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ORIGINAL ARTICLE

Regular arrangement of collecting venules under endoscopy for predicting a *Helicobacter pylori*-negative stomach: A systematic review and meta-analysis

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KEYWORDS
Helicobacter pylori;
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Abstract
Background and aims: The regular arrangement of collecting venules (RAC) refers to the appearance of multiple regular tiny veins in the body of the stomach and is considered to be very effective for identifying gastric mucosa with non-*Helicobacter pylori* infection. This meta-analysis was conducted to systematically evaluate the value of the sign in predicting a *Helicobacter pylori*-negative stomach and the relevant factors that may affect the performance of this prediction.
Methods: Two biomedical databases (PubMed and EMBASE) were systematically searched through April 20, 2020. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and area under the SROC curve (AUC) were calculated.
Results: Fourteen articles with 4070 patients were included. The pooled sensitivity, specificity, PLR, NLR, DOR and AUC for the RAC in predicting non-Hp infection were 0.80 (0.67–0.89), 0.97 (0.93–0.98), 24.8 (12.2–50.8), 0.21 (0.12–0.36), 120 (47–301) and 0.97 (0.19–1.00), respectively.
Conclusions: The RAC is a valuable endoscopic feature for the prediction of patients without Hp infection.

Abbreviations: Hp, *Helicobacter pylori*; RAC, regular arrangement of collecting venules; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the SROC curve; PRISMA-DTA, Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies; TP, true positive; TN, true negative; FP, false positive; FN, false negative; QUADAS-II, Quality Assessment of Diagnostic Accuracy Studies II.

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PALABRAS CLAVE
Helicobacter pylori;
Disposición regular de vénulas colectoras;
Metaanálisis

Disposición regular de vénulas colectoras con endoscopia para predecir un estómago negativo para *Helicobacter pylori*: revisión sistemática y metaanálisis

Resumen
Objetivos: La disposición regular de vénulas colectoras (RAC, en inglés) se refiere a la aparición de múltiples venas minúsculas regulares en el cuerpo del estómago y se considera muy eficaz para identificar la mucosa gástrica con infección no causada por *Helicobacter pylori*. Este metaanálisis se llevó a cabo para evaluar sistemáticamente el valor del signo en la predicción de un estómago negativo para *Helicobacter pylori* (Hp) y los factores relevantes que pueden afectar a la obtención de esta predicción.
Métodos: Se realizaron búsquedas sistemáticas en dos bases de datos biomédicas (PubMed y EMBASE) el 20 de abril de 2020. Se calcularon la sensibilidad, la especificidad, el cociente de probabilidad positiva (PLR), el cociente de probabilidad negativa (CPN), el cociente de probabilidad de diagnóstico (NLR) y el área bajo la curva SROC (AUC) agrupados.
Resultados: Se incluyeron 14 artículos con 4.070 pacientes. La sensibilidad, especificidad, PLR, NLR, DOR y AUC agrupados para la RAC en la predicción de la infección no debida a Hp fueron de 0,80 (0,67-0,89), 0,97 (0,93-0,98), 24,8 (12,2-50,8), 0,21 (0,12-0,36), 120 (47-301) y 0,97 (0,19-1,00), respectivamente.
Conclusiones: La RAC es una característica endoscópica útil para la predicción de pacientes sin infección por Hp.

Introduction

Helicobacter pylori (Hp) is considered to be a major risk factor for gastric cancer. Other risk factors[1] include age, sex, smoking, ethnicity, family history, and so on. At present, it is recommended that once a Hp infection is found, unless for some special reason, it needs to be treated or eradicated.[2] In the past, Japanese endoscopists found that the appearance of a large number of red spots in the stomach body was a characteristic discovery in the normal stomach, indicating that the gastric mucosa was not infected with Hp. The discovery was called the ''regular arrangement of collecting venules'' (RAC).[3] Therefore, Japanese endoscopists began to use the RAC to make a preliminary diagnosis of whether the patient was infected with Hp. Many studies have shown that the RAC has good diagnostic efficacy for a normal stomach without an Hp infection.[4,5] However, some studies suggest that the effectiveness of this prediction may be affected by the age of the patient or other factors.[6] Therefore, we conducted this meta-analysis to systematically evaluate the value of RAC in predicting Hp-negative stomach, and to analyze the value of this predictive efficiency in different ages and ethnicities.

