagnosis of Gastritis and Gastric Neoplasms

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Rationale of the study

Helicobacter pylori-seropositive rates are decreasing in South Korea. Seroprevalence was 74.3% in 1990, but it decreased to 43.9% in 2016. In Koreans, most gastric cancers are related to *H. pylori* infection. *H. pylori*-negative gastric cancers were found only in 2.3% among the 1,833 Korean gastric cancer patients. Despite these facts, the national guideline still recommends biennial gastroscopy for all Koreans aged between 40 and 75 years. Therefore, 8,462,570 (63.1%) Koreans underwent gastric cancer screening among the target population of 13,404,927 individuals in 2021.

In *H. pylori*-seroprevalent populations, diagnostic criteria for naive status should be strict based on histology, endoscopy, and serum pepsinogen (PG) assay findings. Naive condition should be diagnosed only when both invasive and non-invasive *H. pylori* tests show negative

findings. Furthermore, there should be no intestinal metaplasia and atrophy on serum PG assay, endoscopy, and histology findings in H. pylori-naive participants. Based on those findings, *H. pylori* infection will be confirmed when invasive tests or urea breath test was positive. *H. pylori*-naive status will be diagnosed if there was no eradication history, no serologically detected atrophy (PG I ≤70 ng/mL and PG I/II ≤3), and no intestinal metaplasia or atrophy on endoscopy and histology.

This study aimed to determine the validity of blood tests for gastric cancer screening according to the *H. pylori* infection status. We tried to identify significant variables using GastroPanel tests and traditional serum PG assays according to the presence gastric neoplasms.

Study design

Study Type	Observational
Observational Study Model	Cohort
Time Perspective	Prospective
Biospecimen Retention	Samples Without DNA
Biospecimen Description	Blood sample
Enrollment	1490 [Actual]

Primary objective: To determine the validity of blood tests for gastric cancer screening

Endpoints:

- Primary endpoint: Significant blood test findings (*H. pylori* IgG, PGI, PG II, I/II ratio, G-17) indicating the presence gastric neoplasms
- Secondary endpoint: Test findings according to the types of gastric neoplasms

Expected results: GastroPanel test and conventional serum pepsinogen findings would differ according to the presence and types of gastric neoplasms.

Analyzed criteria: Gastric neoplasms were diagnosed when microscopic findings correspond to the international classification of diseases-10 categories C16, D002, D131, and C1884. Adenocarcinomas (C16 and D002) were further divided into advanced gastric cancers (AGCs) and early gastric cancers (EGCs) after resecting the cancers. Gastric adenomas were confirmed among benign neoplasms of the stomach (D131), after the resection. Following excision of submucosal tumors, neuroendocrine tumors (NETs) and gastrointestinal stromal tumors (GISTs) were verified as C16. Primary gastric mucosa-associated lymphoid tissue (MALT) lymphomas were identified as C1884 using the gastric biopsy specimens.

Main variables/endpoints of the analysis

Age (years)
Male sex
Status of *H. pylori* infection
GastroPanel test findings *H. pylori* IgG (EIU) PG I (μg/L) PG II (μg/L) I/II ratio Gastrin-17 (pmol/L)
Conventional serum assays (Chorus tests and HBI PG assays) *H. pylori* IgG (AU/mL) PG I (mg/dL) PG II (mg/dL) I/II ratio

Safety variables: No adverse events during the study period (May 1, 2023 ~ August 30, 2024)

Visits and examinations

Initial visit:

- Blood test for *H. pylori* immunoglobulin G, pepsinogen, and gastrin-17 levels
- Upper gastrointestinal endoscopy and gastric biopsy

Follow-up visit:

- ^{13}C-urea breath test if there is a discrepancy between the *H. pylori* test findings

Study population

Short description of the main inclusion and exclusion criteria

Study Population:	Adult population who visited our center for gastric cancer screening using serum assays
Sampling Method:	Non-Probability Sample
Minimum Age:	18 Years
Maximum Age:	99 Years
Sex:	All
Gender Based:	No
Accepts Healthy Volunteers:	No

Criteria:	Inclusion Criteria: • Individuals who visited for gastric cancer screening Exclusion Criteria: • History of gastrectomy • Renal insufficiency • Severe comorbidities requiring prompt management

Sample size and statistical analysis

Prior to the study, sample size calculation was done for the validation of GastroPanel test in Koreans. Briefly, two–sided tests were used at a significance level of 0.05. Using PASS 2023 (NCSS, LLC. Kaysville, Utah, USA), the power was 0.842 when 414 individuals are included.

Chi-square test was used for categorical variables, while t-test was used for continuous variables to compare the differences between the patients with gastric neoplasms and the controls. When the data showed asymmetrical distribution, Fisher's-exact was used to present categorical variables as proportion, while Kruskal-Wallis test was used to present continuous variables as median value with ranges. ANOVA with Bonferroni correction was used to assess differences between the three groups for continuous variables, while chi-square test with Bonferroni correction was used for categorical variables. Thereafter, independent variables for gastric neoplasms were identified using logistic regression analysis. The results are shown as odds ratio (OR) with 95% confidence intervals (CIs). Correlation analysis was used to identify associations between the blood test results and the severity of

atrophy. The results are shown as correlation coefficient (*r*) values. Furthermore, receiver operating characteristic (ROC) curve analysis was done, and presented as area under the curve (AUC). ROC curves were compared using the McNemar's test. Using PASW statistics (version 28.0; SPSS Inc., Chicago, IL, USA), a *p*-value less than 0.05 was considered significant.

Duration of the study

Study Start:	May 1, 2023 [Actual]
Primary Completion:	August 30, 2024

Additional features on the main concept of the study

Serum pepsinogen (PG) assays are another method used to quantify the severity of atrophy, in addition to endoscopic and microscopic measurements. In contrast to traditional serum PG assays, GastroPanel tests incorporate the measurement of gastrin-17 (G-17), a substance exclusively secreted by the gastric antrum. The G-17 level decreases to less than 1 pmol/L following distal gastrectomy or in the presence of antral atrophy, but it increases to 30 pmol/L when corpus atrophy develops. European studies using GastroPanel tests revealed that gastric atrophy can be identified with low G-17 levels of <1 pmol/L. Nonetheless, this metric is difficult to apply in *H. pylori*-seroprevalent areas where corpus atrophy is common. A Chinese study showed that gastric cancer development is linked to both low (<0.5 pmol/L) and high (>4.7 pmol/L) G-17 levels; however, these are less helpful in clinical practice because G-17 levels of >4.7 pmol/L are frequently observed even in the absence of atrophy. Altogether, it is still uncertain whether adding a G-17 measurement to PG assays would contribute to the detection of gastric neoplasms. Hence, we attempted to identify actual blood levels for

detecting gastric neoplasms rather than focusing on identifying high-risk individuals. Additionally, we tried to confirm the significance of the test results according to the type of gastric neoplasm.