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Corresponding author
Sun-Young Lee, MD, PhD
Department of Internal Medicine,
Konkuk University School of Medicine,
120-1 Neungdong-ro, Gwangjin-gu
Seoul 05030, Korea
E-mail: sunyoung@kuh.ac.kr

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Pepsinogen Assay Findings in Individuals With Gastric Atrophy and Intestinal Metaplasia

Sun-Young Lee

Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea

Serum pepsinogen (PG) testing is widely used as a non-invasive biomarker for gastric atrophy; however, its clinical interpretation varies depending on the severity and distribution of gastritis as well as on the assay methods. Autoimmune gastritis is characterized by markedly decreased PG I levels and PG I/II ratios, along with increased gastrin levels, reflecting profound corpus atrophy. In contrast, *Helicobacter pylori*–associated atrophy typically shows moderate reductions in PG I levels and PG I/II ratios, with variability according to the extent of antral and corpus involvement. Accumulating evidence indicates that PG testing is more effective at identifying severe atrophy and higher Operative Link on Gastritis Assessment stages than detecting mild atrophy. Notably, cutoff values differ substantially between assay systems, with higher PG I and PG I/II cutoff values observed in GastroPanel tests than in East Asian kits interpreted with the ABC method. Overall, PG testing is useful for detecting advanced corpus atrophy and stratifying gastric cancer risk when combined with gastrin measurement, but has limited sensitivity for early-stage disease. Monitoring low PG I/II ratios and high gastrin levels may improve risk assessment, particularly in patients with corpus atrophy or persistent intestinal metaplasia after *H. pylori* eradication.

Keywords Atrophic gastritis; Gastrin; *Helicobacter pylori*; Pepsinogens; Metaplasia.

INTRODUCTION

Pepsinogen (PG) is a precursor of pepsin, a gastric protease, that is converted into pepsin to aid in food digestion.[1] Pepsinogen I (PG I) is made by the chief cells and mucous neck cells in the gastric corpus, and pepsinogen II (PG II) is made by the gastric oxyntic glands and the duodenal Brunner's gland.[2] Low PG I levels correlate with the severity of atrophy and intestinal metaplasia (IM) in the gastric corpus, whereas high PG II levels correlate with active inflammation induced by *Helicobacter pylori*.[3] Therefore, gastroscopy is recommended when PG I levels or PG I/II ratios are low, especially in the absence of *H. pylori* infection.[4] In addition to low PG I levels and low PG I/II ratios, high gastrin levels help discriminate patients

with gastric neuroendocrine tumors (NETs), adenomas, and adenocarcinomas.[5]

Despite the widespread use of serum PG testing, its clinical interpretation remains challenging because of the variability in cutoff values across different assay systems and patient populations.[6] This inconsistency may lead to misclassification of high-risk individuals in clinical practice. Moreover, discrepancies between serologic findings and endoscopic or histologic atrophy may occur, especially in individuals with advanced or heterogeneous gastric mucosal changes. Such discrepancies highlight the need for cautious interpretation of PG results and underscore the complementary role of endoscopy. This review aims to not only summarize PG I levels, PG I/II ratios, and gastrin levels according to the severity and location of gastric atrophy and IM but also critically evaluate differences in diagnostic performance across assay methods and clinical conditions. Furthermore, practical considerations for interpreting PG test results in real-world settings are discussed, with their implications for gastric cancer risk stratification.

CORPUS-DOMINANT ATROPHY (TYPE A GASTRITIS)

Type A gastritis consists of autoimmune gastritis (AIG) that manifests as atrophy or IM in the corpus without involving the antrum. In *H. pylori*-endemic areas, AIG is diagnosed when serum anti-parietal cell antibodies (APCAs) or anti-intrinsic factor antibodies are positive in patients with corpus-dominant atrophy detected by endoscopy or microscopy.[7] During gastroscopy, transparent submucosal vessels are observed in the corpus without gastric folds and atrophic borders. Typical microscopic findings include loss of parietal cells, chief cells, and gastric glands in the corpus replaced by IM, pseudopyloric metaplasia, and enterochromaffin-like (ECL) cells.[7]

PG assay findings in patients with AIG

Patients with AIG show lowest PG I levels and PG I/II ratios among all types of gastritis because of loss of chief cells (Table 1). In a Chinese study, most patients with AIG showed low PG I/II ratios of ≤1 and low PG I levels of <10 ng/mL.[8] In a Japanese study, PG I/II ratios <1.8, PG I levels <20.1 ng/mL, and gastrin levels >355 pg/mL were useful for discriminating patients with AIG.[9] A study from Türkiye reported that PG I/II ≤1.9 and PG I ≤13.5 ng/mL detected AIG with high sensitivity and specificity.[10] Compared with Japanese kits, GastroPanel tests (Biohit Oyj) yield higher cutoff values for PG I/II ratios (≤3.1 vs. ≤2.33).[11] The only exception is a study from Russia showing a low PG I/II cutoff ratio of ≤2 for detecting AIG even with the use of GastroPanel tests.[12] In that study, 80.2% of the participants had *H. pylori* infection; hence, PG I/II ratios were further decreased because of increased PG II levels.