Methods

Data sources, search strategy and study selection

The study was conducted in accordance with Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA).[7]

We defined a systematic search strategy and searched 2 electronic databases, PubMed and EMBASE, through April 20, 2020. The following comprehensive search terms were used: (''H pylori'' or ''Hp'' or Helicobacter pylori) and (''RAC'' or ''IRAC'' or ''Regular arrangement of collecting venules'' or ''Irregular arrangement of collecting venules''). Document screening was independently carried out by two authors (Lunan Li and Huiqin Gao). Any inconsistencies were discussed in our group to obtain an accurate result. In the process, no search limits or filters were used. EndNote X9 was used for data management.

Studies were included when they fulfilled both of the following conditions: 1. The study had a negative control group. 2. Sufficient data was included to calculate the true positive (TP), true negative (TN), false positive (FP) and false negative (FN). However, conference papers were excluded even if they met the above conditions. We included the first published article when multiple studies focused on the same population.

Data extraction and quality assessment

Data extraction and quality assessment were independently completed by two individuals (Lunan Li and Huiqin Gao). Any inconsistencies were carried out by a panel discussion to maintain a consistent result.

The following information about the studies was recorded: year of publication, first author of the study, study type, country, characteristics of included patients (number, gender) and whether the study provided TP, TN, FP and FN. The Quality Assessment of Diagnostic Accuracy Studies II (QUADAS-II) [8]tool was used to evaluate the included articles.

Data analysis

We performed a bivariate random-effects model[9] to calculate the pooled sensitivity, specificity, positive

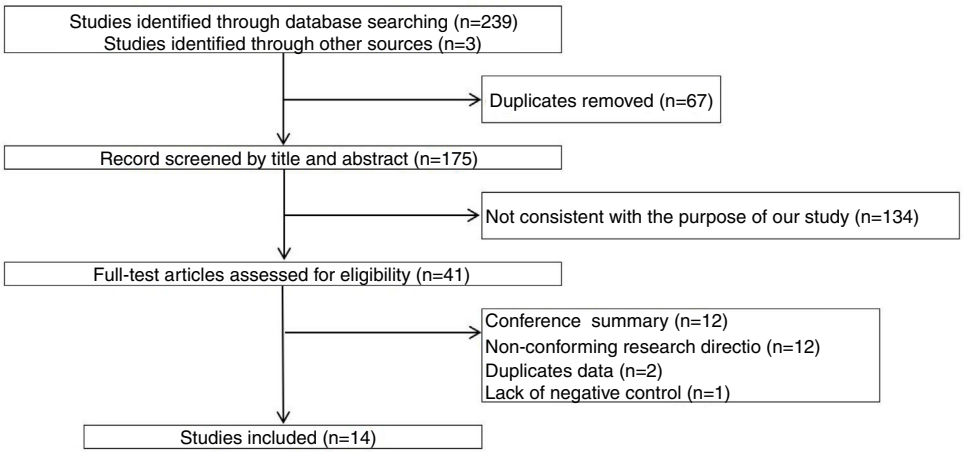

Figure 1 Flow diagram.

Table 1 Quality evaluation for included articles using the QUADAS-II tool.

Author	Year	Risk of bias				Applicability concerns		
		Patient selections	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Alaboudy A	2011	Low	Low	Low	Unclear	Low	Low	Low
Anagnostopoulos GK	2007	Low	Low	Low	Unclear	Low	Low	Low
Cho JH	2013	Low	Low	Low	Low	Low	Low	Low
Garces-Duran R	2019	Unclear	Low	Low	Low	Low	Low	Low
Gonen C	2009	Low	Low	Low	Low	Low	Low	Low
Hidaka N	2010	Low	Low	Low	Unclear	Low	Low	Low
Katake Y	2013	Unclear	Low	Low	Unclear	Low	Low	Low
Kato T	2013	Low	Low	Low	Low	Low	Low	Low
Machado RS	2008	Low	Low	Low	Low	Low	Low	Low
Mao T	2016	Unclear	Unclear	Low	Unclear	Low	Low	Low
Na S	2011	Low	Unclear	Low	Unclear	Low	Low	Low
Nakayama Y	2004	Low	Low	Low	Low	Low	Low	Low
Yagi K	2002	Unclear	Low	Low	Unclear	Low	Low	Low
Yoshii S	2019	Unclear	Low	Low	Low	Low	Low	Low

