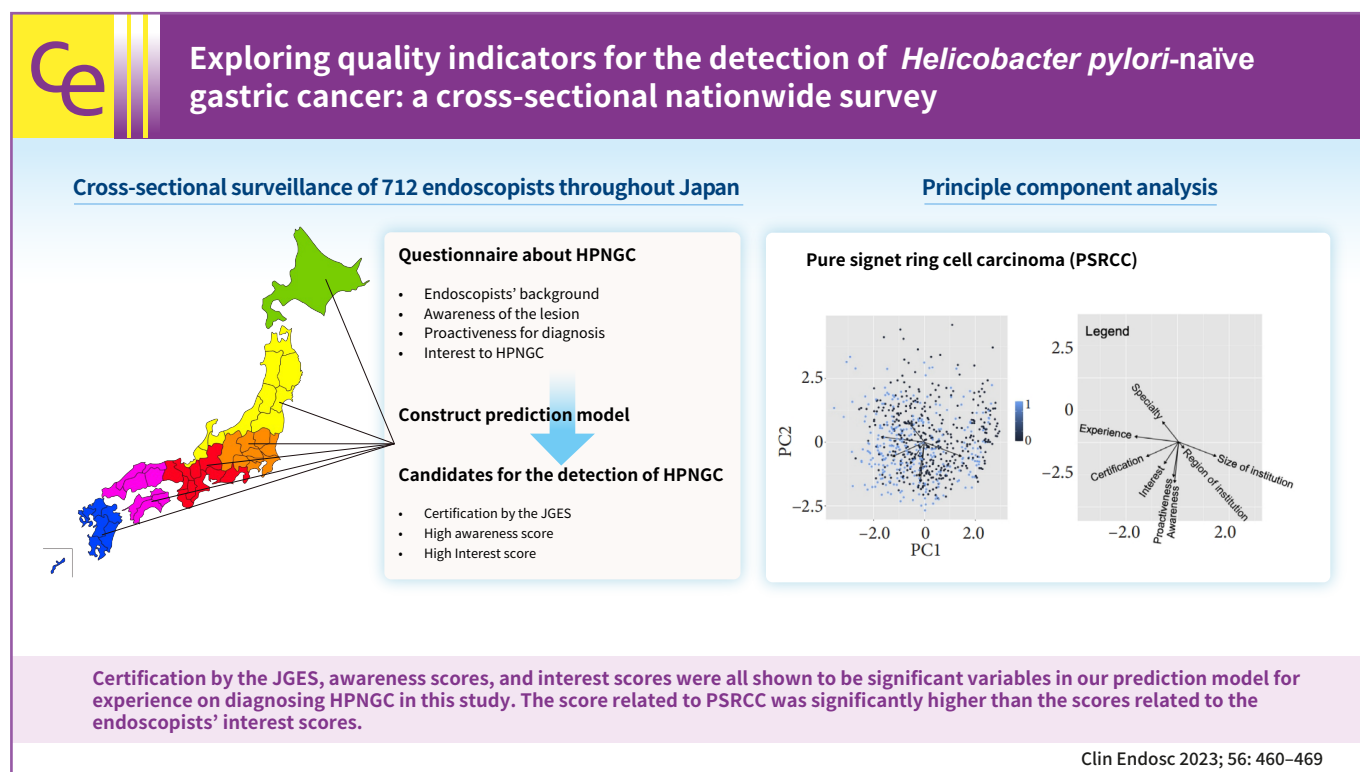




Exploring quality indicators for the detection of *Helicobacter pylori*-naïve gastric cancer: a cross-sectional nationwide survey

Fumiaki Ishibashi^{1,2}, Toshiaki Hirasawa³, Hiroya Ueyama⁴, Yohei Minato⁵, Sho Suzuki¹

¹Department of Gastroenterology, International University of Health and Welfare Ichikawa Hospital, Chiba; ²Endoscopy Center, Koganei Tsurukame Clinic, Tokyo; ³Department of Gastroenterology, Cancer Institute Hospital, Tokyo; ⁴Department of Gastroenterology, Juntendo University School of Medicine, Tokyo; ⁵Department of Gastrointestinal Endoscopy, NTT Medical Center Tokyo, Tokyo, Japan



Received: June 10, 2022 Revised: July 4, 2022 Accepted: July 11, 2022

Correspondence: Fumiaki Ishibashi

Department of Gastroenterology, International University of Health and Welfare Ichikawa Hospital, 6-1-14, Konodai, Ichikawa-shi, 272-0827 Chiba, Japan

E-mail: ishibashi@tsurukamekai.jp

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background/Aims: Diagnosis of *Helicobacter pylori*-naïve gastric cancer (HPNGC) is becoming increasingly important. This study aimed to explore the quality indicators for HPNGC detection.

Methods: We conducted a cross-sectional, nationwide, web-based survey of gastrointestinal endoscopists in Japan. In addition to questions about the number of HPNGC cases detected in a year and basic information, the questionnaire also consisted of 28 questions: (1) 18 about HPNGC awareness, (2) six about diagnostic proactiveness, and (3) four about interest in HPNGC.

