Association Between Regular Arrangement of Collecting Venules and Helicobacter Pylori Status in Routine Endoscopy

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Abstract

Background: The sensitivity of regular arrangement of collecting venules (RAC)-positive pattern for predicting Helicobacter pylori (H. pylori)-negative status greatly altered from 93.8% to 48.0% in recent two decades of various studies, while the reason behind it remained obscure. The aim of this study was to investigate the value of RAC as an endoscopic feature for judging H. pylori status in routine endoscopy and reviewed the underlying mechanism.

Methods: A prospective study with high-definition non-magnifying endoscopy was performed. RAC-positive and RAC-negative patients were classified according to the collecting venules morphology of the lesser curvature in gastric corpus. Gastric biopsy specimens were obtained from the lesser and greater curvature of corpus with normal RAC-positive or abnormal RAC-negative mucosal patterns. H. pylori status was established by hematoxylin and eosin staining and immunohistochemistry.

Results: 41 RAC-positive and 124 RAC-negative patients were enrolled from June 2020 to September 2020. The prevalence of H. pylori infection in patients with RAC-positive pattern and RAC-negative pattern was 7.3% (3/41) and 71.0% (88/124), respectively. Among all 124 RAC-negative patients, 36 (29.0%) patients were H. pylori-negative status. Ten patients (32.3%) demonstrated RAC-positive pattern in 31 H. pylori-eradicated cases. The sensitivity, specificity, positive predictive value, and negative predictive value of RAC-positive pattern for predicting H. pylori negative status were 51.4% (95%CI, 0.395-0.630), 96.7% (95%CI, 0.900-0.991), 92.7% (95%CI, 0.790-0.981), and 71.0% (95%CI, 0.620-0.786), respectively.

Conclusions: RAC presence can accurately rule out H. pylori infection of gastric corpus, and H. pylori-positive status cannot be predicted only by RAC absence in routine endoscopy.

Trial registration

The present study is a non-interventional trial.

Background

Helicobacter pylori (H. pylori) infection has been involved in over 60% of people in the world [1], which is a well-known risk factor for gastric disorders including active gastritis, peptic ulcer, MALT lymphoma and adenocarcinoma [2]. Invasive and noninvasive diagnostic tests for H. pylori have been extensively used in the clinical practice [3–5]. Among these methods, endoscopic approach is a potential benefit, which can provide real-time mucosal findings and prompt targeted biopsy. In recent years, the technological developments in magnifying endoscopy have allowed accurate diagnosis of H. pylori infection by evaluating the pit and vascular patterns [4]. However, magnifying endoscopy is less commonly used in routine clinical practice, and the procedure requires more time and expenditure, and specialized training. Therefore, diagnosis of H. pylori by non-magnifying endoscopy would still be of great interest to the general endoscopists.

By using non-magnifying endoscopy, regular arrangement of collecting venules (RAC) in the gastric body is generally recognized as a characteristic feature of a normal stomach without H. pylori infection [6]. In 2002, Yagi et al. [6] study had indicated that the presence of RAC at the distal part of the lesser gastric curvature for predicting H. pylori-negative normal stomach had more than 90% sensitivity and specificity. RAC pattern becomes invisible when gastric body mucosa was affected by H. pylori infection [7]. However, in numerous subsequent studies between 2004 and 2019, RAC absence was associated with H. pylori positive status in varied proportion from 47.3–94.4% among different cases [8–17]. Hence, the absence of RAC did not always indicate the positive status of H. pylori. So, the aim of our study was to investigate the prevalence of H. pylori in daily routine endoscopy without magnification, and evaluate the association between RAC pattern and H. pylori status.

