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Endoscopic Kyoto classification of *Helicobacter pylori* infection and gastric cancer risk diagnosis

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Abstract

Recent advances in endoscopic technology allow detailed observation of the gastric mucosa. Today, endoscopy is used in the diagnosis of gastritis to determine the presence/absence of *Helicobacter pylori* (*H. pylori*) infection and evaluate gastric cancer risk. In 2013, the Japan Gastroenterological Endoscopy Society advocated the Kyoto classification, a new grading system for endoscopic gastritis. The Kyoto classification organized endoscopic findings related to *H. pylori* infection. The Kyoto classification score is the sum of scores for five endoscopic findings (atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness with or without regular arrangement of collecting venules) and ranges from 0 to 8. Atrophy, intestinal metaplasia, enlarged folds, and nodularity contribute to gastric cancer risk. Diffuse redness and regular arrangement of collecting venules are related to *H. pylori* infection status. In subjects without a history of *H. pylori* eradication, the infection rates in those with Kyoto scores of 0, 1, and ≥ 2 were 1.5%, 45%, and 82%, respectively. A Kyoto classification score of 0 indicates no *H. pylori* infection. A Kyoto classification score of 2 or more indicates *H. pylori* infection. Kyoto classification scores of patients with and without gastric cancer were 4.8 and 3.8, respectively. A Kyoto classification score of 4 or more might indicate gastric cancer risk.

Key words: Gastric cancer; *Helicobacter pylori*; Endoscopy; Kyoto classification; Atrophy; Intestinal metaplasia; Enlarged fold; Nodularity; Diffuse redness; Regular arrangement of collecting venules

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Core tip: The Kyoto classification organizes endoscopic findings based on *Helicobacter*

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pylori (*H. pylori*) infection. The score of the Kyoto classification is the sum of scores of five endoscopic findings (atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness with or without regular arrangement of collecting venules) and ranges from 0 to 8. A high score is believed to reflect a higher risk of current *H. pylori* infection and gastric cancer. A Kyoto classification score of 0 indicates no *H. pylori* infection. A Kyoto classification score of ≥ 2 indicates current *H. pylori* infection. A Kyoto classification score of ≥ 4 might indicate gastric cancer risk.

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INTRODUCTION

Gastric cancer is the third most common cancer in the world and is the cancer with the third greatest number of mortalities. If gastric cancer is detected at an early stage, it can be cured via endoscopic submucosal dissection^[1,2]. Although periodic endoscopic examination is important for detecting early gastric cancer, efficient surveillance requires identification of high-risk populations^[3-7]. The genetic risks of gastric cancer have been reported to include hereditary cancer syndrome, single nucleotide polymorphisms, and family history^[8-12]. Environmental risks include *Helicobacter pylori* infection, smoking, excessive salt consumption, and lack of vegetable. Among them, the association between *H. pylori* infection and the development of gastric cancer is well established, and *H. pylori* virulence factors (cagA, vacA, iceA, and dupA) are known^[13-16]. The International Agency for Research on Cancer categorized *H. pylori* infection as a type I carcinogen and it is considered the primary cause of gastric cancer. On the other hand, *H. pylori* eradication reduces gastric cancer risk^[17-20]. Therefore, the accurate assessment of *H. pylori* infection status is important. Nowadays, endoscopic examination is required to diagnose *H. pylori* infection status. In 2013, the Japan Gastroenterological Endoscopy Society advocated the Kyoto classification, a new grading system for endoscopic gastritis. In this review, we focus on up-to-date reports regarding the Kyoto classification to help improve endoscopic practice.

DEFINITION OF KYOTO CLASSIFICATION OF GASTRITIS

Thanks to advances in endoscopic technology, it is now possible to observe the gastric mucosa in minute detail. Today, endoscopy is used in the diagnosis of gastritis to determine the presence/absence of *H. pylori* infection and evaluate the risks of gastric cancer. The Kyoto classification of endoscopic findings was advocated when the 85th Congress of the Japan Gastroenterological Endoscopy Society was held in Kyoto in 2013. The purpose of the Kyoto classification was to evaluate the gastric mucosa, as this presents a potential risk of developing gastric cancer^[21,22]. In this classification, 19 endoscopic findings related to gastritis, including atrophy, intestinal metaplasia, enlarged folds (tortuous folds), nodularity, diffuse redness, regular arrangement of collecting venules (RAC), map-like redness, foveolar-hyperplastic polyp, xanthoma, mucosal swelling, patchy redness, depressed erosion, sticky mucus, hematin, red streak, spotty redness, multiple white and flat elevated lesions, fundic gland polyp, and raised erosion, are characterized. Among them, atrophy, intestinal metaplasia, enlarged folds, and nodularity, which may be related to gastric cancer risk, and diffuse redness with or without RAC, which is related to *H. pylori* infection status, are accounted for in the Kyoto classification score (Table 1)^[22].

