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*Retrospective Cohort Study*

**Gastric cancer incidence based on endoscopic Kyoto classification of gastritis**

Toyoshima O *et al.* GC incidence based on Kyoto classification

## **Abstract**

### **BACKGROUND**

Gastric cancer (GC) incidence based on the endoscopic Kyoto classification of gastritis has not been systematically investigated using time-to-event analysis.

### **AIM**

To examine GC incidence in an endoscopic surveillance cohort.

### **METHODS**

This study was retrospectively conducted at the Toyoshima Endoscopy Clinic. Patients who underwent two or more esophagogastroduodenoscopies were enrolled. GC incidence was based on Kyoto classification scores, such as atrophy, intestinal metaplasia (IM), enlarged folds (EFs), nodularity, diffuse redness (DR), and total Kyoto scores. Hazard ratios (HRs) adjusted for age and sex were calculated using a Cox hazard model.

### **RESULTS**

A total of 6718 patients were enrolled (median age 55.0 years; men 44.2%). During the follow-up period (max 5.02 years; median 2.56 years), GC developed in 34 patients. The average frequency of GCs per year was 0.19%. Kyoto atrophy scores 1 [HR with score 0 as reference: 3.66, 95% confidence interval (CI): 1.06-12.61], 2 (11.60, 3.82-35.27), IM score 2 (9.92, 4.37-22.54), EF score 1 (4.03, 1.63-9.96), DR scores 1 (6.22, 2.65-14.56), and 2 (10.01, 3.73-26.86) were associated with GC incidence, whereas nodularity scores were not. The total Kyoto scores of 4 (HR with total Kyoto scores 0-1 as reference: 6.23, 95%CI: 1.93-20.13,  $P = 0.002$ ) and 5-8 (16.45, 6.29-43.03,  $P < 0.001$ ) were more likely to develop GC, whereas the total Kyoto scores 2-3 were not. The HR of the total Kyoto score for developing GC per 1 rank was 1.75 (95%CI: 1.46-2.09,  $P < 0.001$ ).

### **CONCLUSION**

A high total Kyoto score ( $\geq 4$ ) was associated with GC incidence. The endoscopy-based diagnosis of gastritis can stratify GC risk.

**Key Words:** Gastric cancer; Gastritis; Endoscopy; Atrophy; Intestinal metaplasia; Kyoto classification

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**Core Tip:** A high total Kyoto score ( $\geq 4$ ) was associated with gastric cancer (GC) incidence. Adjusted hazard ratios (HRs) for the total Kyoto scores of 4 and 5-8 were high at 6.23 and 16.45, respectively, compared to the total Kyoto scores of 0-1. The HR of the total Kyoto score for developing GC per 1 rank was 1.75.

## INTRODUCTION

<sup>2</sup> Gastric cancer (GC) is a global health problem and the third most common cause of cancer-related deaths worldwide<sup>[1]</sup>. *Helicobacter pylori* (*H. pylori*) infection is estimated to account for 89% of GC cases, and *H. pylori*-related gastritis is a precursor of GC<sup>[2-6]</sup>. Evaluation of *H. pylori*-related gastritis is clinically important because it allows for the risk stratification of GC<sup>[2,7-9]</sup>. Endoscopy detects early GCs and precisely diagnoses gastritis. Periodic endoscopic screening can reduce deaths from GC<sup>[10]</sup>. Recent advances in endoscopic technology allow for more accurate endoscopic diagnosis of gastritis<sup>[11,12]</sup>.

The endoscopy-based Kyoto classification of gastritis was advocated by the Japan Society for Gastrointestinal Endoscopy in 2013. This classification aims to ensure that the endoscopic diagnosis of gastritis is unified and matched with the histopathology<sup>[13]</sup>. Recently, the Kyoto classification has been widely used in clinical practice and vigorously studied worldwide<sup>[14,15]</sup>. To assess GC risk, the Kyoto classification individually scores five *H. pylori*-related gastritis findings, such as atrophy, intestinal

metaplasia (IM), enlarged fold (EF), nodularity, and diffuse redness (DR), and defines their sum as the total Kyoto score.

