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Original Article

Regular arrangement of collecting venules and the Kimura-Takemoto classification for the endoscopic diagnosis of *Helicobacter pylori* infection: Evaluation in a Western setting

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Background: The regular arrangement of collecting venules (RAC) and the Kimura-Takemoto classification of atrophic change (KTC) are simple and easy-to-use criteria which have been shown to reliably predict or rule out a *Helicobacter pylori* infection of the stomach. Although these features have been investigated extensively in Asia, their significance in the West has not been evaluated.

Methods: In a series of 200 consecutive gastroscopic examinations (single examiner, single center), the presence or absence of RAC and the KTC grade (open type vs closed type) were recorded prospectively. *Helicobacter pylori* infection was defined as a positive histology or a positive rapid urease test. Furthermore, multivariate analysis of endoscopic predictors of *H. pylori* infection based on the Kyoto classification of gastritis was performed.

Results: Two hundred patients were examined of which 57 had a *H. pylori* infection (28%). Both RAC and KTC had excellent negative predictive values of about 90% and sensitivity values of up to 85%. In multivariate analysis, atrophic change and diffuse redness without RAC were significantly associated with *H. pylori* infection.

Conclusion: Regular arrangement of collecting venules and KTC are simple endoscopic features which should be given attention by Western endoscopists and can be easily used to rule out a *H. pylori* infection of the stomach.

Key words: endoscopy, gastroscopy, *Helicobacter pylori*, infection, stomach

INTRODUCTION

VARIOUS ENDOSCOPIC CRITERIA have been described to predict or rule out a *Helicobacter pylori* infection of the stomach. An easily detectable feature of a healthy stomach without *H. pylori* infection is the regular arrangement of collecting venules (RAC). Multiple publications on RAC have shown a high sensitivity and specificity for the prediction of *H. pylori* uninfected stomachs. For example, Yagi *et al*.[1] demonstrated a sensitivity of 93.8% and specificity of 96.2% of RAC in the identification of the normal stomach without *H. pylori*. On the other hand, the irregular arrangement of collecting venules or its absence is significantly associated with *H. pylori* infection of the stomach. This has also been demonstrated in various publications with excellent sensitivity and specificity values of about 90%.[2,3] The collecting venules can be described as minute red spots on the mucosal surface. In the close-up view, they have a starfish like appearance. In the normal stomach without *H. pylori* infection, inspection of the body shows a regular arrangement of these collecting venules (Fig. 1) while the *H. pylori* infected stomach is expected to have an irregular arrangement or absence of these venules (Fig. 2). A further criterion closely associated to *H. pylori* infection is the degree or severity of atrophy of the gastric mucosa.[4] The endoscopic evaluation of atrophic change, initially described by Kimura and Takemoto,[5] can be simplified to include two grades: closed type atrophy, where atrophic change is limited to the lesser curvature, as well as open type atrophy, where atrophic change includes both the lesser and the greater curvature of the stomach body. In the Kyoto classification of gastritis, various endoscopic features have been evaluated to be associated with *H. pylori* infection.[6–8] These features include atrophy, intestinal metaplasia, enlarged folds, nodularity of the mucosa and diffuse redness with or without the presence of RAC. Basically, a Kyoto classification score of ≥2 indicates

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H. pylori infection while a score of 0 indicates no *H. pylori* infection.[7,8] All the studies mentioned above were done predominantly in Asia. The question we sought to answer in this study, was the significance of RAC and Kimura-Takemoto classification of atrophic change (KTC) as well as the endoscopic features described in the Kyoto classification in the endoscopic prediction of *H. pylori* infection in a Western population. This report is the first to evaluate RAC, KTC and other endoscopic features of the Kyoto classification of gastritis for the diagnosis of *H. pylori* infection in Europe.