Methods

Patients collection

We designed a prospective study including inpatients and outpatients who underwent upper GI endoscopy from June 2020 to September 2020. Consecutive patients with more than 18-years old were invited to attend the study. The following baseline characteristics were collected: age, sex, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and history of H. pylori eradication in the last one year. Patients were excluded if they had previous partial gastrectomy, the diseases such as cirrhosis, chronic respiratory disorders, inflammatory bowel disease, collagen disease, and taken regular use of anticoagulants. The study protocol was approved by the institutional review board of West China Forth Hospital, Sichuan University (No. HXSY-EC-2020064). All participating patients gave written informed consents.

RAC pattern classification of corpus by non-magnifying endoscopy

After routine examination of the whole stomach by high-resolution endoscopy (GIF-H290; Olympus Optical Co. Ltd., Tokyo, Japan), the close-up observation of corpus was performed with a distance no more than 10 mm between the endoscope tip and mucosal surface, as described previously [13]. The collecting venules (CVs) morphology at the lesser gastric curvature was classified [18]: regular arrangement of CVs as RAC positive pattern (Figure 1a), obscure and irregular arrangement of CVs as RAC negative pattern. Some researchers further divided RAC-negative corpus mucosa into several types [3, 13-15, 19], such as spotty redness, diffuse redness, mosaic pattern, cleft-like appearance, untypical pattern, et al. (Figure 1b-f).

Biopsy specimens in the corpus and diagnosis of H. pylori infection

H. pylori infection in some patients only affected gastric antrum [6], and RAC appeared only in gastric body and fundus [7]. To ensure that H. pylori has infected the body of stomach, and explore the relationship between RAC pattern and corpus H. pylori status, two biopsy specimens were taken directly from
the lesser curvature and greater curvature in the corpus, avoiding some certain areas such as erosion, ulceration and gastric mucosa with a suspicion of intestinal metaplasia. These two sites are recommended by the update Sydney System for gastric corpus biopsy [20], and the gastric body greater curvature is a better site to detect current H. pylori infections [21].

The muscularis mucosae side of each biopsy specimen was stretched and fixed on filter paper, then bathed in a 10% formalin solution. 5-μm sections of paraffin wax embedded tissues were stained. A diagnosis of H. pylori infection was achieved if bacillary and/or coccoid H. pylori was identified on histopathological examination with H&E assay and/or monoclonal immunohistochemistry (IHC) (mouse monoclonal antibody, MX014, MXB Biotechnologies, Fuzhou, China). In general, only rod-shaped H. pylori can be identified in the H&E sections considering that coccoid H. pylori may mimic other bacteria or cell debris on H&E preparations [21]. To avoid the interference of impurities in IHC sections, more than 5 spherical H. pylori per high power field was identified as coccoid H. pylori positive (Figure 2). All the assessment of gastric specimens was conducted by two pathologists, who were blinded to the clinical and endoscopic findings.

Statistical analysis
With the assumption that RAC would have a sensitivity of 90% with a confidence level of 95% and precision of 10%, a total of 158 patients were required. Continuous data with normal distribution were presented as mean ± SD, continuous data without normal distribution were presented as median and interquartile range (IQR) and for nominal variables data were presented as percentages. The normality was tested using the Kolmogorov-Smirnov test. Regarding the association between RAC pattern and H. pylori status, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence intervals (CI) were calculated [22]. Chi-square test and Mann-Whitney U-test were used to compare RAC-positive and RAC-negative group. The inter- and intraobserver reproducibility was calculated by using kappa values as described by Landis and Koch [23]. A P value of less than 0.05 was required for significance. All statistical analyses were performed using SPSS statistical software (version 22 SPSS Inc., Chicago, US).

Results
Study subjects and baseline characteristics
Demographics and endoscopic mucosal patterns were summarized in Table 1. A total of 165 patients were enrolled with a median age of 52 years (IQR 41, 61; range 18-79 years), and 107 (64.8%) patients were male. The age distribution of RAC-positive and RAC-negative groups was different, and RAC was more common in cases under 50 years old (P < 0.05). There was no difference in RAC between NSAIDs user and non-user groups (P < 0.05). 10 patients (32.3%) demonstrated RAC-positive pattern in 31 H. pylori-eradicated cases.