Results: Valid responses were obtained from 712 endoscopists. The Japan Gastroenterological Endoscopy Society-certified endoscopists had a significantly higher HPNGC detection rate than the nonspecialists (0.42% vs. 0.32%, respectively; $p=0.008$). The results of the multiple regression analysis showed that Japan Gastroenterological Endoscopy Society certification and high awareness and interest scores were independent predictors of the HPNGC detection rate ($p=0.012$, $p<0.001$, $p=0.024$, respectively). Principal component analysis showed that the endoscopists who attended conferences for collecting information on HPNGC had a higher level of awareness.

Conclusions: To improve the detection of HPNGC, it is necessary to increase the awareness of the disease. It is hoped that relevant societies will play an important role in endoscopists' education.

Keywords: Endoscopy; *Helicobacter pylori*; Stomach neoplasms

INTRODUCTION

Helicobacter pylori (HP) infection plays an important role in the development of gastric cancer.^{1,2} Several randomized control trials have shown that HP eradication reduces the risk of carcinogenesis.^{3,4} The widespread use of HP eradication therapy has reduced the incidence of new gastric cancer cases⁵ and decreased the prevalence of HP in Japan over time.^{6,7}

HP-naïve gastric cancer (HPNGC), rather than HP-associated gastric cancer, has been increasingly detected in recent years. The first reported HPNGC was pure signet ring cell carcinoma (PSRCC).⁸ With the increased awareness of PSRCC, it has become a major component of reported HPNGC cases.⁹ Studies on the genomic landscape of PSRCC have shown that not all PSRCCs carry the *CDH-1* mutation, making it a hereditary and a sporadic cancer.^{10,11} The second reported HPNGC was gastric adenocarcinoma of the fundic-gland type (GA-FG).¹²⁻¹⁴ GA-FG was initially reported as HPNGC, but later shown to also occur in HP-positive or post-HP eradication mucosa, making it important to understand endoscopic findings.¹⁵ Raspberry-like tumors are treated as adenocarcinomas in the Japan Gastric Cancer Association guidelines¹⁶ but are internationally reported as foveolar-type gastric adenoma.¹⁷

The Lauren and World Health Organization (WHO) classifications are often used to classify gastric cancer.¹⁸⁻²⁰ HPNGC, such as PSRCC, GA-FG, and raspberry-like tumors, have different endoscopic findings compared to the intestinal-type gastric cancer, including tubular adenocarcinoma, according to the Lauren classification. Localized atrophy, submucosal tumors,

and hyperplastic polyps are similar in appearance and may not be diagnosed by biopsy without an accurate understanding of their characteristics.²¹ Experience with endoscopy is necessary to differentiate HPNGC from these common, benign changes. Indeed, we have reported the importance of the number of years of endoscopic experience and gastric observation time as quality indicators for HPNGC detection.²² We have also reported that for the efficient HPNGC detection, a review by another endoscopist is effective in controlling endoscopic quality.²³ However, HPNGC does not have a widely recognized and consensus classification worldwide, and its disease concept is still being established.^{19,20} The WHO classification and other criteria for the classification of gastric cancers define them as tumors that invade the submucosa; therefore, HPNGC, such as raspberry-like tumors with a low rate of invasion into the submucosa, have been classified as adenomas or dysplasias. Differences in the diagnostic criteria for HPNGC in Japan and other countries may hinder the understanding of this disease.²⁴ The only way for endoscopists to expand their understanding of HPNGC is to actively collect information by attending scientific meetings and educational lectures, or by searching the literature; therefore, disease awareness is an urgent issue. Furthermore, real-world data on the endoscopists' actual understanding of HPNGC in Japan and the number of cases diagnosed annually are lacking. The purpose of this study was to determine the endoscopists' awareness and interest in HPNGC in their practice through a nationwide survey in Japan and to explore the quality indicators for HPNGC detection.

METHODS

Study design

This was a cross-sectional study of endoscopists in Japan using a web-based questionnaire survey.

Survey participants

Endoscopists from all over Japan were included in the study. Subscribers to the Endoscopy Atlas, an e-mail newsletter published by Toshiaki Hirasawa for endoscopists in Japan and endoscopists at facilities affiliated with the authors and research collaborators were eligible. On November 1, 2021, an e-mail was sent to all participants simultaneously, explaining the study outline. If they agreed to participate, they were directed to a system that allowed them to respond to a web-based questionnaire with anonymity assured. The deadline for obtaining consent and response was November 15, 2021.

The study participants who gave consent were asked about the type of facility they worked in (health checkup facility [examination center], clinic, general hospital, or tertiary hospital), the prefecture where their facility was located, their specialty (physician, surgeon, or other), whether they were certified by the Japan Society of Gastroenterological Endoscopy (JGES), and the number of endoscopies they performed in a year. The basic attributes of the survey participants were also analyzed.