GastroPanel tests generally yield twice higher PG I levels than East Asian kits interpreted with the ABC method, leading to different thresholds for defining atrophy.[13] A study reported that advanced corpus atrophy (PG I/II ≤2 and PG I ≤30 ng/mL) measured by a latex-enhanced turbidimetric immunoassay (L-TIA) kit (HBI Co.) was more consistent with serologic atrophy determined by the GastroPanel test than corpus atrophy (PG I/II ≤3 and PG I ≤70 ng/mL) determined by the ABC method.[14] Similarly, another Korean study revealed that a criteria using

Table 1. Studies on cutoff values of pepsinogen levels for detecting autoimmune gastritis

Test (company)	Number of participants (country)	Cutoff value (sensitivity, specificity)	*H. pylori* positive rate	Study
ELISA (Biohit)	344 (France)	PG I/II ≤3.1 (95.3%, 97.4%) PG I ≤38.7 pg/mL (97.7%, 97.4%)	14.9% in AIG (30.3% in controls)	Chapelle et al. (2023)[11]
	87 (Latvia)	PG I/II <3 (79%, 90%)	63.0% in AIG (45.5% in controls)	Krike et al. (2022)[56]
	237 (Russia)	PG I/II ≤2 (80.7%, 78.5%) PG I <22.5 μg/L (72.6%, 88.0%)	80.2%	Chebotareva et al. (2025)[12]
ELISA (Eiken)	332 (Japan)	PG I/II <1.8 (83.9%, 93.7%) PG I <20.1 ng/mL (90.3%, 91.0%) Gastrin >355 pg/mL (83.9%, 93.4%)	19.4% in AIG (35.2% in controls)	Kishikawa et al. (2022)[9]
ELISA (Epitope)	147 (Türkiye)	PG I/II ≤1.9 (100%, 100%) PG I ≤13.5 ng/mL (100%, 100%)	77.4% in AIG (71.9% in controls)	Ogutmen and Bektas (2022)[10]
CLEIA (Fujirebio)	344 (France)	PG I/II ≤2.33 (95.6%, 95.6%) PG I ≤16.3 pg/mL (95.6%, 97.1%)	14.9% in AIG (30.3% in controls)	Chapelle et al. (2023)[11]
CLEIA (Abbott)	28 (Japan)	PG I/II <2.1 (100%, 95%) PG I <14.5 ng/mL (83%, 85%)	0% (64.3% with past infection)	Wada et al. (2022)[57]

ELISA, enzyme-linked immunosorbent assay; PG, pepsinogen; AIG, autoimmune gastritis; CLEIA, chemiluminescent enzyme immunoassay.

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PG I/II ≤3 and PG I ≤70 ng/mL measured by the L-TIA kit was consistent with a combination of PG I/II ≤5.3 and PG I ≤100 ng/mL measured by GastroPanel tests.[15] These differences may arise from different calibration methods used in PG assays.[16]

Test findings in patients with AIG according to *H. pylori* infection status

Patients with both AIG and *H. pylori* infection exhibit higher PG II levels and lower PG I levels than those without *H. pylori* infection.[17] Compared with *H. pylori*–naïve patients with AIG, *H. pylori*–exposed patients with AIG show lower gastrin levels because of atrophy in the antrum.[18] Notably, *H. pylori* infection status is often confused in patients with AIG because non–*H. pylori*, urease-producing bacteria are increased because of high gastric pH, which leads to false-positive test findings in the rapid urease tests and urea breath tests.[19] Furthermore, spontaneous regression of *H. pylori* may occur in AIG because of severe atrophy and IM.

Diagnosis of AIG in *H. pylori*–infected stomachs is challenging owing to full-thickness inflammation that conceals AIG (Fig. 1). Early-stage AIG may start with autoimmune activity following *H. pylori* infection, and APCA plays an important role in progression of corpus atrophy.[20] Conversely, some autoimmune activities are suppressed because *H. pylori* inhibits CD4+ T helper 1 (Th1) cells.[21] In that study, suppression of Th1-mediated AIG development was terminated after *H. pylori* eradication, allowing autoreactive Th1 cells to produce autoantibodies that attack parietal cells. As a result, some cases of AIG were detected after *H. pylori* eradication.

Gastrin levels and gastric cancer risk in patients with AIG

H. pylori gastritis is not rare entity in patients with AIG who develop gastric cancer.[22] In a recent study, gastric adenocarcinoma was 15.6 times more common in patients with gastric NETs with ≥3 risk factors, such as severe corpus atrophy, micronodular ECL hyperplasia, positive *H. pylori* serology findings, low hemoglobin levels, low vitamin B_{12} levels, low ferritin levels, and high gastrin levels.[23] Patients with AIG and *H. pylori* gastritis with high gastrin levels require gastroscopic surveillance because parietal cell loss leads to overproduction of gastrin, which binds to the cholecystokinin-2 receptor to stimulate parietal cells and proliferate ECL cells.[24] Avoiding long-term use of potassium-competitive acid blockers (PCABs) and proton pump inhibitors (PPIs) is important in patients with gastric atrophy because these drugs further stimulate gastrin production.[25]