Endoscopic atrophy (Kimura-Takemoto classification)

Atrophy includes "pathological" atrophy and "endoscopic" atrophy. Atrophy is pathologically defined as a loss of glandular tissue^[23]. The Kyoto classification adopted Kimura-Takemoto classification of endoscopic atrophy^[24]. Kimura *et al*^[24] defined a visible capillary network, low niveau, and yellowish pale in color as atrophic features, while diffuse redness with high mucosal height as characteristics of

Table 1 Kyoto classification score

Kyoto classification	Score
Atrophy	
None, C1	0
C2 and C3	1
O1-O3	2
Intestinal metaplasia	
None	0
Antrum	1
Corpus and antrum	2
Enlarged folds	
Absence	0
Presence	1
Nodularity	
Absence	0
Presence	1
Diffuse redness	
None	0
Mild (with RAC)	1
Severe	2
Kyoto score	0-8

RAC: Regular arrangement of collecting venules.

non-atrophy. We show endoscopic images and a schematic diagram in [Figure 1](#). “Endoscopic” atrophy has been reported to correlate well with “pathological” atrophy^[25-29]. In the Kyoto classification score, non-atrophy (C0) and C1 were scored as Atrophy score 0, C2 and C3 as Atrophy score 1, and O1 to O3 as Atrophy score 2.

Endoscopic intestinal metaplasia

Intestinal metaplasia typically appears grayish-white and slightly elevated plaques surrounded by mixed patchy pink and pale areas of mucosa, forming an irregular uneven surface ([Figure 2A](#)). A villous appearance, whitish mucosa, and rough mucosal surface are useful indicators for endoscopic diagnosis of intestinal metaplasia^[30]. Image-enhanced endoscopy, including narrow-band imaging (NBI), blue laser imaging, and linked color imaging, has improved the visibility of endoscopic findings and accuracy of endoscopic diagnosis of intestinal metaplasia^[31-39]. A white opaque substance on the surface epithelium and light blue crest on the mucosal epithelial rim visualized using magnified NBI are associated with intestinal metaplasia^[40-42].

In the Kyoto classification score, the absence of intestinal metaplasia was scored as Intestinal metaplasia score 0, the presence of intestinal metaplasia within the antrum as Intestinal metaplasia score 1, and intestinal metaplasia extending into the corpus as Intestinal metaplasia score 2. The Intestinal metaplasia score is diagnosed by using white light imaging. Intestinal metaplasia diagnosis based on image-enhanced endoscopy using NBI, blue laser imaging, linked color imaging, and chromo-endoscopy is not included in the Kyoto score.

Map-like redness (synonymous with mottled patchy erythema) is defined as multiple flat or slightly depressed erythematous lesions that have various shapes, sizes, and red densities ([Figure 2B](#))^[6,43]. When using biopsy specimens of map-like redness, intestinal metaplasia is frequently observed (87.3%)^[43]. The mechanism of the appearance of map-like redness is thought to be strengthening of the contrast between non-atrophic mucosa and atrophic mucosa after diffuse redness has disappeared following successful eradication^[21]. Map-like redness is not always found following eradication. However, when it is observed, there is virtually no doubt that it is indicative of post-eradication gastric mucosa^[22].

Enlarged folds

An enlarged fold is defined as a fold with a width of 5 mm or more that is not flattened or is only partially flattened by insufflation of the stomach ([Figure 2C](#)). Rugal hyperplasia is a synonym for enlarged folds.