Questionnaire list

HPNGC is defined as gastric cancer in which HP infection is not involved in carcinogenesis. Specifically, HPNGC includes PSRCC, GA-FG, and raspberry-type tumors. At the beginning of this survey, the study participants were informed that HPNGC was defined as gastric cancer found in patients who were not infected with *H. pylori*. “HP naïve” status was determined by at least two of the following tests: serum anti-HP-IgG antibody, urea breath test, HP antigen in stool, and direct observation of HP in biopsy specimens; additionally, the absence of gastric atrophy and prior HP eradication treatment were mandatory. In addition to questions about the actual number of HPNGC cases detected in a year, the questionnaire also included a total of 28 questions as follows: (1) eighteen were about their awareness of HPNGC (two general questions, six about GA-FG, five about raspberry-like tumors, and five about PSRCC); (2) six about their diagnostic proactiveness (e.g., frequency of biopsy and attitude towards consulting a gastrointestinal pathologist); and (3) four on their interest in the disease

(e.g., whether the endoscopist attended conferences and educational lectures and whether the endoscopist used web media such as article searches, social network services, e-mail newsletters, and blog articles) (Table 1). All questions were answered with “yes” or “no”.

Data analysis

The scores for awareness, diagnostic proactiveness, and interest in the disease were based on the number of “yes” answers given to each question out of all questions (out of 100 points). In addition, for questions about awareness, the answers for GA-FG, raspberry-like tumors, and PSRCC were scored separately on a 100-point scale based on the percentage of “yes” answers to each question.

In the first step of the analysis, experience in diagnosing HPNGC was used as the primary outcome to determine its relationship with endoscopist characteristics. We first investigated whether there were differences in the experience in diagnosing HPNGC based on the endoscopists’ background. We then investigated whether there were differences in awareness, diagnostic proactiveness, and interest in the disease based on the endoscopists’ background.

The second step of the analysis was to build a predictive model for the HPNGC detection rate. Candidate predictors were explored using logistic regression analysis, with the endoscopists’ background factors, awareness, diagnostic proactiveness, and interest in the disease as the explanatory variables and experience in diagnosing HPNGC as the objective variable. The odds ratio (OR) and 95% confidence interval (CI) for each variable in this model were used to identify the candidate predictors for HPNGC detection.

In the last step of the analysis, principal component analysis (PCA) was performed based on all the parameters of all the endoscopists to determine the candidate predictors of HPNGC detection extracted in the second step of the analysis.

All statistical analyses were performed using the R software 4.0.4 (The R Foundation for Statistical Computing, Vienna, Austria).²⁵ Student *t*-test was used to compare the means between the two groups, one-way ANOVA was used to compare three or more means, and multiple comparisons were made between all the groups using the Bonferroni method. In the logistic regression analysis, the OR with 95% CI and the *p*-value of each explanatory variable compared with the reference were calculated. PCA was performed using the prcomp package of R software. The ggbiplot package of R and PRISM software

Table 1. Questionnaire list

Category	No.	Question detail
Basic information	1	Please select the medical institution where you primarily work: examination center, clinic, general hospital, tertiary hospital.
	2	Please tell us the location of the medical institution where you primarily work, by prefecture.
	3	Please select your areas of expertise: physician, surgeon, other.
	4	Are you certified as an endoscopist by the Japanese Society of Gastrointestinal Endoscopy?
	5	How many upper gastrointestinal endoscopies do you perform per year?
	6	Over the past 5 years, on average, how many cases of HPNGC have you detected per year?
Awareness	1	When diagnosing <i>Helicobacter pylori</i> uninfected gastric cancer, do you consider all endoscopic findings, pathological findings, clinical findings, and the history of <i>H. pylori</i> eradication?
	2	Do you know that HPNGC has different clinicopathological features than <i>H. pylori</i> -associated gastric cancer?
	3	Are you familiar with the concept of GA-FG?
	4	Are you familiar with the concept of GA-FG?
	5	Have you ever detected GA-FG?
	6	Do you know the characteristics of the endoscopic image of GA-FG?
	7	Do you know the location of the stomach where GA-FG is most likely to be detected?
	8	Do you know whether GA-FG is most often found as elevated, flat or depressed?
	9	Are you familiar with the concept of foveolar type adenocarcinoma (raspberry-like gastric cancer)?
	10	Have you ever found raspberry-like gastric cancer?
	11	Do you know the characteristics of the endoscopic image of raspberry-like gastric cancer?
	12	Do you know the endoscopic differences between raspberry-like gastric cancer and hyperplastic polyps?
	13	Do you know the location of the stomach where raspberry-like gastric cancer is most likely to be detected?
	14	Are you familiar with the concept of PSRCC?
	15	Have you ever detected PSRCC?
	16	Do you know the characteristics of the endoscopic image of PSRCC?
	17	Do you know the location of the stomach where PSRCC is most likely to be detected?
	18	Do you know that PSRCC and signet ring cell carcinoma, as an undifferentiated type of carcinoma occurring in <i>H. pylori</i> positive cases, have different developmental progression?
Proactiveness	1	If you suspect HPNGC, do you perform an aggressive biopsy?
	2	In a case where HPNGC is grossly suspected and a previous biopsy of the same site did not reveal a diagnosis of cancer, do you perform another biopsy even if there is no gross change at the current examination?
	3	If an elevated lesion has superficial vasodilation, do you perform a biopsy to differentiate it from GA-FG, even if the lesion is suspected of being a fundic-gland polyp?
	4	If a reddish, elevated lesion is found in an <i>H. pylori</i> uninfected patient with no atrophy of the background mucosa, do you perform a biopsy to differentiate a lesion from a raspberry-like gastric cancer, even if the lesion is likely to be a hyperplastic polyp?
	5	If an <i>H. pylori</i> uninfected patient with no atrophy of the background mucosa has a depressed lesion with a faded color tone, do you biopsy the lesion to differentiate it from PSRCC, even if it is more likely to be a localized atrophic mucosa?
	6	If endoscopically diagnosed as HPNGC and biopsy results are Group 1 or Group 2, do you consult with a gastrointestinal pathologist?
Interest	1	Do you collect information about HPNGC by attending scientific meetings and lectures?
	2	Do you collect information about HPNGC through web media such as social networking sites, blogs, e-mail newsletters (mail magazine), and articles?
	3	Do you think it is important to detect HPNGC without missing it?
	4	Would you like to continue to collect information about HPNGC?