H. pylori infection status in RAC-positive and RAC-negative pattern
H. pylori positive rate was different between RAC-positive and RAC-negative group (7.3% versus 71.0%, P < 0.05). In RAC-positive group, H. pylori-negative status was revealed in 92.7% (38/41) patients. In RAC-negative group, 29.0% (36/124) of patients were H. pylori-negative status. Among 88 (71.0%, 88/124) H. pylori-positive patients in RAC-negative group, 80 had both spherical and rod shape, 5 had only spherical shape and 3 had only rod shape. In RAC-negative subgroups, the H. pylori-positive rate was 80.6%, 80.0%, 81.6%, 52.6% and 37.5% for spotty redness, diffuse redness, mosaic pattern, cleft-like appearance, and an untypical pattern, respectively (Table 2). RAC presence at the lesser gastric curvature was associated with a 51.4% sensitivity (95%CI, 0.395-0.630) and a 96.7% specificity (95%CI, 0.900-0.991) for estimating H. pylori-negative status. PPV and NPV were 92.7% (95%CI, 0.790-0.981) and 71.0% (95%CI, 0.620-0.786), respectively.

Inter- and intraobserver agreement assessment
The k-values for inter- and intraobserver agreement for the endoscopic mucosal patterns were significant. The k-values for inter- and intraobserver agreement for the assessment of H. pylori status were also significant (Table 3).

Discussion
RAC presence has been well known as a characteristic endoscopic feature in H. pylori-negative normal stomach [6, 7]. In 2002, Yagi et al. [6] researchers have indicated that the presence of RAC for predicting H. pylori-negative normal stomach had 93.8% sensitivity and 96.2% specificity. In many subsequent studies [8–17], the RAC-positive pattern also demonstrated a high specificity between 85.7% and 100%, however, the sensitivity of RAC-positive pattern varied from 93.5–48.0%. In our study, RAC presence has only 51.4% sensitivity and 71.0% NPV for predicting H. pylori-negative status in routine clinical practice despite a good specificity (96.7%) and PPV (92.7%). These studies strongly supported the idea that the presence of RAC in the lesser corpus can accurately identify H. pylori-negative gastric body mucosa [24], but RAC absence did not always point out H. pylori-positive corpus mucosa.

In clinical practice, many H. pylori-related and -unrelated factors can cause the disappearance of RAC, such as chronic active gastritis caused by current H. pylori infection, chronic inactive gastritis after H. pylori eradication, H. pylori-negative gastritis, and gastropathy induced by liver cirrhosis, et al [6, 25–28]. In patients with chronic active gastritis, in addition to the disappearance of RAC, H. pylori status can be assessed by combination with other endoscopic manifestations, such as diffuse redness, spotty redness and swelling of areeae gastricae [14]. Shiota et al. [29] and Nordenstedt et al. [30] had found H. pylori-negative gastritis in 17.7% and 21% of patients with histologic gastritis. Although H. pylori negative gastritis is a condition that cannot be ignored, the diagnosis process is complicated and difficult to apply in daily work [29, 30]. Thus, we have not further evaluated such patients with H. pylori-negative gastritis in the present study. In inclusion criteria, the patients with liver cirrhosis have been excluded. NSAIDs were also one of the common causes of gastropathy. Our results revealed that no significant differences in RAC pattern were found in a small group of patients treated with NSAIDs, which was consistent with previous studies [17].
H. pylori-eradicated cases have been arising considering the preventive effect of H. pylori eradication therapy for gastric cancer [31]. However, RAC will not reappear immediately after H. pylori eradication. Yagi et al. [26] have revealed that RAC did not recover for over one year in 68% subjects after successful H. pylori eradication. Garces-Duran et al. [17] also found that about half of past H. pylori-eradicated patients were RAC-negative. Thus, RAC would be invisible in a considerable proportion of H. pylori-eradicated patients. We found that RAC was still absent in about two-thirds of patients (67.7%, 21/31) with H. pylori eradication history. These results revealed that RAC absence did not always indicate H. pylori-positive status in patients with H. pylori eradication history. Although detailed medical records were very vital for identifying the eradicated cases, some patients still failed to provide past H. pylori eradication clearly. In addition, partially eradicated patients may come from unintended H. pylori sterilization because of the infectious diseases in other organs. Besides, H. pylori may be also naturally eradicated without bactericidal therapy. These conditions made it difficult for us to accurately judge the past infection of H. pylori in clinical practice. Therefore, we investigated the total H. pylori prevalence in RAC-negative patients, and found that only 71.0% (88/124) subjects were H. pylori positive. 29.0% (36/124) of patients were H. pylori-negative status although RAC disappeared, which resulting in the low sensitivity (51.4%) and NPV (71.0%).