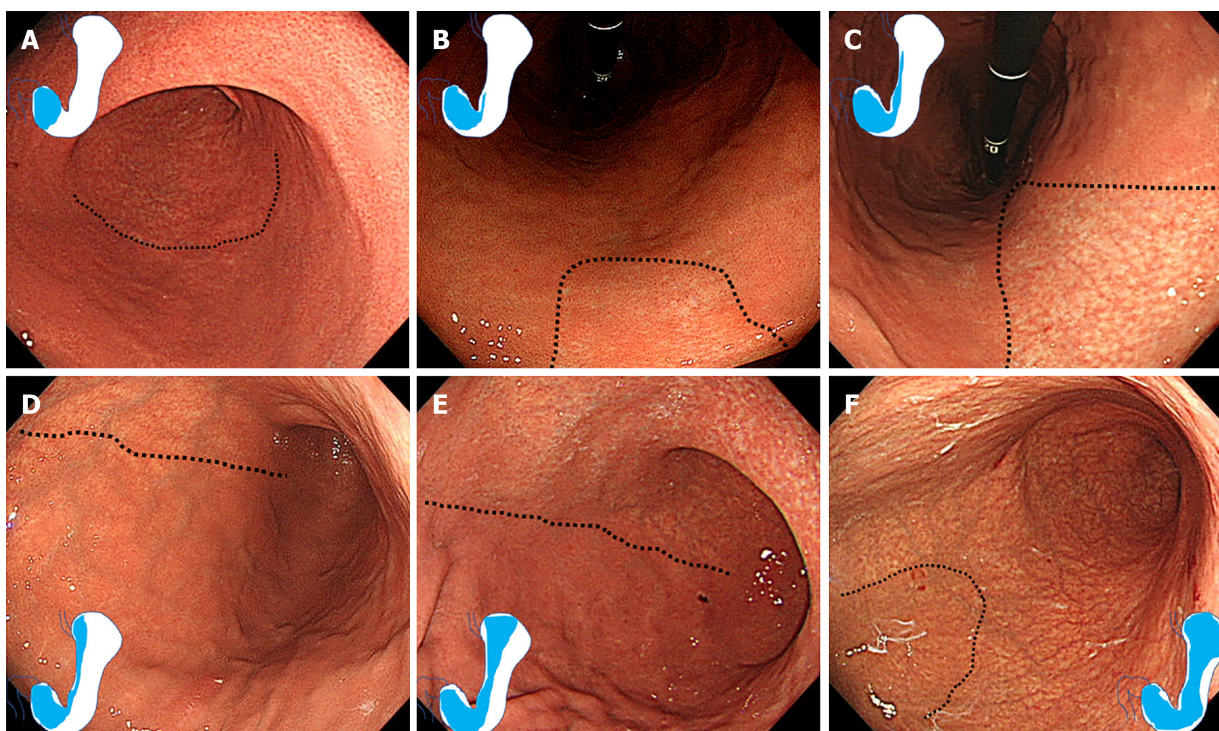


Figure 1 Kimura-Takemoto classification of endoscopic atrophy. Atrophic borders are indicated by a dotted line. A: C1 (Atrophy is limited to the antrum); B: C2 (Atrophy is limited to the minor area of the lesser curvature of the body); C: C3 (Atrophy exists in the major area of the lesser curvature of the body but does not extend beyond the cardia); D: O1 (Atrophy extends to the fundus over the cardia. Atrophic border of the body lies between the lesser curvature and anterior wall); E: O2 (Atrophic border of the body lies on the anterior wall); F: O3 (Atrophy is widespread with the border between the anterior wall and greater curvature).

In the Kyoto classification score, the absence and presence of enlarged folds was scored as Enlarged folds score 0 and 1, respectively.

Nodularity

Nodular gastritis is characterized by a miliary pattern resembling “goose flesh” mainly located in the antrum (Figure 2D). Nodularity can be more clearly seen following the use of indigo carmine spray. Lymphoid follicles and/or intense inflammatory cell infiltration are observed in biopsy specimens of nodularity^[44]. Nodular gastritis displays a female predominance and improves gradually with age. A high serum *H. pylori* antibody titer is correlated to nodularity^[45-49].

In the Kyoto classification score, the absence and presence of nodularity was scored as Nodularity score 0 and 1, respectively.

Diffuse redness

Diffuse redness refers to uniform redness with continuous expansion observed in non-atrophic mucosa mainly in the corpus (Figure 2E) and is typical of endoscopic superficial gastritis^[22,24]. Congestion and dilation of the subepithelial capillary network in the gastric mucosa with inflammatory change of the mucosal surface color to red^[50]. Since the assessment of the severity of diffuse redness is affected by the setting of the endoscope and monitor, objective assessment may be difficult.

On the other hand, RAC is a condition in which the collecting venules are arranged in the corpus. From a distance, it appears like numerous dots. From up close, it has the appearance of a regular pattern of starfish-like shapes (Figure 2F).