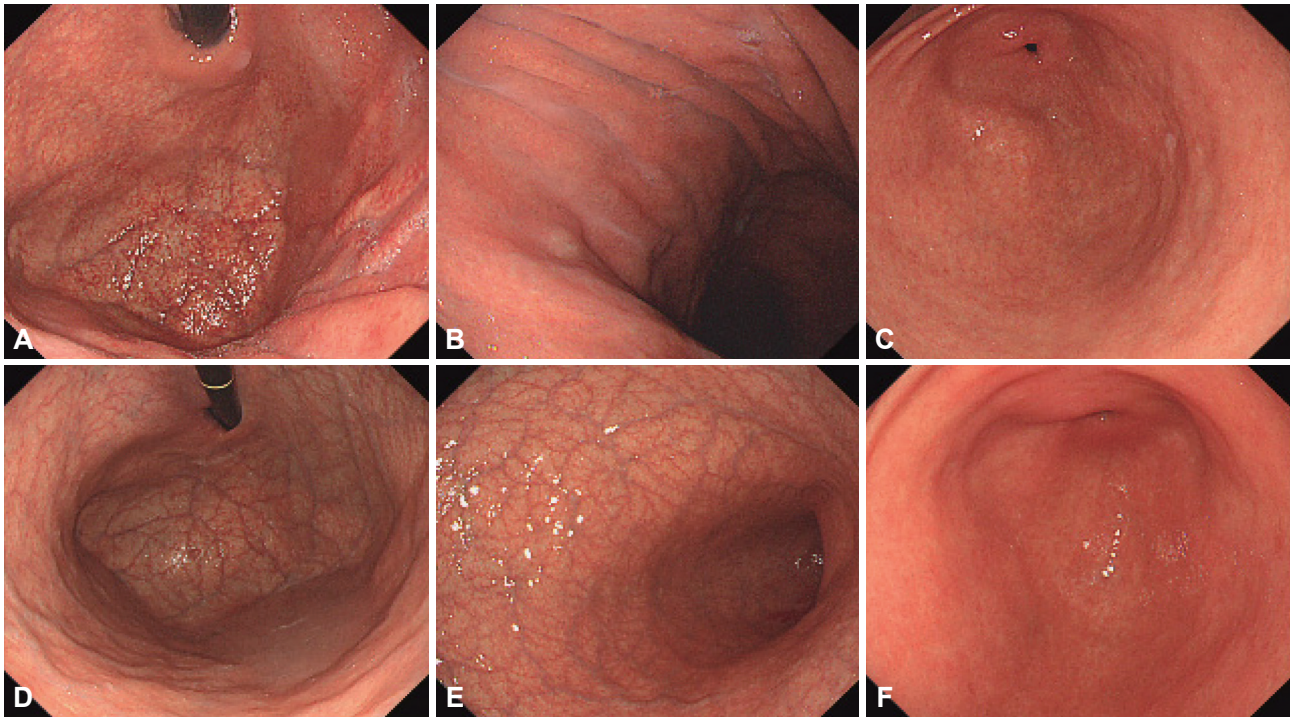

Fig. 1. Autoimmune gastritis masked by *H. pylori*–associated inflammation. A: Diffuse redness in the fundus and upper body indicates *H. pylori* infection. B: Thick gastric folds and diffuse redness are observed in the greater curvature side of the body. C: The antrum has irregular mucosal nodularity, indicating metaplastic gastritis. D: One year after successful *H. pylori* eradication, diffuse redness is replaced by atrophy. Serologic atrophy (PG I: 15.5 ng/mL, PG II: 17.4 ng/mL, and PG I/II: 0.9) was reported. E: Atrophy is observed without gastric folds. APCA revealed positive test finding. F: There are no notable findings in the antrum. APCA, anti-parietal cell antibodies; PG, pepsinogen.

ANTRUM-DOMINANT ATROPHY (TYPE B GASTRITIS)

Type B gastritis consists of atrophy and IM initiated by *H. pylori* infection, which starts from the opposite side of AIG.[26] When atrophy is limited in the antrum, PG I levels are stable, but PG I/II ratios decrease because of high PG II levels.[27] In addition, gastrin-17 (G-17) levels are low because of the loss of

Table 2. Studies on cutoff values for detecting the severity of gastric atrophy based on the updated Sydney system or the operative link on the gastritis assessment stage