Several investigations have clarified that not only individual Kyoto scores but also the total Kyoto score are associated with *H. pylori* infection and GC risks<sup>[14]</sup>. For example, the total Kyoto score was associated with *H. pylori* infection, presence of GC<sup>[16-19]</sup>, and GC risk indicators, such as serum pepsinogen titer, serum *H. pylori* antibody titer, histological distribution of neutrophil infiltration in the gastric mucosa, and genotype of the single nucleotide polymorphism. Collectively, total Kyoto scores of 0,  $\geq 2$ , and  $\geq 4$  indicated a normal stomach, *H. pylori*-infected gastritis, and gastritis at risk for GC, respectively<sup>[14]</sup>.

To date, GC incidence based on the Kyoto classification scores has not been systematically investigated using time-to-event analysis. Therefore, we examined GC incidence according to the five individual Kyoto scores and the total Kyoto score in the endoscopic surveillance cohort and verified the GC risks of endoscopic gastritis in Japan, which is a high GC morbidity area.

## **MATERIALS AND METHODS**

### ***Study design and overview***

This cohort study was retrospectively conducted at the Toyoshima Endoscopy Clinic. We obtained data from the Toyoshima Endoscopy Clinic Database. This study was approved by the institutional review board of the Yoyogi Mental Clinic (approval no. RKK227). Written informed consent was obtained from patients at the time of esophagogastroduodenoscopy (EGD) to use their data for research purposes. The study's protocol was published on our institute's website ([www.ichou.com](http://www.ichou.com)) so that patients could opt out of the study. All clinical investigations were conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

### ***Patients***

This study enrolled patients who underwent two or more EGDs at the Toyoshima Endoscopy Clinic, an urban area in Tokyo, Japan, between April 2017 and April 2022. We excluded patients with a previous surgical gastrectomy at baseline and those who underwent the last EGD within one month after the index EGD. The indications for the index EGD included screening, surveillance for gastritis or other upper gastrointestinal diseases, and examination for symptoms or abnormal findings on other tests. *H. pylori* status was determined using serum anti-*H. pylori* antibodies, urea breath test, histology, and/or endoscopy.

### ***Kyoto classification score***

In the Kyoto classification, the total Kyoto score was developed as a GC risk score<sup>[14]</sup>. The total Kyoto score is calculated as the sum of the following five Kyoto scores: Atrophy, IM, EF, nodularity, and DR, and ranges from 0 to 8 (Supplementary Table 1). Atrophy was classified based on the extent of mucosal atrophy using the Kimura-Takemoto classification<sup>[20]</sup>. Non-atrophy and Closed I, Closed II and III, and Open I to III were scored as atrophy scores of 0, 1, and 2, respectively. The IM commonly appears as a grayish-white, slightly elevated patch. IM scores of 0, 1, and 2 were defined as the absence of IM, IM limited to the antrum, and IM extending into the corpus, respectively. EF was defined as a width of  $\geq 5$  mm in the greater curvature of the corpus, which was not flattened by stomach insufflation. The absence and presence of EF were scored as 0 and 1, respectively. Nodularity was identified by a miliary pattern resembling “goose flesh”, which was typically located in the antrum. The absence and presence of nodularity were scored 0 and 1, respectively. DR indicated uniform redness observed in the non-atrophic mucosa, mainly in the greater curvature of the corpus. The regular arrangement of collecting venules (RAC) in the corpus appears as numerous dots, which are starfish-like shapes in close view. DR scores of 0, 1, and 2 were defined as the absence of DR, mild DR and/or DR with partial RAC, and severe DR without RAC, respectively<sup>[14]</sup>.

### **EGD**

EGDs were performed by gastrointestinal endoscopists using the Olympus' (Tokyo, Japan) endoscopic system (EVIS X1 or LUCERA ELITE) and endoscope (GIF-XZ1200, GIF-1200N, GIF-HQ290, GIF-H290Z, or GIF-XP290N). The T-File System (STS-MEDIC Inc., Tokyo, Japan) was used to file endoscopic images and document endoscopic findings.