In the Kyoto classification score, the absence of diffuse redness was scored as Diffuse redness score 0, mild diffuse redness or diffuse redness with RAC as Diffuse redness score 1, and severe diffuse redness or diffuse redness without RAC as Diffuse redness score 2.

Kyoto classification score

The Kyoto classification score for gastritis is based on the sum of scores of the five endoscopic findings and ranges from 0 to 8 (Table 1). A high score is believed to reflect increased risk of *H. pylori* infection and gastric cancer. In a study that evaluated the usefulness and convenience of the Kyoto classification, a mini-lecture improved the accuracy of endoscopic diagnosis^[51].

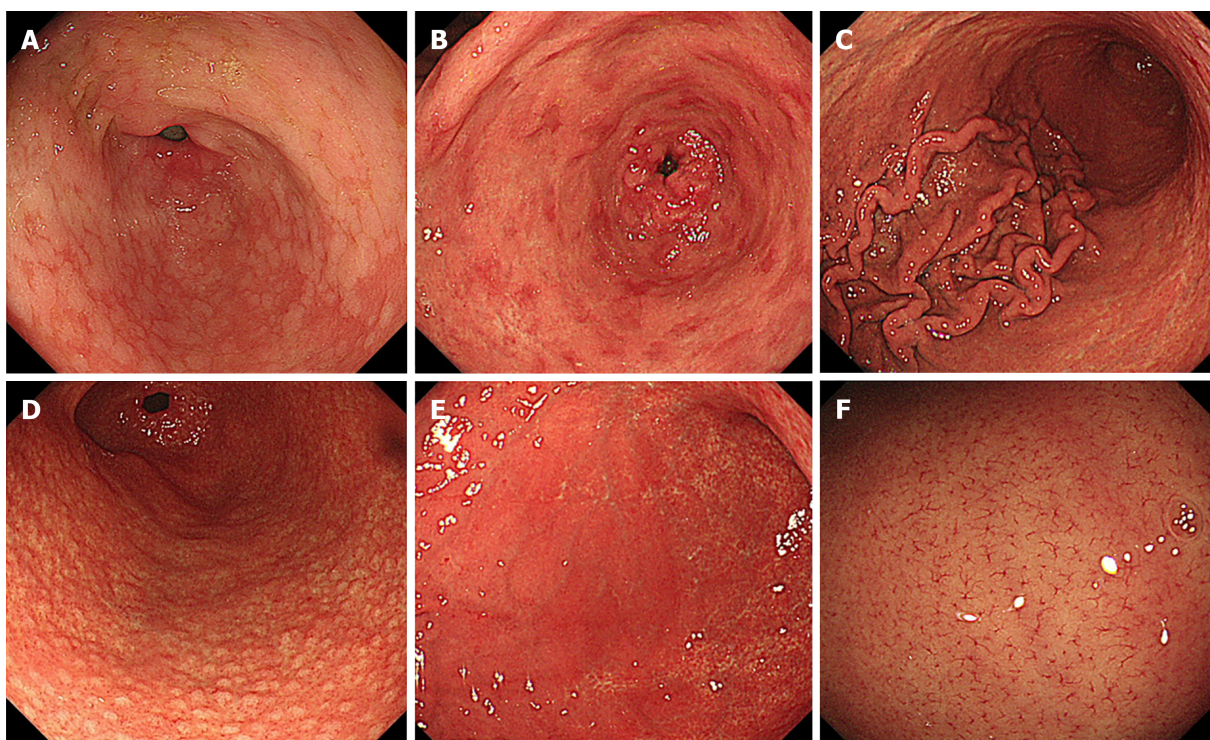


Figure 2 Endoscopic findings of Kyoto classification. A: Intestinal metaplasia; B: Map-like redness; C: Enlarged folds; D: Nodularity; E: Diffuse redness; F: Regular arrangement of collecting venules in weakly magnified image.

DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION BY ENDOSCOPIC FINDINGS

There are several reports to investigate the relationship between endoscopic findings and *H. pylori* infection^[52-56]. Table 2 shows the diagnostic values of the Kyoto classification for *H. pylori* infection^[57-62]. Enlarged folds had a relatively good positive predictive value (56.2–86.0%). Although nodularity had a low sensitivity (6.4%–32.1%) for *H. pylori* infection, it had excellent specificity for a current infection (95.8%–98.8%). Diffuse redness had a good positive predictive value (65.6%–91.5%). RAC had a high sensitivity for non-infection (86.7%–100%).