METHODS

IN 200 CONSECUTIVE gastroscopic examinations performed by an experienced endoscopist in a German tertiary care center, the results of RAC and KTC were noted. All patients gave written informed consent prior to the intervention. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice and local regulations and was approved by the Institutional Review Board. Prior to data collection, the endoscopist was trained in the diagnostic skill of recognition and description of RAC and KTC by experienced Japanese endoscopists. All examinations were done in the endoscopy unit of the University Hospital Augsburg. Patients included in the study underwent gastroscopy for a variety of reasons. The indication for gastroscopy did not influence inclusion or exclusion from the study. However, patients with a prior history of *H. pylori* infection or of eradication therapy were excluded from the study. Patients with hypertensive gastropathy as well as patients with a contraindication for biopsy of the stomach were also excluded. All patients were above 18 years of age. The presence or absence of RAC at the gastric angle was noted prospectively. Additionally, a simplified version of the Kimura-Takemoto classification (KTC) was recorded. According to Kimura and Takemoto, the closed type is further subdivided into C-1, C-2 and C-3 while the open type is further subdivided into O-I, O-II and O-III. However, for the purpose of this study, two groups for the KTC were formed: non-atrophy/C1 (Fig. 3) and atrophy (Fig. 4) including C-2/C-3 and O-1/O-2/O-3. All examinations were done with an Olympus GIF-180 or GIF-190 gastroscope (Olympus Medical Systems, Tokyo, Japan). For each patient, biopsies to determine the *H. pylori* infection status using histology or the urease test were taken. For histology, H&E as well as Giemsa staining was performed. Two biopsies (lesser and greater curvature) were taken from the antrum and from the body, respectively, while the urease test was done using one biopsy from the antrum and one further biopsy from the body of the stomach. Patients with a positive histology or a positive urease test or a positive histology and a positive urease test were considered *H. pylori* positive while those with a negative histology and urease test were considered as *H. pylori* negative. The urease test was left to develop a color change for a maximum time of 24 h. Finally, a multivariate analysis to determine the most important endoscopic features of the Kyoto classification criteria[9] which were associated with endoscopic diagnosis of *H. pylori* infection was performed.

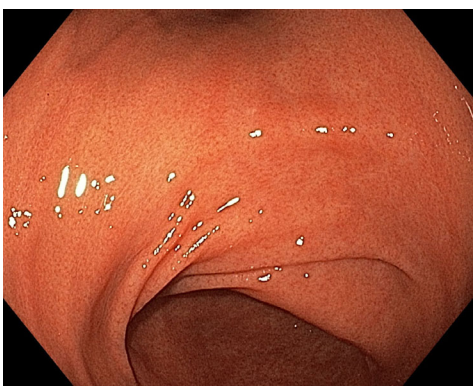

Figure 1 Regular arrangement of collecting venules (RAC) at the level of the gastric angle and the lesser curvature.

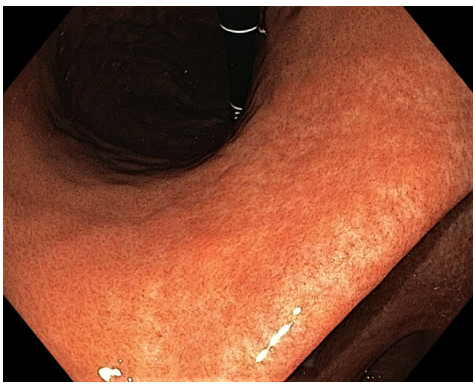

Figure 2 Absence of regular arrangement of collecting venules (RAC) at the level of the gastric angle.

Data analysis

For the statistical analysis, a simple two-by-two table was used to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) for RAC and KTC as predictors of *H. pylori* infection. Also, a pooled analysis of RAC and KTC was done, combining both

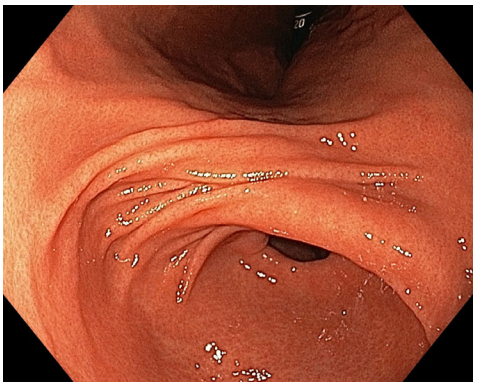

Figure 3 Endoscopic view of a non-atrophic mucosa at the level of the gastric angle.

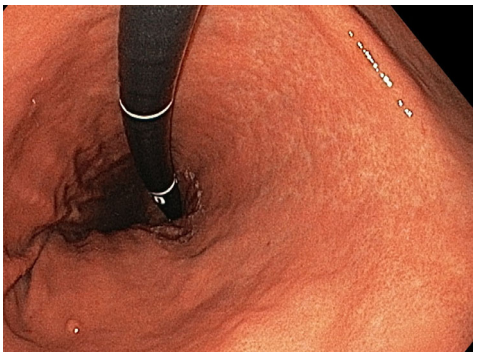

Figure 4 Endoscopic view of atrophic gastric mucosa; the level of atrophy involves majority of the lesser curvature.