HPNGC, *Helicobacter pylori*-naïve gastric cancer; GA-FG, gastric adenocarcinoma of the fundic-gland type; PSRCC, pure signet ring cell carcinoma.

were used to draw the graphs. The mean values in the text and graphs are presented as mean±standard deviation. Statistical significance was set at p -value <0.05.

Ethical statements

This study was approved by the Institutional Review Board of the Shinjuku Tsurukame Clinic on October 19, 2021 (approval number: 2105) and was conducted from November 1 to November 15, 2021.

RESULTS

Baseline characteristics of the study participants

Valid responses were obtained from 713 endoscopists during the study period. The basic attributes of these endoscopists are listed in Table 2. Twenty-eight (3.9%) were trainees with less than five years of endoscopic experience, while 366 (51.3%) were skilled endoscopists with more than 20 years of experience. Most of the endoscopists worked in clinics, general hospitals, and tertiary hospitals, and only 38 (5.3%) worked in examination centers. Most of the endoscopists who participated in the study specialized in internal medicine (641, 89.9%). A total of 507 endoscopists (71.1%) were JGES-certified. Additionally, 261 (36.6%) endoscopists had never detected HPNGC. The response rates were compared to the JGES councilors and the population in each region to identify any regional differences in the number of valid responses, and no significant differences were found (Supplementary Fig. 1).

Differences in experience in diagnosing HPNGC based on the endoscopists' background

We investigated whether there were differences in the experience in diagnosing HPNGC based on the endoscopists' background. Interestingly, trainees with less than five years of endoscopic experience were more likely to detect HPNGC (Fig. 1A). There were no differences in the experience in diagnosing HPNGC based on the size and location of the institution (Fig. 1B, C). Being a physician or surgeon was not associated with experience in identifying HPNGC (Fig. 1D). In contrast, JGES-certified endoscopists had more experience in diagnosing HPNGC than nonspecialists (66.0% vs. 53.4%) (Fig. 1E). We then compared awareness, proactiveness, and interest scores with the endoscopists' background. Endoscopists with fewer years of endoscopic experience had lower awareness scores than endoscopists with more years of experience (p <0.05) (Fig. 2A).

Awareness and proactiveness scores were higher for endoscopists working in tertiary hospitals than for those working in clinics (p <0.05) (Fig. 2B). Differences in affiliation location did not affect any of the scores (Fig. 2C). Endoscopists in internal medicine had higher awareness scores than those in surgical medicine (p <0.05) (Fig. 2D). JGES-certified endoscopists had higher awareness and proactiveness scores than nonspecialists (p <0.001 and p =0.005, respectively) (Fig. 2E).

Predictors of the detection of HPNGC

We constructed a predictive model for the experience in diagnosing HPNGC using a multiple regression model. Logistic regression analysis was performed to determine whether the backgrounds of all the endoscopists and awareness, proac-

Table 2. Background characteristics of the study participants (n =713)

Characteristic	n (%)
Experience in endoscopy (yr)	
<5	28 (3.9)
<10	110 (15.4)
<15	98 (13.7)
<20	111 (15.6)
≥20	366 (51.3)
Type of facility	
Examination center	38 (5.3)
Clinic	199 (27.9)
General hospital	289 (40.5)
Tertiary hospital	187 (26.2)
Place of facility (prefecture)	
Kanto and Koshinetsu	390 (54.7)
Tohoku and Hokuriku	47 (6.6)
Tokai and Kinki	133 (18.7)
Chugoku and Shikoku	53 (7.4)
Kyusyu and Okinawa	70 (9.8)
Hokkaido	20 (2.8)
Specialty	
Physician	641 (89.9)
Surgeon	65 (9.1)
Other	7 (1.0)
Certification by the JGES	
Certified	507 (71.1)
Not certified	206 (28.9)
Experience on diagnosing HPNGC	
Experienced	452 (63.4)
Not experienced	261 (36.6)

JGES, Japanese Gastroenterological Endoscopy Society; HPNGC, *Helicobacter pylori*-naïve gastric cancer.