''Low'' indicate low risk of bias; ''unclear'' represent unclear risk of bias; QUADAS II = Quality Assessment of Diagnostic Accuracy Studies.

likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), area under the SROC curve (AUC) and corresponding 95% confidence intervals (CIs). The heterogeneity was calculated by the I^2 statistic, and $I^2 < 50\%$ indicated no significant heterogeneity.[10] Subgroup analysis was used to analyze the statistical significance of the RAC in predicting an Hp-negative stomach among different ages and ethnicities. A p-value less than 0.05 was considered statistically significant. Publication bias was assessed by Deeks' asymmetry test, and $p < 0.05$ was considered significant.[11] Stata 13 was used to perform the statistical analysis.

Results

The study selection process is shown in Fig. 1. A total of 242 studies were identified by the database search. After removing 67 duplicates and 134 studies that were not consistent with our purpose, 41 studies were assessed. Among these, 12 studies were conference summaries, 2 studies were duplicates, 12 studies did not provide relevant information, and one study lacked a negative control group. Ultimately, 14 studies with 4070 patients [3–6,12–21] were included. The QUADAS-II quality assessment for each study is presented in Table 1. There was unclear bias in our included studies, but none of them were excluded from our meta-analysis. The TP, FP, FN, TN and characteristics of each study are presented in Table 2. Subgroup analysis for pooled sensitivity, pooled specificity, PLR, NLR and DOR are presented in Table 3.

The pooled sensitivity, pooled specificity, PLR, NLR, DOR and AUC for RAC in predicting an Hp-negative stomach were 0.80 (0.67–0.89), 0.97 (0.93–0.98), 24.8 (12.2–50.8), 0.21 (0.12–0.36), 120 (47–301) and 0.97 (0.19–1.00), respectively. The I^2 value was 0.00 (0.00–100.00) for the summary sensitivity and 0.00 (0.00–100.00) for the summary specificity (Fig. 2). Subgroup analysis was conducted for age

Table 2 Summary of the characteristic in the meta-analysis.

Year	Author	Study type	Country	Number	Gender*	tp	fp	fn	tn
2011	Alaboudy A	Retrospective	Japan	390	198M 192W	22	2	95	185
2007	Anagnostopoulos GK	Unclear	United Kingdom	95	52M 43W	64	0	5	26
2013	Cho JH	Prospective	Korea	617	296M 321W	230	24	28	335
2019	Garces-Duran R	Prospective	Spain	140	68M 72W	47	0	49	44
2009	Gonen C	Prospective	Turkey	129	32M 97W	24	14	5	84
2010	Hidaka N	Unclear	Japan	87	38M 49W	57	0	5	25
2013	Katake Y	Unclear	Japan	723	510M 213W	189	4	24	506
2013	Kato T	Prospective	Japan	275	127M 148W	60	9	65	131
2008	Machado RS	Prospective	Brazil	99	45M 54W	59	1	8	31
2016	Mao T	Unclear	China	256	118M 138W	98	15	15	128
2011	Na S	Retrospective	Korea	263	132M 131W	53	4	75	131
2004	Nakayama Y	Prospective	Japan	52	24M 28W	29	0	3	20
2002	Yagi K	Unclear	Japan	557	271M 286W	153	8	15	381
2019	Yoshii S	Prospective	Japan	498	376M 122W	269	37	33	146

Gender* M = man; Gender* W = women; tp = true positive; tn = true negative; fp = false positive; fn = false negative.

Table 3 The subgroup analysis results.