In these reports [6, 8–17] on the relationship between RAC pattern and H. pylori status, the sensitivity of RAC varied greatly from 93.8–48.0%, which may be related to different baseline characteristics of the patients and multiple methods of H. pylori status judgment. Among the 11 studies, four studies [9, 11, 13, 17] simultaneously detected H. Pylori in gastric body and antrum by histological examination and rapid urease test (RUT), and showed that the sensitivity of RAC decreased from 92.8–49.0% due to the difference in baseline characteristics. For example, in Garces-Duran et al. [17] study the patients with NSAIDs usage and past H. pylori infection were enrolled, and the sensitivity was only 49.0%. In the present study, we did not also exclude analogous patients and the sensitivity was low (51.4%). Even if the patients with H. pylori eradication history were excluded in inclusion criteria, the sensitivity was only 66.7% in Yan et al. [15] study and 48.0% in Kato et al. [14] study. Indeed, in clinical work, it is very difficult for us to completely exclude insidious past H. pylori infection, especially unintended H. pylori sterilization and spontaneous eradicators mentioned above. Interestingly, the two studies [14, 15] only detected H. pylori in gastric body by histology and/or RUT. Therefore, the prevalence of H. pylori could only reflect the H. pylori status in the corpus, which was similar to our study. One studies [10] merely detected H. pylori in the antrum by histology and RUT, which can not reveal the infection of H. pylori in gastric body because in some patients the infection only affected gastric antrum [6]. Indeed, it was not appropriate to use RAC in the body to predict H. pylori status in the antrum in this study.

RAC absence is one of the main manifestations of chronic active gastritis due to H. pylori current infection [6, 7, 12]. Gastric mucosal active inflammation should relieve shortly after eradication of H. pylori, however, RAC was still negative in some patients [17, 26]. Mild chronic inflammation in gastric mucosa can persist for more than 5 years after successful H. pylori eradication therapy in up to one-fifth of patients [32]. The appearance of RAC was the endoscopic manifestation of normal gastric corpus mucosa without pathologic changes [33, 34]. Saghier et al. [35] study has showed that foveolar length of corpus mucosa in H. pylori gastritis patients was significantly increased than that of normal H. pylori-uninfected gastric corpus. In a recent study from our team [36], we found that the prolongation of gastric foveolae could result in the invisibility of RAC. We revealed that in addition to H. pylori current infection, chronic inactive gastritis in H. pylori-eradicated patients can also cause RAC disappearing through the prolongation of gastric foveolae. Therefore, along with the increase of H. pylori-eradicated patients, the subjects with RAC-negative and H. pylori-negative entity are further accumulating, which can lead to decreasing sensitivity. Hence, only RAC disappearance was not a reliable feature to judge H. pylori positive status in daily practice. In fact, in Yagi et al. study [6], the predicting corpus mucosa of RAC presence was not only H. pylori negative status but also normal pathological features. However, in many studies [8–17], only H. pylori status was evaluated, ignoring gastric mucosa pathological abnormality, in particular the changes of gastric foveolae length. In a word, RAC presence was the endoscopic manifestation of normal gastric corpus mucosa with normal histology [33, 34], which can not only exclude H. Pylori infection, but also eliminate the pathological abnormalities of corpus mucosa caused by other factors.