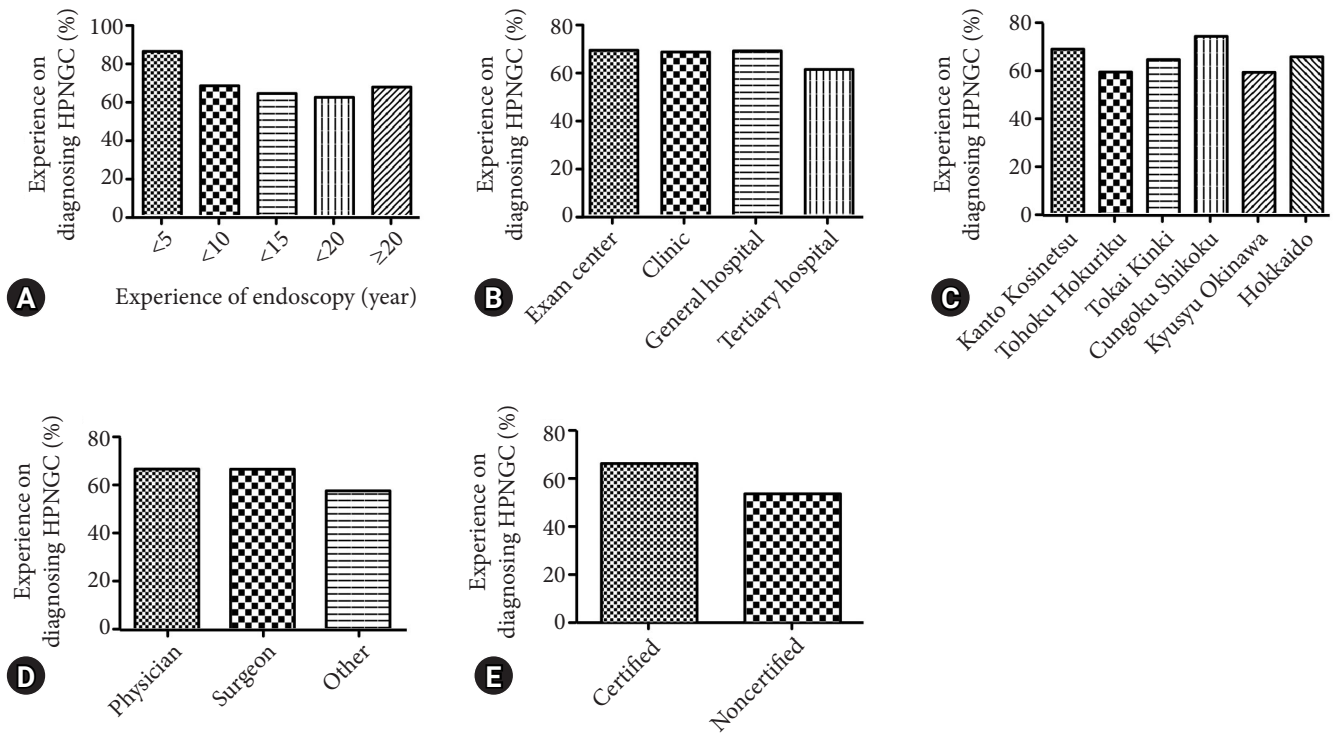


Fig. 1. Relationship between the endoscopist background and the *Helicobacter pylori*-naïve gastric cancer (HPNGC) detection rate. (A) Relationship with experience in endoscopy (years). (B) Relationship with the size of the endoscopist's facility. (C) Relationship with the location (prefecture) of the facility where the endoscopist is affiliated. (D) Relationship with the endoscopist's area of expertise. (E) Relationship with whether the endoscopist obtained the Japan Gastroenterological Endoscopy Society certification as an endoscopist.

tiveness, and interest scores were explanatory variables and potential predictors of experience in diagnosing HPNGC. Consequently, being a JGES-certified endoscopist and having a high awareness score were found to be significant predictors of HPNGC detection (OR, 1.55; 95% CI, 1.07–2.26; $p=0.022$ and OR, 1.52; 95% CI, 1.05–2.20; $p=0.027$, respectively) (Table 3).

PCA for components of the awareness and interest score

Finally, we attempted to determine the more important factors among the components of the awareness and interest scores. The awareness score was subdivided into scores for GA-FG, raspberry-like tumors, and PSRCC, and added to the analysis. For the interest score, we added factors like attending scientific meetings and lectures hosted by academic societies or using web media such as article searches, social network services, e-mail newsletters, and blog articles. The background, awareness, proactiveness, and interest scores of all the endoscopists were represented two-dimensionally using PCA, and the weights of each component of the awareness and interest scores

were visualized (Fig. 3F). Among the components of the awareness score, no specific trend was found for the scores related to GA-FG and raspberry-like tumors (Fig. 3A, B). In contrast, the score related to PSRCC was significantly higher than the scores related to the endoscopists' interest scores (Fig. 3C). Among the components of the interest score, attending scientific meetings was more strongly associated with factors that had a positive impact on the endoscopists' HPNGC detection rate (Fig. 3D, E).

DISCUSSION

HPNGC is difficult to diagnose without a thorough understanding of its endoscopic characteristics. Since HPNGC is often missed during endoscopy screening, it is important to educate endoscopists about identifying HPNGC. However, no studies have investigated the relevance of educating endoscopists about HPNGC and whether it truly improves the identification rate of HPNGC. This study was the first to explore