Test (company)	Number of participants (country)	Diagnosis	Cutoff value (sensitivity, specificity)	*H. pylori* positive rate	Study
ELISA (Biohit)	162 (Japan)	Moderate to severe atrophy	PG I/II <3 and/or PG I ≤30 μg/L (40%, 94%)	NA	Iijima et al. (2009)[29]
	404 (Finland)	Moderate to severe atrophy in the antrum	PG I <25 μg/L and fasting G-17 <5 pmol/L (79%, 91%)	34%	Väänänen et al. (2003)[58]
			PG I <25 μg/L and postprandial G-17 <5 pmol/L (83%, 95%)		
ELISA (Eiken)	157 (Kazakhstan)	Moderate to severe atrophy in the corpus	PG I/II ≤2 and PG I ≤30 ng/mL (50.0%, 90.9%)	NA	Mezmale et al. (2019)[28]
			PG I/II ≤3 and PG I ≤70 ng/mL (50.0%, 73.5%)		
	646 (Indonesia)	Moderate to severe atrophy in the corpus	PG I/II <4.75 (81.5%, 78.7%) PG II >12.45 ng/mL (59.3%, 77.1%)	9.1%	Miftahussurur et al. (2022)[59]
	146 (Nepal)	OLGA stages ≥I	PG I/II <4.65 (71.7%, 61.1%)	43.8%	Miftahussurur et al. (2015)[33]
		OLGA stages ≥II	PG I/II <3.45 (86.7%, 66.4%)		
	252 (Myanmar)	OLGA stage ≥I	PG I/II ≤6.25 (62.9%, 76.1%)	48.0%	Myint et al. (2015)[34]
		OLGA stage ≥II	PG I/II ≤5.35 (81.8%, 67.2%)		
CLEIA (Eiken)	319 (Japan)	Moderate to severe atrophy	PG I/II <4.0 (82.6%, 82.9%)	69.0%	Takao et al. (2011)[38]
		Moderate to severe atrophy in the corpus	PG I/II <3.2 (73.6%, 74.6%)		
		≥Closed–type atrophy*	PG I/II <3.9 (68.0%, 66.0%)		
		≥Open–type atrophy*	PG I/II <2.9 (67.9%, 70.4%)		
CLEIA (Fujirebio)	162 (Japan)	Moderate to severe atrophy	PG I/II ≤2.0 and PG I ≤30 μg/L (45%, 96%)	NA	Iijima et al. (2009)[29]
L-TIA (Shima)	2558 (Korea)	≥Mild atrophy	PG I/II <3.0 (63.7%, 60.9%)	60.2%	Lee et al. (2014)[37]
		≥Closed–type atrophy*	PG I/II <3.2 (64.1%, 60.2%)		
CMIA (Abbott)	996 (China)	Mild to moderate atrophy	PG I/II ≤5.15 (41.7%, 74.5%)	40%	Tong et al. (2017)[30]
			PG I ≤50.3 ng/mL (63.9%, 49.1%)		
		Severe atrophy	PG I/II ≤4.28 (76.9%, 83.4%)		
			PG I ≤53.6 ng/mL (76.9%, 47.0%)		
	1922 (China)	Mild to moderate atrophy	PG I/II ≤9.8 (71.1%, 51.8%)	39.4%	Tong et al. (2021)[31]
			PG I ≤73.1 ng/mL (55.7%, 62.1%)		
		Severe atrophy	PG I/II ≤9.09 (88.1%, 53.0%)		
			PG I ≤63.9 ng/mL (59.3%, 67.2%)		
	273 (Vietnam)	OLGA stages ≥II	PG I/II ≤5.2 and PG I ≤63.5 ng/mL (49.4%, 82.1%)	34.1%	Nguyen et al. (2022)[36]
		≥Closed–type 3 atrophy*	PG I/II ≤4.6 and PG I ≤69.0 ng/mL (73.0%, 83.9%)		
CMIA (Shenzen)	300 (China)	OLGA stages II–IV	PG I/II <2.08 (67.80%, 84.23%)	25.7%	Zhang et al. (2025)[32]

*Kimura–Takemoto classification.
ELISA, enzyme-linked immunosorbent assay; PG, pepsinogen; G-17, gastrin-17; NA, not available; OLGA, Operative Link on Gastritis Assessment; CLEIA, chemiluminescent enzyme immunoassay; L-TIA, latex-enhanced turbidimetric immunoassay; CMIA, chemiluminescent microparticle immunoassay.

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G cells in the antrum.

PG levels for detecting the severity of atrophy based on the updated Sydney system

Studies that reported cutoff values for detecting moderate-to-severe atrophy are summarized in Table 2. For detecting more severe atrophy in the corpus, a combination of PG I/II ≤2 and PG I ≤30 ng/mL showed good diagnostic utility with the aid of Japanese assay kits.[28] Similar to the findings in patients with AIG, East Asian kits showed lower PG I/II cutoff ratios than did GastroPanel tests (≤2.0 vs. <3).[29]

In two large-scale studies, patients with severe atrophy had lower PG I/II ratios and PG I levels than those with mild-to-moderate atrophy.[30,31] Sensitivities and specificities for detecting mild-to-moderate atrophy were unsatisfactory in both studies; therefore, PG assay is better suited for detecting patients with severe atrophy than those with mild or moderate atrophy.

PG levels for detecting the severity of atrophy based on the Operative Link on Gastritis Assessment stage

Similar to the updated Sydney system, PG assays perform better in detecting higher Operative Link on Gastritis Assessment (OLGA) stages with severe atrophy (Table 2). A Russian study reported that either PG I/II ≤2 or PG I <22.5 μg/L is useful for detecting OLGA stages III–IV in patients with AIG.[12] A Chinese study reported that PG I/II <2.08 is useful for detecting OLGA stages II–IV.[32] Studies from Nepal and Myanmar showed lower PG I/II cutoff values for detecting OLGA stages ≥II than for detecting OLGA stage ≥I.[33,34] Given the lower sensitivities and specificities for detecting OLGA stage I reported in those studies, PG assays should be used for detecting OLGA stages II–IV.

PG levels for detecting the severity of atrophy based on the Kimura–Takemoto classification

During gastroscopy, the extent of gastric atrophy can be categorized from closed-type 0 (C-0, no atrophy) to Op (open-type pan-atrophy) according to the Kimura–Takemoto classification.[35] A study from Vietnam revealed that a combination of PG I/II ≤4.6 and PG I ≤69.0 ng/mL helped identify individuals with ≥C-3 atrophy.[36] In their study, the sensitivities and specificities were higher when the Kimura–Takemoto classification was used instead of the OLGA stage. In Korea, PG I/II <3.2 could be used to detect closed-type atrophy; however, the sensitivity and specificity were too low to apply in daily practice.[37] In a Japanese study, a lower PG I/II cutoff ratio was needed for detecting open-type atrophy compared with that for closed-type atrophy (<2.9 vs. <3.9).[38] Taken together, PG assay showed higher accuracy for detecting open-type atrophy than closed-type atrophy.