Yoshii *et al.*^[61] reported that endoscopic atrophy has a specificity of 75.5% for the diagnosis of past *H. pylori* infection. Furthermore, intestinal metaplasia and map-like redness also have a higher specificity (92.6% and 98.0%, respectively) for the diagnosis of past *H. pylori* infection.

Diagnosis of *H. pylori* infection based on Kyoto classification score

Several studies investigated the relationship between the total Kyoto classification score and *H. pylori* infection. We reported an association between total Kyoto classification score and serum *H. pylori* antibody titer^[48]. Kyoto scores were 0.1, 0.4, 1.9, and 2.3 for negative-low, negative-high, positive-low, and positive-high titers of *H. pylori* antibody, respectively. Kyoto scores increased in line with the *H. pylori* antibody titer. In subjects with a negative-high *H. pylori* antibody titer, the Kyoto classification had an excellent area under the receiver operating characteristics curve (0.886) for predicting *H. pylori* infection with a cutoff value of 2. A Kyoto score of ≥ 2 could predict *H. pylori* infection with an accuracy of 90%^[63]. In 870 subjects with no history of *H. pylori* eradication therapy, *H. pylori* infection rates in those with Kyoto classification scores of 0, 1, and ≥ 2 were 1.5%, 45%, and 82%, respectively^[64].

High Kyoto scores do not always correspond to an active *H. pylori* infection. False diagnosis can occur due to either a spontaneous negative conversion or an unintentional eradication. In cases of spontaneous negative conversion, the harsh environment of the intestinal metaplasia removes the *H. pylori* infection spontaneously. In cases of unintentional eradication, the *H. pylori* infection is eradicated after the treatment of other infectious diseases with antibiotics.

Essentially, a Kyoto classification score of ≥ 2 indicates *H. pylori* infection. On the other hand, a Kyoto classification score of 0 indicates no *H. pylori* infection.

Table 2 Diagnostic value of Kyoto classification for *Helicobacter pylori* infection

Endoscopic findings	Ref.	Year	No. of subjects	Sensitivity	Specificity	PPV	NPV
Diagnosis for current <i>H. pylori</i> infection							
Enlarged folds	Kato <i>et al</i> ^[59]	2013	275	58.5	79.5	76.9	62.2
Enlarged folds	Mao <i>et al</i> ^[60]	2016	256	60.2	92.3	86.0	74.6
Enlarged folds	Yoshii <i>et al</i> ^[61]	2019	498	23.1	96.6	56.2	87.0
Nodularity	Laine <i>et al</i> ^[57]	1995	52	32.1	95.8	90.0	54.8
Nodularity	Kato <i>et al</i> ^[59]	2013	275	5.3	98.8	75.0	59.4
Nodularity	Yoshii <i>et al</i> ^[61]	2019	498	6.4	98.3	41.7	84.9
Diffuse redness	Kato <i>et al</i> ^[59]	2013	275	83.4	66.9	73.8	78.4
Diffuse redness	Mao <i>et al</i> ^[60]	2016	256	57.5	95.8	91.5	74.7
Diffuse redness	Yoshii <i>et al</i> ^[61]	2019	498	60.0	94.7	65.6	93.3
Diagnosis for negative <i>H. pylori</i> infection							
RAC	Yagi <i>et al</i> ^[58]	2002	557	91.1	97.9	95.0	96.2
RAC	Kato <i>et al</i> ^[59]	2013	275	93.6	48.0	87.0	66.8
RAC	Mao <i>et al</i> ^[60]	2016	256	86.7	90.2	87.5	89.6
RAC	Garcés-Durán <i>et al</i> ^[62]	2019	140	100.0	49.0	47.3	100.0

PPV: Positive predictive value; NPV: Negative predictive value; RAC: Regular arrangement of collecting venules; *H. pylori*: *Helicobacter pylori*.

GASTRIC CANCER RISK ASSESSED BASED ON ENDOSCOPIC FINDINGS OF KYOTO CLASSIFICATION

There are several reports of gastric cancer risk assessed based on endoscopic findings^[65-69]. Three Japanese cohort studies revealed the association of endoscopic atrophy with gastric cancer incidence (Table 3). They showed that the gastric cancer incidence of mild, moderate, and severe atrophy is 0.04%–0.10%/year, 0.12%–0.34%/year, and 0.31%–1.60%/year, respectively^[70-72]. Shichijo *et al*^[71] reported that cancer incidence was extremely high, affecting 16.0% of patients with severe atrophy over 10-year periods. Gastric cancer risk increases according to the extent of the gastric atrophy.