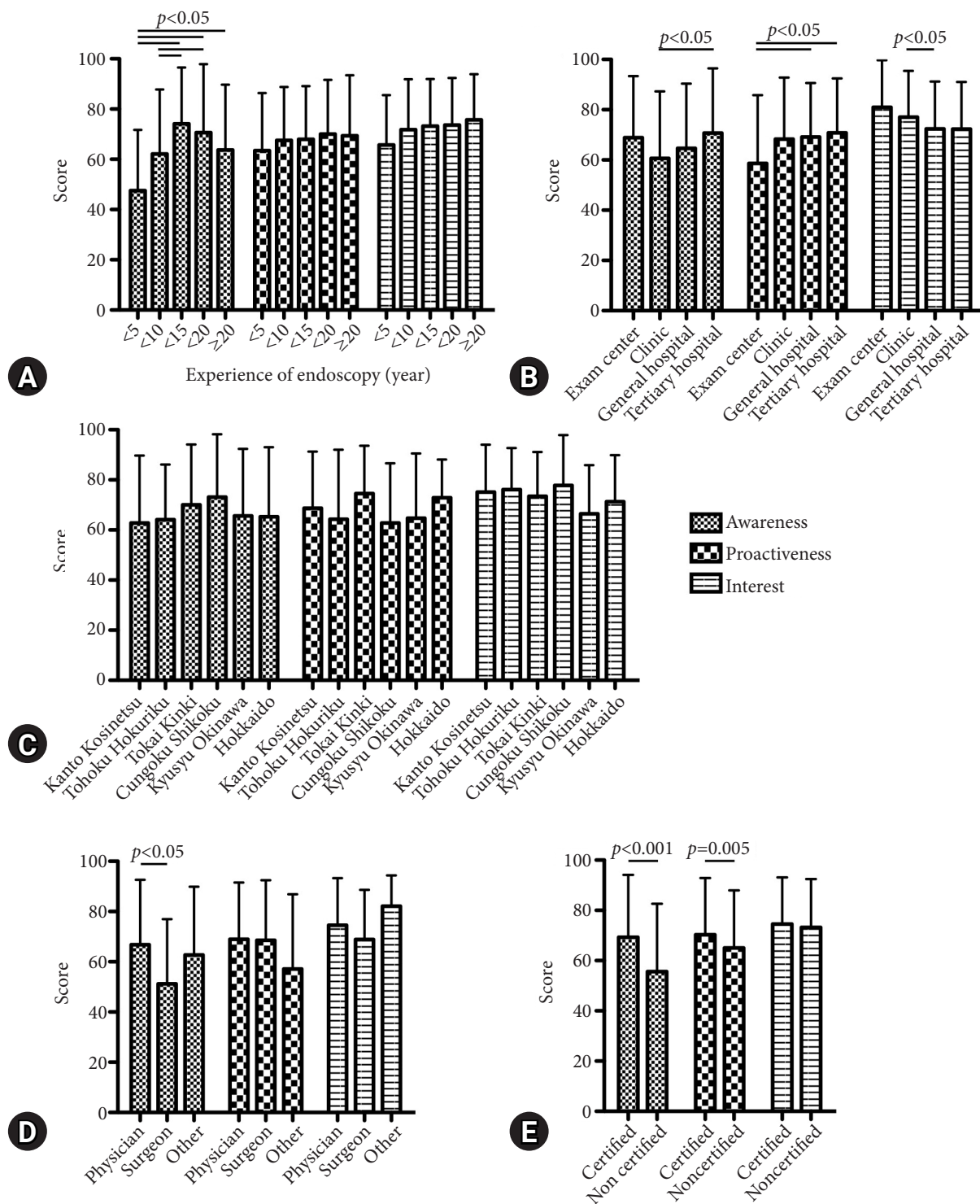


Fig. 2. Association of endoscopist background with awareness, proactiveness, and interest scores. (A) Relationship with experience in endoscopy (years). (B) Relationship with the size of the endoscopist's facility. (C) Relationship with the location (prefecture) of the facility where the endoscopist is affiliated. (D) Relationship with the endoscopist's area of expertise. (E) Relationship with whether the endoscopist obtained the Japan Gastroenterological Endoscopy Society certification.

Table 3. Logistic regression analysis to explore the predictors for the detection of HPNGC

Explanatory variable	Category	Odds ratio (95% CI)	p-value
Experience in endoscopy	<10 yr (reference)	1.00	0.478
	≥10 yr	0.84 (0.51–1.37)	
Size of institution	Examination center (reference)	1.00	0.542
	Clinic	0.79 (0.36–1.70)	
	General hospital	0.81 (0.38–1.72)	
	Tertiary hospital	0.58 (0.26–1.28)	
Region of institution	Kanto and Koshinetsu (reference)	1.00	0.236
	Tohoku and Hokuriku	0.68 (0.36–1.29)	
	Tokai and Kinki	0.84 (0.55–1.30)	
	Chugoku and Shikoku	1.33 (0.71–2.53)	
	Kyusyu and Okinawa	0.70 (0.41–1.19)	
	Hokkaido	0.90 (0.34–2.38)	
Specialty	Physician (reference)	1.00	0.885
	Surgeon	1.04 (0.59–1.83)	
	Others	0.65 (0.14–3.09)	
Board certified by the JGES	Not certified (reference)	1.00	0.022
	Certified	1.55 (1.07–2.26)	
Awareness score	<50 (reference)	1.00	0.027
	≥50	1.52 (1.05–2.20)	
Proactiveness score	<50 (reference)	1.00	0.432
	≥50	0.85 (0.56–1.28)	
Interest score	<50 (reference)	1.00	0.833
	≥50	1.04 (0.72–1.51)	

HPNGC, *Helicobacter pylori*-naïve gastric cancer; CI, confidence interval; JGES, Japanese Gastroenterological Endoscopy Society.

quality indicators using experience in diagnosing HPNGC as an outcome.