PG levels after successful *H. pylori* eradication

Although PG assay is not a confirmatory test, a decrease in PG II levels and an increase in PG I/II ratios suggest successful *H. pylori* eradication.[39] Reportedly, an increase in the PG I/II ratio was more profound in patients with severe corpus atrophy.[40] Patients with *H. pylori* infection and PG I/II ratios <3.0 showed ≥40% increase in PG I/II ratio after eradication, whereas those with PG I/II ratio between ≥3.0 and <5.0 showed ≥25% increase. Moreover, patients with PG I/II ratios ≥5.0 showed only ≥10% increase after successful eradication. These changes were mostly observed within 1–2 years after eradication.

PG levels after reinfection or new infection

Seroconversion of anti-*H. pylori* IgG titer may occur in seronegative individuals; however, only 9.8% have true *H. pylori* infection.[41] Compared with patients without true infection, those with new infection or re-infection had higher PG II levels and lower PG I/II ratios in that study. In Koreans, PG I/II ratios <4.35 and PG II levels >12.95 ng/mL suggest *H. pylori* infection.[42] In a previous study, compared with 256 *H. pylori*–naïve individuals, 1003 patients with infection and 743 with past infections had lower PG I/II ratios and higher incidence of gastric cancer.[43] In that study, *H. pylori*–naïve individuals showed mean PG I level of 51.0±15.6 ng/mL, PG II level of 8.4±3.0 ng/mL, and PG I/II ratio of 6.2±1.3.

PAN-ATROPHY UNRELATED TO AIG

Antrum-dominant atrophy may progress to pan-atrophy if *H. pylori* is not eradicated at an early stage.[44] In patients with pan-atrophy and no clear history of *H. pylori* eradication, spontaneous regression or unintended eradication at a later stage can be suspected. Despite the severe atrophy observed on gastroscopy, patients with pan-atrophy may have normal PG test findings (Fig. 2). Different from AIG, such discrepancies between the endoscopic and serologic test findings are not rare in *H. pylori*–induced pan-atrophy. Therefore, *H. pylori*–related pan-atrophy should be considered if PG assay findings are within the normal range in patients with severe atrophy on gastroscopy (Fig. 3).

PG levels in patients with atrophy in the corpus

Several studies have reported cutoff values for detecting corpus atrophy without testing autoimmune antibodies for AIG (Table 3). High gastrin levels, low PG I levels, and low PG I/II ratios were useful for detecting corpus atrophy in those studies. A study from Iran revealed that either G-17 <2.6 pmol/L or