Our study had some limitations: Firstly, our study only explored the relationship between RAC and H. Pylori infection in gastric corpus mucosa, and H. pylori status of gastric antrum mucosa was not evaluated. Therefore, H. Pylori status of gastric corpus cannot be represented the entire stomach. Secondly, histological detection of H. pylori can reduce the accuracy because of patchy distribution of the bacteria. Combination of multiple methods was helpful to more accurate detection of H. pylori such as urea breath test, serological examination, PCR and culturing. However, PCR and H. pylori culturing was not convenient in daily clinical practice. In addition, urea breath test and serological examination cannot distinguish the patients in which the gastric body was only affected, and not be performed in the present study. Thirdly, RAC accuracy may be influenced by patient age [37]. We did not conduct age stratification analysis due to the limited sample size. Lastly, this was a single-center study, with a limited number of cases and a short time span. In future, more patients can be included to analyze different detective methods of H. pylori and different patient subgroups to strengthen our results.

**Conclusions**

The present study has demonstrated that RAC presence can accurately rule out the H. pylori infection of gastric corpus, but the positive status of H. pylori cannot be effectively predicted only by the absence of RAC in routine endoscopy. In patients with RAC-negative pattern, other endoscopic features should be combined to improve the diagnosis of H. pylori.

**Abbreviations**

H. pylori: *Helicobacter pylori*, RAC: regular arrangement of collecting venules; CVs: collecting venules; IHC: immunohistochemistry; IQR: interquartile range; NSAIDs: nonsteroidal anti-inflammatory drugs; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; RUT: rapid urease test; UBT: urea breath test.

**Declarations**

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Not applicable.

Authors’ contributions
LJ designed the study. YC and OY conducted the experiments, analyzed data, and drafted the manuscript. LX and ZP performed the pathological assessment. YC, OY, CL, and CQ were involved in the collection of gastric specimens, data analysis, and reviewed the paper. All authors read and approved the final manuscript.

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Availability of data and materials
All data analyzed during this study are included in this published article.

Ethics approval and consent to participate
The study protocol was approved by the Institutional Review Board of West China Forth Hospital, Sichuan University (No. HXSY-EC-2020064). All participating patients gave written informed consents.

Consent for publication
Not applicable.

Competing interests
Authors declare no conflicts of interest for this article.

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Tables

Table 1 Baseline characteristics of the patients in current study

| Characteristics                  | Total (n=165) | RAC positive (n=41) | RAC negative (n=124) | P value |
|----------------------------------|---------------|---------------------|----------------------|---------|
| Age, years (median, IQR)         | 52 (41, 61)   | 40 (30, 51)         | 49 (37, 58)          | 0.005   |
| Age                              |               |                     |                      |         |
| < 50 years                       | 89 (53.9)     | 29                  | 60                    | 0.01    |
| ≥ 50 years                       | 76 (46.1)     | 12                  | 64                    |         |
| Gender                           |               |                     |                      |         |
| Male                             | 107 (64.8)    | 28                  | 79                    | 0.59    |
| Female                           | 58 (35.2)     | 13                  | 45                    |         |
| NSAIDs                           |               |                     |                      |         |
| Yes                              | 31 (18.8)     | 11                  | 20                    | 0.39    |
| No                               | 100 (60.6)    | 36                  | 64                    |         |
| Unknown                          | 34 (20.6)     |                     |                      |         |
| R. pylori status                 |               |                     |                      |         |
| Positive                         | 91 (55.2)     | 3                   | 88                    | < 0.001 |
| Negative                         | 74 (44.8)     | 38                  | 36                    |         |
| R. pylori eradicated             |               |                     |                      |         |
| Yes                              | 31 (18.8)     | 10                  | 21                    | 0.48    |
| No                               | 101 (61.2)    | 26                  | 75                    |         |
| Unknown                          | 33 (20.0)     |                     |                      |         |

IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; RAC, regular arrangement of collecting venules.