The Kyoto classification scores were assessed using white light imaging without magnification. The endoscopists diagnosed the Kyoto classification scores on-site during EGD, and it was retrospectively reviewed by experienced endoscopists. Endoscopists performed EGDs after learning from textbooks and journal articles on the Kyoto classification of gastritis<sup>[14,21]</sup>.

### **GC**

GC was histologically diagnosed based on biopsy or resected specimens. GC morphology and histology were classified based on the Japanese classification of gastric carcinoma<sup>[22]</sup> and Lauren's classification<sup>[23]</sup>, respectively.

### **Outcomes**

This cohort study evaluated GC incidence based on patients' age, sex, *H. pylori* status, and endoscopic Kyoto classification scores of gastritis, such as atrophy, IM, EF, nodularity, DR, and total Kyoto scores. The primary outcome was GC incidence according to the total Kyoto score. We performed a time-to-event analysis with the start time as the date of index EGD. Data were censored on the date of the last EGD. The effects of Kyoto classification scores on GC development were estimated. The total Kyoto scores were categorized into 4 (*i.e.*, 0-1, 2-3, 4, and 5-8) based on the frequency of GC increasing stepwise with the total Kyoto scores of 0-1, 2-3, and  $\geq 4$  in a cross-sectional study<sup>[24]</sup> and the number of patients in this study. The secondary outcomes were GC incidence according to the Kyoto atrophy, IM, EF, nodularity, and DR scores.

### *Statistical analysis*

Baseline characteristics were compared between GC and non-GC groups using binomial logistic regression model. Kaplan-Meier curves were constructed according to patient age, sex, *H. pylori* status, and Kyoto classification scores (*i.e.*, atrophy, IM, EF, nodularity, DR, and the total Kyoto scores). Statistical differences were estimated using the log-rank tests. The average frequency of GCs per year was calculated by dividing the number of events by the total person-years of observation. Hazard ratios (HRs) with 95% confidence intervals (CIs) for GC development were estimated using the Cox proportional hazards regression model. In multivariate analysis, HRs were adjusted for patient age and sex. A *P*-value < 0.05 (two-sided) was defined as statistically significant. Statistical analysis was conducted using BellCurve for Excel version 4.03 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

## **RESULTS**

### *Patient enrollment*

A total of 30585 EGDs in 16969 patients were performed during the study period. Six thousand seven hundred forty-four patients underwent two or more EGDs. Of these, 19 patients with a previous surgical gastrectomy and 7<sup>3</sup> with a follow-up period of less than 1<sup>1</sup> mo were excluded. A total of 6718 patients were enrolled.

<sup>1</sup> The baseline patient characteristics are shown in Table 1. The median age of the patients was 54 years with the interquartile range (IQR) of 46-64 years. Men accounted for 44.2% of the cases. The proportion of patients with *H. pylori* status of uninfected, eradicated, and currently infected was 55.9%, 33.7%, and 10.4%, respectively. Patients were followed up for up to 5.02 years (median 2.56 years, IQR 1.74-3.64 years). The median (IQR) of Kyoto classification scores were 0 (0-1) for atrophy; 0 (0-0) for IM, EF, nodularity, and DR; and 0 (0-2) for total Kyoto. Supplementary Table 2 is shown with the mean and standard deviation. During the follow-up period, 37 GCs occurred in 34 patients. The characteristics of GCs are presented in Table 2. All GCs were superficial and within the submucosal depth. Lauren's intestinal type made up 89.1% of GCs.

### ***GC incidence***

Kaplan-Meier curves of GC development according to patient demographic characteristics are shown in Figure 1. In this study, the average frequency of GCs was 0.19%/year. Age and *H. pylori* status were associated with GC incidence (both  $P < 0.001$ ), whereas sex was not.