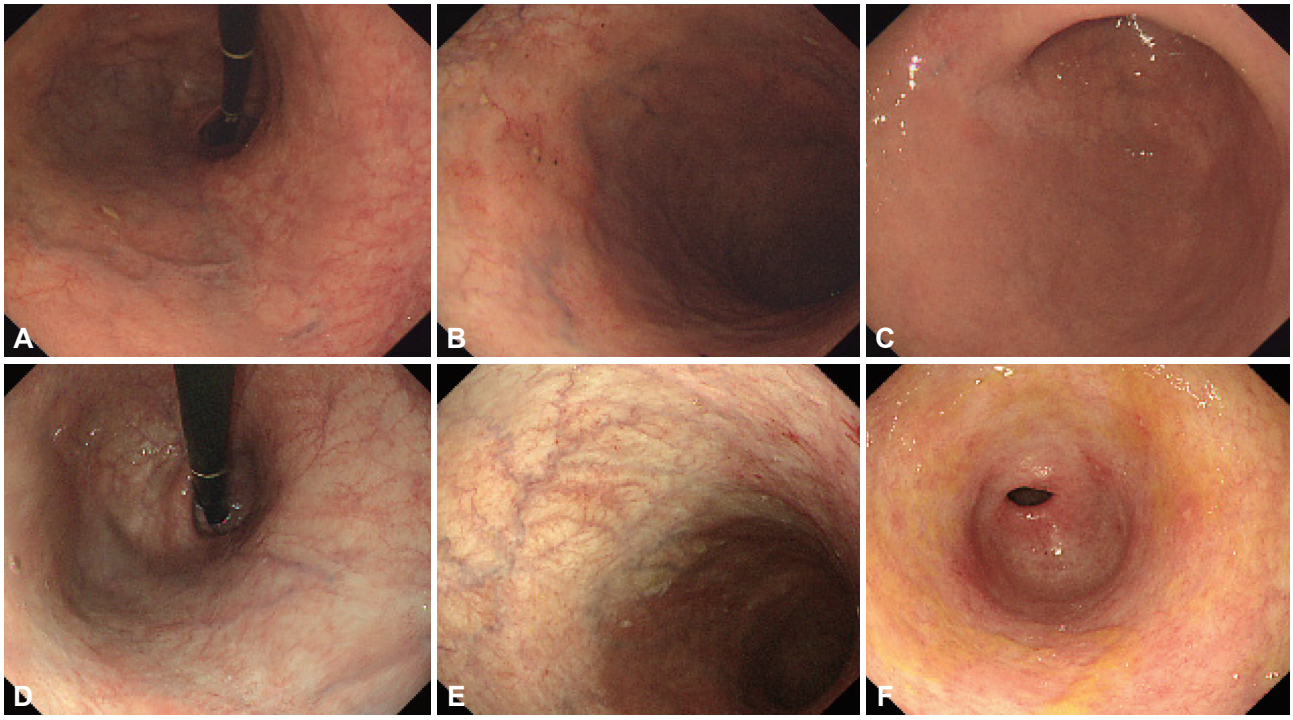

Fig. 2. Pan-atrophy in *H. pylori*–exposed stomach unrelated to autoimmune gastritis. A: Atrophy is observed without a gastric fold. B: A flat and raised subepithelial lesion is seen on the greater curvature side of the upper body. Primary low-grade, MALT lymphoma was diagnosed using the biopsied specimens. The Giemsa staining result was positive, and *H. pylori* was eradicated. C: Atrophy is observed in the antrum. D: Four years later, the atrophic mucosa looks whitish and pale compared with that in the initial test findings. Despite severe endoscopic atrophy, there was no serologic atrophy (PG I: 34.2 ng/mL, PG II: 9.3 ng/mL, and PG I/II: 3.7). E: After MALT lymphoma regression, the gastric body is replaced by atrophy. Both APCA and AIFA testing returned negative results. F: The antrum exhibits atrophy and IM, with small erosions. MALT, mucosa-associated lymphoid tissue; IM, intestinal metaplasia; APCA, anti-parietal cell antibody; AIFA, anti-intrinsic factor antibody; PG, pepsinogen.

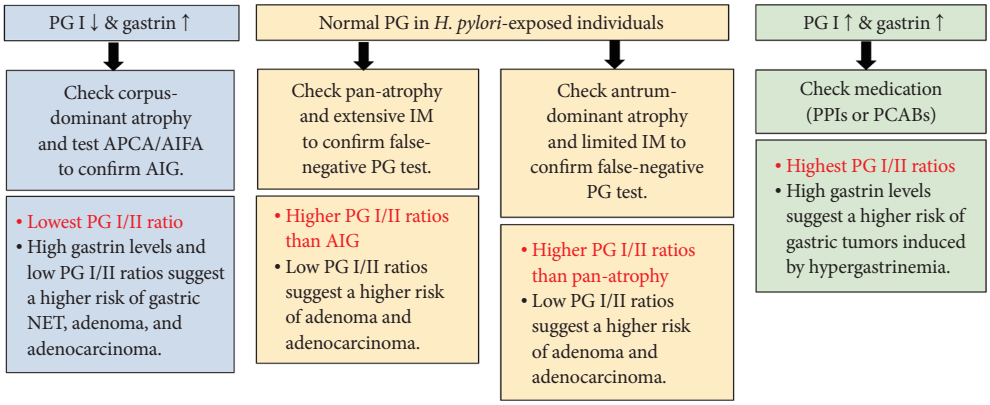

Fig. 3. Brief interpretation of serum pepsinogen and gastrin levels. PG, pepsinogen; APCA, anti-parietal cell antibody; AIFA, anti-intrinsic factor antibody; AIG, autoimmune gastritis; NET, neuroendocrine tumor; IM, intestinal metaplasia; PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker.

>40 pmol/L was useful for detecting atrophy in the fundus.[45] As shown in a previous study, G-17 levels can decrease even in the presence of corpus atrophy if there is an advanced atrophy in the antrum.[5]

Studies using Biohit's enzyme-linked immunosorbent assay (ELISA) kits provided a larger range of PG I/II cutoff ratios (from ≤2.2 to ≤10.0) than did Eiken's ELISA kits and other assays (Fig. 4). A study from Chile showed a low PG I/II cutoff value of ≤2.2 even with the use of GastroPanel tests.[46] The majority of participants in that study (79.7%) had *H. pylori* infection; as a result, PG I/II ratios were further reduced due to elevated PG II levels in patients with infection.

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Table 3. Studies on cutoff values for detecting corpus atrophy confirmed by histology

Test (company)	Number of participants (country)	Diagnosis	Cutoff value (sensitivity, specificity)	*H. pylori* positive rate	Study
ELISA (Biohit)	81 (China)	Corpus atrophy	PG I/II <8.1 (89%, 83%) PG I <97.1 μg/L (67%, 76%)	54.3%	Wu et al. (2004)[60]
	309 (Iran)	Atrophy in the fundus	PG I/II <5 (75.0%, 91.0%) PG I <56 μg/L (61.9%, 94.8%) G-17 <2.6 pmol/L or >40 pmol/L (81.0%, 73.3%)	84.5%	Nasrollahzadeh et al. (2011)[45]
	142 (Korea)	Corpus atrophy in the greater curvature side	PG I/II <3.5 (70.0%, 78.4%) PG I <59.3 μg/L (83.3%, 78.4%)	NA	Song et al. (2010)[61]
	567 (Chile)	Corpus–dominant atrophy	PG I/II ≤2.2 (56%, 100%) PG I ≤61.5 μg/L (78%, 91%) G-17 >13.3 pmol/L (67%, 96%)	79.7%	Rollan et al. (2006)[46]
	308 (Brazil)	Corpus atrophy	PG I <30 μg/L (50.0%, 93.2%)	29.9%	Mattar et al. (2020)[62]
L-TIA (Shima)	95 (Korea)	Corpus atrophy	PG I/II ≤3.5 (68.4%, 81.6%)	24.2%	Kim et al. (2015)[63]
RIA (Sorin)	284 (14 European countries)	*H. pylori*–related corpus–dominant or multifocal atrophy	PG I/II <4.7 (77.1%, 87.4%)	90%	Broutet et al. (2003)[64]
	226 (Sweden)	Corpus atrophy	PG I/II <2.5 (62%, 95%) Gastrin >116 ng/L (60%, 83%)	39.3%	Sanduleanu et al. (2003)[65]
	544 (UK)	Corpus atrophy	PG I <80 ng/mL and *H. pylori*–seropositive (88.9%, 92.3%)	5.3%	Knight et al. (1996)[66]