parameters for the prediction of *H. pylori* infection. Additionally, a subgroup analysis of patients who were not on proton-pump-inhibitors (PPI; $n = 95$) was performed, also using a two-by-two table as described above. Furthermore, an assumption of *H. pylori* prevalence rate in an adult German population of about 40% was used.[10,11] Additionally, sensitivity and specificity values of 90% for the gold standard (histology/urease test) were assumed because of literature reports which have shown these values to be in a range between 80% and 98%.[11] As such, calculations using an assumption of a conditional independence and known sensitivities and specificities of the reference standard using a frequentist maximum likelihood method were performed.[12]

For multivariate analysis, a stepwise logistic regression model was implemented. Multivariate analysis of endoscopic predictors of *H. pylori* infection according to the Kyoto classification was performed using MedCalc Software Version 19.3.1 (MedCalc Software, Ostend, Belgium). Odds ratios were computed for endoscopic features including RAC, atrophy, diffuse redness, enlarged folds, nodularity and intestinal metaplasia.

RESULTS

A TOTAL OF 200 examinations (119 male, 81 female) were included in the study. Median age of patients was 72 years with a range between 21 and 98 years. Overall, 73 patients (36.5%) tested positive for *H. pylori*. Sensitivity, specificity, PPV and NPV for RAC in the diagnosis of *H. pylori* infection was 80.77%, 57.43%, 40% and 89.47%, respectively. Sensitivity, specificity, PPV and NPV for KTC in the diagnosis of *H. pylori* infection was 80.39%, 69.66%, 48.24% and 90.99%, respectively. For the combination of RAC and KTC, sensitivity, specificity, PPV and NPV in the diagnosis of *H. pylori* infection was 84.44%, 66.96%, 50.67% and 91.46%, respectively. The results for RAC, KTC and the combination of RAC and KTC are shown in Table 1. In the subgroup analysis of patients ($n = 95$) without PPI medication sensitivity, specificity, PPV and NPV for RAC in the diagnosis of *H. pylori* infection was 75%, 71.43%, 57.14% and 84.91%, respectively. Sensitivity, specificity, PPV and NPV for KTC in this subgroup was 84.73%, 71.43%, 60% and 90%, respectively. For the combination of RAC and KTC, sensitivity, specificity, PPV and NPV was 85.19%, 72.22%, 60.53% and 90.7%, respectively. The results for RAC, KTC and the combination of RAC and KTC in patients without PPI medication are shown in Table 2. When a *H. pylori* prevalence rate of 40% was assumed.[11] sensitivity, specificity, PPV and NPV for RAC was 75%, 71.43%, 63.64% and 81.08%, respectively, for KTC 84.73%, 71.43%, 66.32% and 87.27%, respectively, and for combination of RAC and KTC, 85.19%, 72.22%, 67.15% and 87.97%, respectively (Table 3). When the reference standard is considered "imperfect" and an assumption of a conditional independence is utilized the sensitivity and specificity for RAC was 88% and

Table 1 Results for RAC, KTC and the combination of RAC and KTC in all patients ($n = 200$)

	Sensitivity	Specificity	PPV	NPV
RAC	80.77% (67.47–90.37%)	57.43% (49.05–65.51%)	40.00% (34.64–45.61%)	89.47% (82.72–93.79%
KTC	80.39% (66.88–90.18%	69.66% (61.48–77.01%)	48.24% (41.29–55.25%)	90.99% (85.15–94.68%)
RAC/KTC	84.44% (70.54–93.51%)	66.96% (57.44–75.56%)	50.67% (43.41–57.90%)	91.46% (84.27–95.54%)

KTC, Kimura-Takemoto classification of atrophic change; RAC, regular arrangement of collecting venules.

Table 2 Results of RAC, KTC and the combination of RAC and KTC in patients without proton-pump-inhibitor medication (n = 95)

	Sensitivity	Specificity	PPV	NPV
RAC	75% (56.60–88.54%)	71.43% (58.65–82.11%)	57.14% (46.23–67.40%)	84.91% (75.16–91.27%)
KTC	84.73% (67.21–94.72%)	71.43% (58.65–82.11%)	60.00% (49.69–69.50%)	90.00% (79.85–95.34%)
RAC/KTC	85.19% (66.27–95.81%)	72.22% (58.36–83.54%)	60.53% (49.24–70.79%)	90.70% (79.54–96.07%)

KTC, Kimura-Takemoto classification of atrophic change; RAC, regular arrangement of collecting venules.