Figures 2A-E show the cumulative incidence using the Kaplan-Meier method for each Kyoto classification score. Atrophy, IM, EF, and DR scores were associated with GC development (all  $P < 0.001$ ), whereas nodularity was not. The average frequencies of GCs per year were 0.04%, 0.17%, and 0.73% for atrophy scores of 0, 1, and 2; 0.07%, 0.25%, and 1.10% for IM scores of 0, 1, and 2; 0.17% and 0.92% for EF scores of 0 and 1; and 0.06%, 0.55%, and 0.74% for DR scores of 0, 1, and 2, respectively. The total Kyoto score was associated with GC development ( $P < 0.001$ ), as shown in Figure 2F. The average frequencies of GCs were 0.05, 0.07, 0.47, and 1.27% per year for the total Kyoto scores of 0-1, 2-3, 4, and 5-8, respectively.

### ***Multivariate analysis of GC incidence***

Table 3 provides the crude and adjusted HRs for GC development according to Kyoto classification scores. Multivariate analysis showed that atrophy scores 1 (adjusted HR with score 0 as reference: 3.66, 95%CI: 1.06-12.61), 2 (11.60, 3.82-35.27), IM score 2 (9.92, 4.37-22.54), EF score 1 (4.03, 1.63-9.96), DR scores 1 (6.22, 2.65-14.56), and 2 (10.00, 3.73-26.86) were significantly associated with GC incidence, independent of patient age and sex, whereas nodularity score was not.

The total Kyoto scores of 4 (adjusted HR with total Kyoto scores 0-1 as reference: 6.23, 95%CI: 1.93-20.13,  $P = 0.002$ ) and 5-8 (16.45, 6.29-43.03,  $P < 0.001$ ) were more likely to develop GC, whereas the total Kyoto scores of 2-3 were not. In per 1 rank analysis, an adjusted HR of the total Kyoto score for developing GC was 1.75 (95%CI: 1.46-2.09,  $P < 0.001$ ).

## DISCUSSION

We found that high total Kyoto scores, especially  $\geq 4$ , were associated with GC incidence. The adjusted HR of the total Kyoto score for GC development was 1.75 per 1 rank analysis. Additionally, adjusted HRs for the total Kyoto scores of 4 and 5-8 were high at 6.23 and 16.45, respectively, compared to the total Kyoto scores of 0-1. The total Kyoto score was associated with the cumulative incidence of GC ( $P < 0.001$ ). The average frequencies of GCs per year increased with the total Kyoto score (0.05%, 0.07%, 0.47%, and 1.27% for the total Kyoto scores of 0-1, 2-3, 4, and 5-8, respectively). This is the first report that shows that high total Kyoto scores represent GC risks in a time-to-event analysis. This finding is consistent with those of several previous studies. In cross-sectional studies, we and Lin *et al*<sup>[19]</sup> reported that the odds ratios of the total Kyoto score for GC were 1.6 and 1.5 per 1 rank, respectively<sup>[18]</sup>. Liu *et al*<sup>[24]</sup> indicated an increased trend of GC frequency in patients with total Kyoto scores of 0-1, 2-3, and  $\geq 4$ . Some investigators showed that the mean total Kyoto scores of the patients with GC, *H. pylori*-infected GC, and *H. pylori*-eradicated GC were 4.0-4.6, 4.8-5.6, and 4.2, respectively<sup>[18,25,26]</sup>. Taken together, a total Kyoto score  $\geq 4$  was available for determining GC risks.

This cohort study demonstrated that patients with endoscopy-based atrophy, IM, EF, and DR are more likely to develop GC. In contrast, nodularity was not associated with GC incidence. Endoscopic atrophy has been shown to be a predictor of GC development. Shichijo *et al*<sup>[27]</sup> described a significantly higher adjusted HR of severe atrophy for developing GC as 9.3, while we identified significantly higher adjusted HRs of Kyoto atrophy scores 1 and 2 as 3.7 and 11.6, respectively. Several cohort studies have shown that severe endoscopic atrophy is associated with a high incidence of GC, especially in patients who have undergone *H. pylori* eradication<sup>[9,27,28]</sup>. These studies revealed that the average frequencies of GCs per year for non-to-mild, moderate, and severe atrophy were 0.06%-0.15%, 0.12%-0.34%, and 0.31%-1.60%, respectively. Similarly, our study showed that the average frequencies of GCs per year for total Kyoto scores of 0, 1, and 2 were 0.04%, 0.17%, and 0.73%, respectively. Since more than

half of the study patients were uninfected with *H. pylori*, our study may present a lower GC incidence in patients with a Kyoto atrophy score of 0. Two meta-analyses also showed that a high Kyoto atrophy score provided a high-risk ratio of 2.8-8.0<sup>[29,30]</sup>. Thus, our study results are in line with those of previous studies.