The results of this cross-sectional study with more than 700 endoscopists across Japan showed that JGES-certified specialists were more likely than nonspecialists to diagnose HPNGC. However, differences by region and size of the institution they worked in were not found to be directly related to HPNGC detection. Interestingly, the number of years of endoscopic experience was not directly associated with HPNGC detection. The results suggest the importance of obtaining certification from the JGES. Based on these results, we believe that the endoscopic specialist system operated by the JGES has universally ensured the quality of the endoscopists without creating regional disparities.

Certification by the JGES, awareness scores, and interest scores were all shown to be significant variables in our prediction model for experience in diagnosing HPNGC. However, the proactiveness score was not a significant variable. These results suggest that to improve the HPNGC detection rate, it is import-

ant to receive education especially from related societies and to become a JGES-certified endoscopist.

Furthermore, the PCA results indicate that it is important to improve our understanding of PSRCC among the HPNGCs. Surprisingly, PSRCC has low awareness and high interest despite being the classic HPNGC. As previously reported, PSRCC is the most frequently detected HPNGC, and it is important to educate the public about this common disease. It has also been suggested that scientific meetings and lectures play a significant role in gathering information about HPNGC. We believe that it is necessary to further educate endoscopists by providing accurate information about HPNGC, especially through related academic societies.

This study had several limitations. Firstly, the study may have selection bias. Most endoscopists in this study had more than 10 years of endoscopic experience and were JGES-certified, leading to a cohort with fewer less-experienced endoscopists. Secondly, this was a questionnaire-based cross-sectional study, which may have information bias, especially recall bias. Experi-

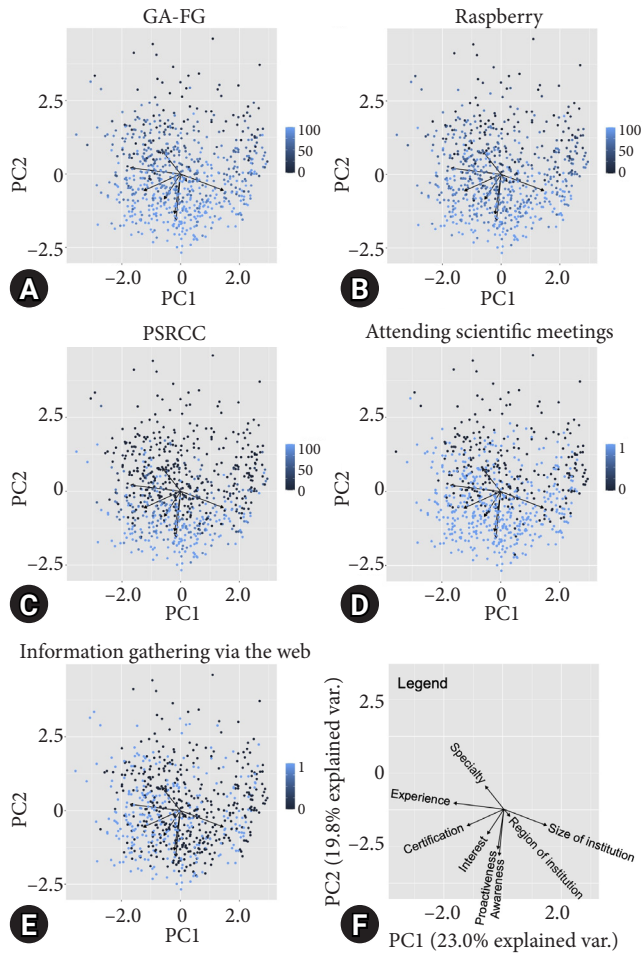


Fig. 3. Principal component analyses (PCAs) of endoscopists' backgrounds, and awareness, proactiveness and interest scores. Each dot indicates the position of the endoscopist on the PCA map. The lighter the blue color of the dots, the higher the score. (A) PCA map classified by scores related to gastric adenocarcinoma of the fundic-gland type (GA-FG) among the components of the awareness score. (B) PCA map classified by scores related to raspberry-like tumors among the components of the awareness score. (C) PCA map classified by scores related to pure signet ring cell carcinoma (PSRCC) among the components of the awareness score. (D) PCA map classified by scores related to attendance at scientific meetings among the components of the interest score. (E) PCA map classified by the scores related to web-based information collection among the components of the interest score. (F) PCA map legend. The size and direction of the black arrows indicate the contribution of each factor.

ence in diagnosing HPNGC, which was the primary outcome, was also based on the assumption of recall; therefore the results related to HPNGC detection may be overestimated. However, it is difficult to investigate the association between HPNGC

awareness and interest scores and HPNGC detection in a prospective or retrospective observational study, and a cross-sectional questionnaire-based study design was employed.

In conclusion, candidates for quality indicators of HPNGC detection were found to be JGES certification, high awareness of HPNGC (especially PSRCC), and high interest in HPNGC. Additionally, participation in related conferences is an important tool for gathering information on HPNGC.