Table 3 Results of RAC, KTC and the combination of RAC and KTC in patients without proton-pump-inhibitor medication (n = 95) assuming a *Helicobacter pylori* prevalence rate of 40 %

	Sensitivity	Specificity	PPV	NPV
RAC	75% (56.60–88.54%)	71.43% (58.65–82.11%)	63.64% (53.02–73.07%)	81.08% (69.74–88.85%)
KTC	84.73% (67.21–94.72%)	71.43% (58.65–82.11%)	66.32% (56.45–74.94%)	87.27% (75.12–93.97%)
RAC/KTC	85.19% (66.27–95.81%)	72.22% (58.36–83.54%)	67.15% (56.39–76.37%)	87.97% (74.46–94.83%)

KTC, Kimura-Takemoto classification of atrophic change; RAC, regular arrangement of collecting venules.

Table 4 Results of RAC, KTC and the combination of RAC and KTC in patients without proton-pump-inhibitor medication (n = 95); Assumption of a conditional independence and known sensitivities and specificities of the reference standard using a frequentist maximum likelihood

	Sensitivity	Specificity
RAC	88%	74.2%
KTC	100%	74.77%
RAC/KTC	100%	75.56%

KTC, Kimura-Takemoto classification of atrophic change; RAC, regular arrangement of collecting venules.

Table 5 Multivariate analysis of the endoscopic predictors of *Helicobacter pylori* infection according to the Kyoto classification

Variable	Odds Ratio	95% CI
Atrophy	15.0706	3.4699–65.4555
Diffuse redness without regular arrangement of collecting venules	40.0959	9.3825–171.3498

Other factors did not show sufficient significance to be included in the model.

74.2%, respectively; for KTC 100% and 74.77%, respectively, and for the combination of both 100% and 75.56%, respectively (Table 4).

Multivariate analysis of endoscopic features according to the Kyoto classification

In a multivariate analysis two endoscopic predictors were shown to be significantly associated with *H. pylori* infection: presence of atrophy (odds ratio 15.07; CI 95% 3.4699–65.4555) and severe diffuse redness without RAC (odds ratio 40.0959; CI 95% 9.3825–171.3498). The other endoscopic predictors according to the Kyoto classification including intestinal metaplasia, enlarged folds and nodularity of the mucosa did not achieve sufficient significance to be included in the stepwise logistic regression model (Table 5).

DISCUSSION

IN GENERAL, THESE results show excellent sensitivity as well as negative predictive values for RAC, KTC and RAC/KTC in a randomly selected patient population as well as in the subgroup analysis of patients without PPI medication. This means that RAC, KTC and RAC/KTC predicted *H. pylori* negativity in uninfected patients correctly in a high proportion of cases. Furthermore, multivariate analysis of the endoscopic criteria described by the Kyoto classification of gastritis showed that both atrophy as well as diffuse redness without RAC were the most important factors associated with the presence of *H. pylori* infection. Although the specificity and positive predictive values seen in this study are not quite as high as in the Asian study reports mentioned above,[1–3] these results should still be considered as satisfactory for a single examiner study in a Western setting. Furthermore, when an assumption of a conditional independence and known sensitivities and specificities of the reference standard using a frequentist maximum likelihood are utilized, then sensitivity and specificity values improved considerably. Endoscopists should be aware of macroscopic features and mucosal changes which could be

associated with the presence of *H. pylori*. It has been shown that when patients are on PPI, testing for *H. pylori* may yield false-negative tests.[13,14] In such cases, it has been recommended to stop PPI at least 2 weeks before performing *H. pylori* testing. The use of endoscopic criteria such as RAC or KTC to predict *H. pylori* infection is not affected by on-going PPI treatment. As such, these criteria can be considered when patients with PPI undergo negative *H. pylori* testing, especially when there is suspicion of false-negative testing. For RAC assessment, endoscopists should be aware that RAC may be observed in the upper part of the stomach if the atrophy of the gastric mucosa has not progressed proximally, even if the patient is infected with *H. pylori*. This may have reduced the accuracy of RAC assessment in this study. The study limitations in our study include the single examiner/single center modus of data collection as well as the small sample size which may have limited the statistical power especially in the subgroup analysis of patients who were not on PPI medication. It would have been preferable to evaluate these criteria on a larger scale in multiple centers and by multiple examiners with different levels of endoscopy experience. Also, the determination of *H. pylori* infection using biopsies of the antrum and body may have been improved if an additional biopsy point at the incisura angularis was included and as recommended by the updated Sydney classification. In conclusion, we have been able to show that RAC and KTC are macroscopic parameters which should be given attention during routine endoscopy. These features are especially good in the prediction of *H. pylori* uninfected stomachs. Further data analysis needs to be done on a larger study population and in a multicenter approach.

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CONFLICT OF INTEREST

AUTHORS DECLARE NO conflicts of interest for this article.

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