ELISA, enzyme-linked immunosorbent assay; PG, pepsinogen; G-17, gastrin-17; NA, not available; L-TIA, latex-enhanced turbidimetric immunoassay; RIA, radioimmunoassay.

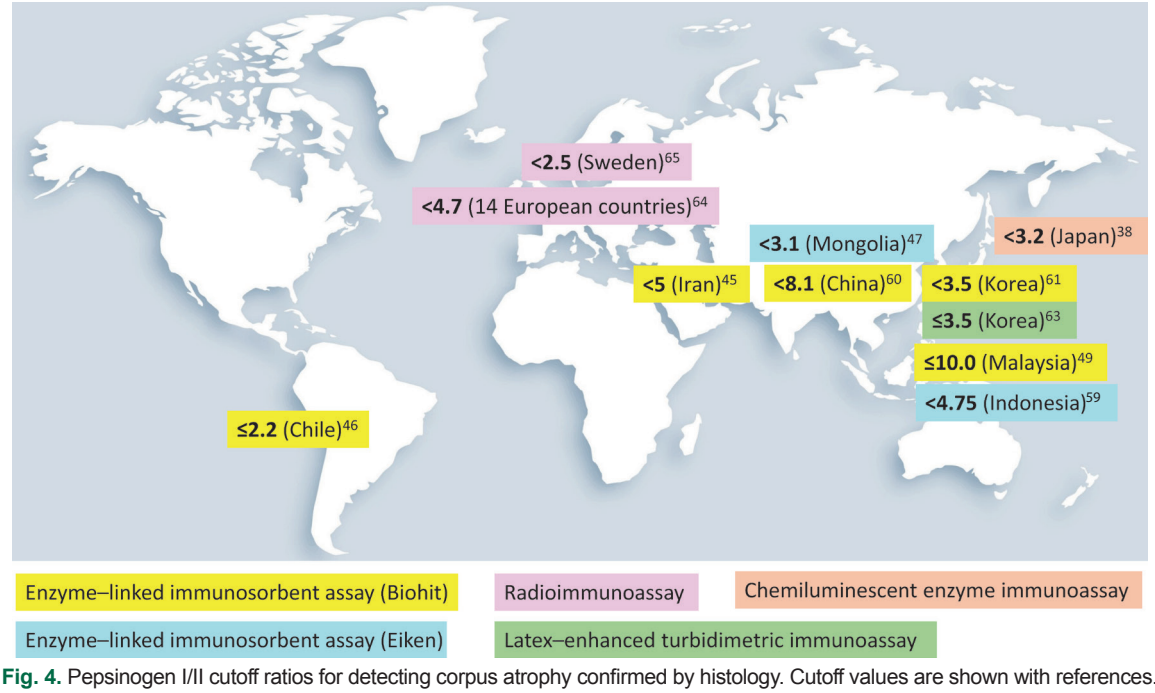

Fig. 4. Pepsinogen I/II cutoff ratios for detecting corpus atrophy confirmed by histology. Cutoff values are shown with references.

PG levels in patients with IM

Few studies have reported cutoff values for detecting IM (Table 4). Two studies revealed that PG I/II levels <3.1 and 3.25 are useful for detecting IM when Japanese kits are used.[47,48] In the later study, the PG assay showed better performance for detecting IM than for detecting mild and moderate atrophy.

Conversely, GastroPanel tests revealed higher cutoff values of PG I/II ≤10.0 and PG I/II <6.0 for detecting IM with low accuracy.[49,50]

A study from Iran reported that a combination of PG I/II ratios ≤3 and G-17 levels >17 pmol/mL is useful for detecting IM in the corpus.[51] Despite its high specificity (97.8%), the sen-

Table 4. Studies on cutoff values for detecting intestinal metaplasia confirmed by histology