Supplementary Material

Supplementary Fig. 1. Councilor of Japan Society of Gastroenterological Endoscopy (JGES) and population distribution in Japan. Supplementary materials related to this article can be found online at <https://doi.org/10.5946/ce.2022.167>.

Conflicts of Interest

The authors have no potential conflicts of interest.

Funding

None.

Author Contributions

Conceptualization: FI, TH, HU, YM; Data curation: FI, TH, HU, YM; Formal analysis: FI, SS; Investigation: FI, SS; Methodology: FI, SS; Software: FI; Supervision: SS; Validation: TH, HU, YM; Visualization: FI, SS; Writing-original draft: FI; Writing-review & editing: all authors.

ORCID

Fumiaki Ishibashi	https://orcid.org/0000-0003-4065-7958
Toshiaki Hirasawa	https://orcid.org/0000-0002-6450-1934
Hiroya Ueyama	https://orcid.org/0000-0002-5370-1009
Yohei Minato	https://orcid.org/0000-0002-1073-8514
Sho Suzuki	https://orcid.org/0000-0003-4831-1409

REFERENCES

1. Nomura A, Stemmermann GN, Chyou PH, et al. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 1991;325:1132-1136.
2. *Helicobacter and Cancer Collaborative Group*. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001;49:347-353.

3. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008;372:392–397.
4. Choi IJ, Kook MC, Kim YI, et al. *Helicobacter pylori* therapy for the prevention of metachronous gastric cancer. *N Engl J Med* 2018; 378:1085–1095.
5. Inoue M. Changing epidemiology of *Helicobacter pylori* in Japan. *Gastric Cancer* 2017;20(Suppl 1):3–7.
6. Wang C, Nishiyama T, Kikuchi S, et al. Changing trends in the prevalence of *H. pylori* infection in Japan (1908–2003): a systematic review and meta-regression analysis of 170,752 individuals. *Sci Rep* 2017;7:15491.
7. Watanabe M, Ito H, Hosono S, et al. Declining trends in prevalence of *Helicobacter pylori* infection by birth-year in a Japanese population. *Cancer Sci* 2015;106:1738–1743.
8. Matsuo T, Ito M, Takata S, et al. Low prevalence of *Helicobacter pylori*-negative gastric cancer among Japanese. *Helicobacter* 2011; 16:415–419.
9. Kiso M, Yoshihara M, Ito M, et al. Characteristics of gastric cancer in negative test of serum anti-*Helicobacter pylori* antibody and pepsinogen test: a multicenter study. *Gastric Cancer* 2017;20:764–771.
10. Nikaido M, Kakiuchi N, Miyamoto S, et al. Indolent feature of *Helicobacter pylori*-uninfected intramucosal signet ring cell carcinomas with CDH1 mutations. *Gastric Cancer* 2021;24:1102–1114.
11. Kiso M, Urabe Y, Ito M, et al. Clinical and genomic characteristics of mucosal signet-ring cell carcinoma in *Helicobacter pylori*-uninfected stomach. *BMC Gastroenterol* 2020;20:243.
12. Ueyama H, Yao T, Nakashima Y, et al. Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. *Am J Surg Pathol* 2010;34:609–619.
13. Ueyama H, Matsumoto K, Nagahara A, et al. Gastric adenocarcinoma of the fundic gland type (chief cell predominant type). *Endoscopy* 2014;46:153–157.
14. Ueyama H, Yao T, Akazawa Y, et al. Gastric epithelial neoplasm of fundic-gland mucosa lineage: proposal for a new classification in association with gastric adenocarcinoma of fundic-gland type. *J Gastroenterol* 2021;56:814–828.
15. Ishibashi F, Fukushima K, Ito T, et al. Influence of *Helicobacter pylori* infection on endoscopic findings of gastric adenocarcinoma of the fundic gland type. *J Gastric Cancer* 2019;19:225–233.
16. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;14:113–123.
17. Shibagaki K, Fukuyama C, Mikami H, et al. Gastric foveolar-type adenomas endoscopically showing a raspberry-like appearance in the *Helicobacter pylori*-uninfected stomach. *Endosc Int Open* 2019;7:E784–791.
18. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;64:31–9.
19. Bosman FT, Carneiro F, Hruban RH, et al. WHO classification of tumors of the digestive system. 4th ed. Lyon: JARC; 2010.
20. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020;76:182–188.
21. Sato C, Hirasawa K, Tateishi Y, et al. Clinicopathological features of early gastric cancers arising in *Helicobacter pylori* uninfected patients. *World J Gastroenterol* 2020;26:2618–2631.
22. Ishibashi F, Kobayashi K, Fukushima K, et al. Quality indicators for the detection of *Helicobacter pylori*-negative early gastric cancer: a retrospective observational study. *Clin Endosc* 2020;53:698–704.
23. Ishibashi F, Kobayashi K, Kawakami T, et al. Quality management system for screening esophagogastroduodenoscopy improves detection of *Helicobacter pylori*-negative interval gastric cancer. *Endosc Int Open* 2021;9:E1900–1908.
24. Lee SY, Yoshida N, Dohi O, et al. Differences in prevalence of lymphovascular invasion among early gastric cancers between Korea and Japan. *Gut Liver* 2017;11:383–391.
25. R Core Team. A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2022 [cited 2022 Mar 3]. Available from: <https://www.R-project.org/>.