Table 4 shows the odds ratio of gastric cancer depending on the presence or absence of the endoscopic findings of the Kyoto classification^[49,73-75]. Gastric atrophy (open-type) was associated with gastric cancer with an odds ratio of 7.2–14.2^[76,77].

Sugimoto *et al*^[74] have reported that endoscopic intestinal metaplasia was associated with early gastric cancer with an odds ratio of 5.0. Intestinal metaplasia is reported to be associated with intestinal-type cancer^[78].

A cross-sectional study reported an odds ratio of 5.0 for enlarged folds of 5 mm or more for gastric cancer patient with *H. pylori*-infected controls as a reference^[73]. It also indicated an upward shift in the distribution of gastric fold widths in *H. pylori*-positive patients with gastric cancer to an odds ratio of 35.5 in those with a fold width of 7 mm. Inflammation-induced DNA methylation of various genes is involved in the development of gastric cancer in gastritis with enlarged folds^[50,73,79-85]. Enlarged folds are reported to be associated with diffuse-type gastric cancer^[73,86].

Nishikawa *et al*^[49] reported an odds ratio of 13.9 for gastric cancer in *H. pylori*-positive patients with nodularity. In a study involving *H. pylori*-positive patients under the age of 29, nodularity provided an odds ratio of 64.2 for gastric cancer. Nodularity is reported to be associated with diffuse-type cancer^[49,87].

RAC was reported to be negatively associated with gastric cancer (odds ratio: 0.4)^[75].

Gastric cancer risk assessed using the Kyoto classification score

Sugimoto *et al*^[74] presented the relationship between total Kyoto classification score and gastric cancer risk. In their cross-sectional study, the total Kyoto classifications scores of patients with and without gastric cancer were 4.8 and 3.8, respectively. This study suggests that a Kyoto classification score of ≥ 4 might indicate gastric cancer risk.

Table 3 Gastric cancer incidence according to endoscopic atrophy

Ref.	Population	No. of subjects	No. of cancers	Duration, yr	Gastric cancer incidence, %/yr		
					Mild	Moderate	Severe
Take <i>et al</i> ^[70] , 2011	Post eradication with peptic ulcer	1674	28	5.6	0.04	0.28	0.62
Shichijo <i>et al</i> ^[71] , 2016	Post eradication	573	21	6.2	0.07 ¹	0.34 ¹	1.60 ¹
Kaji <i>et al</i> ^[72] , 2019	Medical examination	12941	63	3.7	0.10	0.16	0.31
	Post eradication	2571	20	3.7	0.06	0.12	0.42

¹Incidence was calculated by dividing the incidence per 10 years by 10.

CONCLUSION

The Kyoto classification organized endoscopic findings related to *H. pylori* infection. A Kyoto classification score ≥ 2 indicates *H. pylori* infection. An *H. pylori* test is essential for such cases with no history of *H. pylori* eradication.

A Kyoto classification score ≥ 4 might indicate gastric cancer risk. Such cases need careful follow-up. However, research related to the Kyoto score is still scarce and further study is needed.

Table 4 Odds ratios of endoscopic findings for gastric cancer

Endoscopic findings	Ref.	Population	No. of subjects	Odds ratio
Atrophy	Masuyama <i>et al</i> ^[76] , 2015	Without eradication	27777	14.2 ¹
Atrophy	Sekikawa <i>et al</i> ^[77] , 2016	Screening	1823	7.2 ¹
Intestinal metaplasia	Sugimoto <i>et al</i> ^[74] , 2017	Endoscopic gastritis	1200	5.0
Enlarged folds	Nishibayashi <i>et al</i> ^[73] , 2003	<i>H. pylori</i> positive	276	5.0
Nodularity	Nishikawa <i>et al</i> ^[49] , 2018	<i>H. pylori</i> positive	674	13.9
RAC	Majima <i>et al</i> ^[75] , 2019	Post eradication	194	0.4

¹Odds ratio for open-type atrophy calculated with closed-type atrophy as a reference. RAC: Regular arrangement of collecting venules; *H. pylori*: *Helicobacter pylori*.

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