Table 2 R. pylori infection status in endoscopic mucosal patterns

| Mucosal patterns     | Total | R. pylori status (n, %) | P value |
|----------------------|-------|-------------------------|---------|
|                      |       | Negative | Positive |       |
| RAC positive         | 41    | 38 (92.7) | 3 (7.3)  | < 0.001* |
| RAC negative         | 124   | 36 (29.0) | 88 (71.0) |         |
| Spotty redness       | 31    | 6 (19.4)  | 25 (80.6) |         |
| Diffuse redness      | 20    | 4 (20.0)  | 16 (80.0) |         |
| Mosaic               | 38    | 7 (18.4)  | 31 (81.6) |         |
| Cleft                | 19    | 9 (47.4)  | 10 (52.6) |         |
| Untypical pattern    | 16    | 10 (62.5) | 6 (37.5)  |         |

RAC, regular arrangement of collecting venules. *P < 0.001* RAC-positive versus RAC-negative group.
Table 3 Inter- and intraobserver agreement

|                  | Interobserver agreement | Intraobserver agreement |
|------------------|-------------------------|-------------------------|
|                  | % agreement  | k value (95% CI) | % agreement | k value (95% CI) |
| RAC pattern      | 85.6        | 0.74 (0.71-0.78) | 89.4        | 0.88 (0.78-0.96) |
| H. pylori status | 92.7        | 0.86 (0.80-0.92) | 93.5        | 0.94 (0.87-0.98) |

The k-values for inter- and intraobserver agreement for mucosal patterns and H. pylori status were significant. CI, confidence interval.

Table 4 Summary of study characteristics on the association of RAC and H. pylori status

| Author           | Year | Reference methods | History | RUT | UBT | Serology | Culture | Number of patients | Eradicated | Sensitivity (%) | Spe (%) |
|------------------|------|-------------------|---------|-----|-----|----------|---------|-------------------|------------|-----------------|---------|
| Yagi et al⁶      | 2002 | √                 | √       | √   |     |          |         | 557               | Unknown    | 93.8            | 96.1    |
| Nakayama et al⁸  | 2004 | √                 | √       | √   |     |          |         | 52                | Excluded   | 93.5            | 100     |
| Anagnostopoulos et al⁹ | 2007 | √                 | √       | √   |     |          |         | 95                | Unknown    | 92.8            | 100     |
| Machado et al¹⁰  | 2008 | √                 |         |     |     |          |         | 99                | Excluded in 12 months | 88.1    | 96.1 |
| Gonen et al¹¹    | 2009 | √                 | √       | √   |     |          |         | 129               | Excluded   | 82.8            | 85.1    |
| Yan et al¹⁵      | 2010 | √                 |         |     |     |          |         | 112               | Excluded   | 66.7            | 100     |
| Hidaka et al¹²   | 2010 | √                 |         |     |     |          | √       | 87                | Excluded   | 86.7            | 100     |
| Cho et al¹³      | 2013 | √                 | √       | √   |     |          |         | 617               | Excluded   | 89.1            | 93.1    |
| Kato et al¹⁴     | 2013 | √                 |         |     |     |          |         | 275               | Excluded   | 48.0            | 93.1    |
| Tongtawee et al¹⁶| 2015 | √                 |         |     |     |          | √       | 200               | Excluded in 2 months | 53.0    | 100 |
| Garces-Duran et al¹⁷| 2019 | √                 | √       | √   |     |          |         | 140               | Included   | 49.0            | 100     |

UBT, urea breath test; RUT, rapid urease test; Corpus and antrum denoting the corresponding biopsy site.