	Pooled sensitivity	Pooled specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio
Ethnicity					
Asian population	0.79 (0.67–0.92)	0.96 (0.93–0.99)	–	–	–
Other population	0.82 (0.60–1.00)	0.99 (0.98–1.00)	–	–	–
Age					
>50	0.75 (0.53–0.89)	0.96 (0.91–0.98)	18.8 (8.5–41.3)	0.26 (0.13–0.54)	72 (24–213)
≤50	0.85 (0.73–0.93)	0.98 (0.91–1.00)	45.3 (8.9–231.6)	0.15 (0.08–0.29)	303 (55–1669)

and ethnicity. The p values of age and ethnicity were greater than 0.05 (Table 3). The pooled estimates for Asian population were as follows: sensitivity, 0.79 (0.67–0.92); specificity, 0.96 (0.93–0.99); Similarly, the corresponding values for other ethnicity were 0.82 (0.60–1.00), 0.99 (0.98–1.00). The RAC had a sensitivity of 0.75 (0.53–0.89), specificity of 0.96 (0.91–0.98), PLR of 18.8 (8.5–41.3), NLR of 0.26 (0.13–0.54) and DOR of 72 (24–213) for patients older than 50. The corresponding values were 0.85 (0.73–0.93), 0.98 (0.91–1.00), 45.3 (8.9–231.6), 0.15 (0.08–0.29) and 303 (55–1669) for patients younger than 50 years of age.

Sensitivity analysis (Fig. 3) was performed to ensure that our study results were not overly affected by any single included study. Results with and without outliers were compared. The results showed that removing a study[19] increased the pooled sensitivity from 0.80 to 0.83 and the DOR from 120 to 136 but reduced the PLR from 24.8 to 23.8 and the NLR from 0.21 to 0.18. The pooled specificity in both cases was 0.97. The I^2 for heterogeneity for the pooled sensitivity and specificity in both cases was still 0.00. These results show that our meta-analysis was reliable. Deeks' funnel plots (Fig. 4) suggest that no evidence of publication bias was found in this meta-analysis.

Discussion

According to our systematic meta-analysis, the RAC is a valuable sign for predicting patients without an Hp infection, and the summary result did not show significant heterogeneity. When subgroup analysis was conducted, the performance between Asian and other ethnicities and between the two age groups did not show significant differences. Na S [20]showed that the sensitivity and specificity of the RAC in the diagnosis of non-HP infection may be affected by the patient's age. We only divided the age group into two parts; thus, the results of this study need to be further confirmed. In addition, the low *H. pylori* infection rates in Western countries, combined with the high predictive efficiency of the RAC in predicting an HP-negative stomach, suggest that the RAC can be used to reduce the number of gastric mucosal biopsies performed in this population.

The RAC is considered to be a very simple and effective sign for determining gastric mucosa with non-HP infection. We found that endoscopic physicians observed the RAC from different locations, although a gastritis study in Kyoto, Japan showed that the RAC was generally observed