Although the risk of GC in histological IM has been well studied<sup>[2,8,27,31,32]</sup>, few studies have examined GC risks associated with endoscopic IM. A high Kyoto IM score has been identified as a risk factor for GC, especially multiple GC<sup>[14,18]</sup>. This study revealed that endoscopic corpus IM was associated with GC development (adjusted HR: 9.92), which is supported by Sakitani *et al*<sup>[33]</sup>, who clarified histological corpus IM as a predictor of GC. The consistency of IM between endoscopy and histology has been demonstrated<sup>[13]</sup>; we successfully verified endoscopic IM as a risk factor for GC using event history analysis.

Watanabe *et al*<sup>[34]</sup> provided an adjusted HR of EF for GC development as high as 43.3, whereas our study's adjusted HR was 4.03. These results are similar; however, the difference in HRs between them may be attributed to the inclusion of many *H. pylori*-uninfected individuals in the study population. However, whether nodularity is a risk factor for GC remains controversial. Nodularity has been reported to be a juvenile and histologically diffuse-type GC risk<sup>[35,36]</sup>, whereas we have shown in a cross-sectional study that the odds ratio for GC of nodularity is low at 0.5<sup>[18]</sup>. After adjusting for age and sex, no association between nodularity and GC was observed. Although nodularity decreases with age<sup>[37]</sup>, the risk of intestinal-type GC increases with age. Furthermore, intestinal-type cancers are more common than diffuse-type cancers. Therefore, age offsets the association of nodularity with GC, especially in older generations, although nodularity is associated with diffuse-type GC in the young generation<sup>[35]</sup>. As the association between nodularity and the risk of developing GC is still debated, nodularity might be listed separately. For example, the total Kyoto classification score for atrophy 1, IM 0, EF 1, nodularity 1, and DR 1 might be reported as 3 + 1 instead of 4.

Several studies have reported that DR is strongly associated with *H. pylori* infection<sup>[15,38-40]</sup>, but little is known about the association between DR and GC incidence.

This study identified Kyoto DR scores of 1 and 2 as indicators of GC incidence (adjusted HRs: 6.22 and 10.01, respectively). Since DR presents inflammatory cell infiltration caused by *H. pylori*<sup>[13]</sup> and *H. pylori* infection is a definite risk factor for GC<sup>[2,3]</sup>, DR is expressed as a GC risk. Additionally, since the Kyoto DR score includes RAC as a negative factor and RAC is inversely associated with GC development<sup>[41]</sup>, a high Kyoto DR score may be associated with high GC incidence.

<sup>1</sup> This study has some limitations. First, this was a single-center, retrospective cohort study. Although the endoscopy data were well-organized, multi-center, prospective studies are warranted. Second, this study was conducted only in areas with a high GC prevalence in Asia. Therefore, studies in Western countries are warranted. Third, the total Kyoto score has shortcomings in the scoring design, which simply adds five individual Kyoto scores<sup>[14]</sup>. <sup>1</sup> IM is associated with a high risk of intestinal-type GC but a low risk of diffuse-type GC<sup>[18]</sup>. In addition, EF and nodularity are high risks for diffuse-type GC but low risks for intestinal-type GC. Therefore, the evaluation of GC risk using a scoring system that individually predicts the risks of intestinal- and diffuse-type GCs is needed.

## CONCLUSION

In conclusion, a high total Kyoto score of  $\geq 4$  was associated with GC incidence in a cohort study. The endoscopy-based diagnosis of gastritis can stratify GC risk.

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