Test (company)	Number of participants (country)	Diagnosis	Cutoff value (sensitivity, specificity)	*H. pylori* positive rate	Study
ELISA (Biohit)	72 (Malaysia)	IM or corpus atrophy	PG I/II ≤10.0 (83.3%, 77.9%) PG I ≤87.2 μg/L (66.7%, 85.3%)	NA	Loong et al. (2017)[49]
	160 (India)	IM	PG I/II <6.0 (64%, 52%)	38.8%	Ghoshal et al. (2011)[50]
	481 (Iran)	IM in the corpus	PG I/II ≤3 and G-17 >17 pmol/mL (14.8%, 97.8%)	78.7%	Haj–Sheykholeslami et al. (2008)[51]
		Corpus–dominant atrophy	PG I/II ≤3 and G-17 >17 pmol/mL (9.4%, 99.0%)		
ELISA (Eiken)	752 (Mongolia)	IM or corpus atrophy	PG I/II <3.1 (67.2%, 61.0%)	77%	Gantuya et al. (2019)[47]
	353 (Sri Lanka)	IM	PG I/II <3.25 (83.3%, 95.4%) PG I <15.5 U/mL (50.0%, 98.8%)	2.0%	Doohan et al. (2021)[48]
		Moderate atrophy	PG I/II <4.75 (66.7%, 83.3%) PG I <111 U/mL (50.0%, 66.3%)		
		Mild atrophy	PG I/II <7.65 (33.1%, 76.4%) PG I <92.45 U/mL (48.1%, 60.9%)		

ELISA, enzyme-linked immunosorbent assay; IM, intestinal metaplasia; PG, pepsinogen; NA, not available; G-17, gastrin-17.

Table 5. Summary on pepsinogen and gastrin test findings

Condition	Pepsinogen I level	Pepsinogen I/II ratio	Fasting gastrin level	Fasting gastrin-17 level	Risk of gastric cancer
Normal stomach	Normal (30–160 ng/mL)	Normal (>3.0)	Normal (13–109 pg/mL)	Normal (1–7 pg/mL)	No risk
Corpus–dominant atrophy induced by autoimmune gastritis	Extremely low because of the loss of chief cells		High because of compensatory response to high gastric pH	Extremely high (>30 pg/mL), extremely low (<0.4 pg/mL) when combined with *H. pylori*–induced atrophy	Increased in patients with low PG I/II ratios or high gastrin levels
Antrum–dominant atrophy induced by *H. pylori*	Normal	Low in *H. pylori*–infected patients because of high PG II levels	Variable	Low because of the loss of G cells	Increased in patients with low PG I/II ratios
Pan–atrophy induced by *H. pylori*	Low or normal		High or normal	Low or normal	Increased in patients with low PG I/II ratios
Long–term use of PPIs or PCABs	High because of compensatory response to high gastric pH		High because of compensatory response to high gastric pH		Increased in *H. pylori*–exposed patients with high gastrin levels
Ulcerogenic drugs	High		Variable	Low if gastric pH is low	NA
Gastrectomy	Low if the corpus is resected		Variable	Low if the antrum is resected	NA
Renal insufficiency	High because of reduced renal clearance		High because of reduced renal clearance		NA
Gastroparesis	Variable depending on the degree of corpus atrophy and use of drugs		High because of remnant foods in the stomach		NA

PG, pepsinogen; PPI, proton pump inhibitor; PCAB, potassium-competitive acid blocker; NA, not available.

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sitivity was too low (14.8%) for application in clinical practice. Considering the high *H. pylori* infection rate (78.7%) in their study, the PG assay seems to be less accurate for detecting IM, particularly in the presence of *H. pylori* infection.

Gastrin levels and gastric cancer risk after eradication

High gastrin levels and severe atrophy are common in patients who develop metachronous gastric cancer.[52] In a previous study, PPI-independent elevation of gastrin levels over 99 pg/mL (sensitivity 61.6%, and specificity 80.0%) correlated with the occurrence of metachronous gastric cancers. Other two studies also recommended to avoid using PCABs or PPIs after eradication because these drugs increased the risk of metachronous gastric cancers.[53,54] Taken together, *H. pylori*–exposed individuals with corpus atrophy or persistent IM should be monitored for serum gastrin levels when using these drugs.[55] Furthermore, serum PG testing should not be used as a standalone diagnostic tool but as a triage biomarker in gastric cancer screening, as summarized in Table 5.

CONCLUSIONS

Serum PG testing provides valuable information on gastric mucosal status, particularly for identifying AIG and advanced corpus atrophy (OLGA stages II–IV) in the absence of *H. pylori* infection. However, its diagnostic performance is limited in patients with mild atrophy, OLGA stage I, and closed-type atrophy. AIG is characterized by the most profound reductions in PG I/II ratios and PG I levels, whereas *H. pylori*–associated atrophy shows more variable patterns depending on disease distribution. The limitations of PG testing are particularly evident in patients with pan-atrophy, in whom serologic findings may remain within normal ranges despite severe endoscopic atrophy. Thus, careful interpretation in the appropriate clinical context is essential because *H. pylori* infection, recent medications, impaired renal function, dietary factors, age, sex, and genetic backgrounds may further influence PG levels. Furthermore, variability in cutoff values across different assay systems should be considered when using GastroPanel tests instead of East Asian kits interpreted with the ABC method. Future studies should focus on standardizing assay-specific cutoff values and developing integrated diagnostic algorithms that combine serologic, endoscopic, and clinical parameters to improve risk prediction and guide surveillance strategies. In summary, monitoring low PG I/II ratios and high gastrin levels is recommended during gastric cancer surveillance, particularly in patients with corpus atrophy or persistent IM even after *H. pylori* eradication.

ORCID iD

Sun-Young Lee https://orcid.org/0000-0003-4146-6686

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