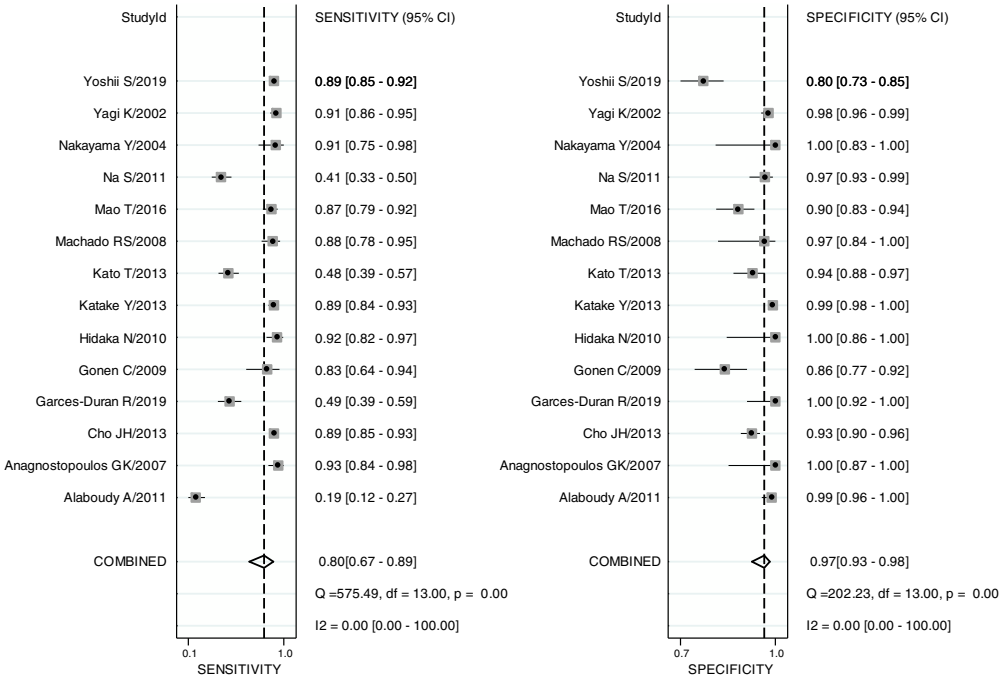

Figure 2 The I^2 for heterogeneity in pooled sensitivity and specificity.

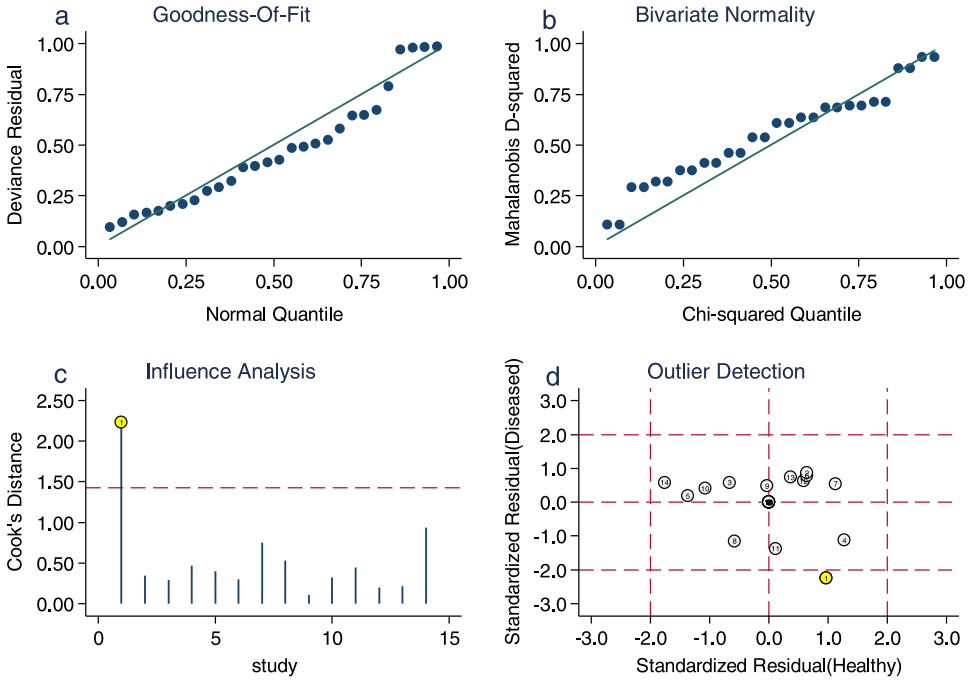

Figure 3 Sensitivity analysis of RAC sign in diagnosing non-Hp infection.

at the lesser curvature and the lower part of the stomach.[22] However, Cho[14] suggested that it is best to observe the RAC in the corpus at the greater curvature. There is no unified point of view about this matter. Therefore, the best observation position for the RAC remains to be determined. Machado[18] suggested that any disease with mucosal infiltration caused by inflammatory cells can lead to the absence of the RAC. However, there is a lack of research to confirm whether this claim is correct, whether it is related to IBD, whether it is affected by the degree of gastritis and the kind of drugs used (PPI, H2 receptor inhibitors, and antibiotics). Machado[18] showed that the RAC can be recovered in some patients after the removal of the Hp infection. However, this phenomenon has not been explained. Therefore, it is worth discussing the relationship between the recovery of the RAC and the risk of gastric cancer. Perhaps through

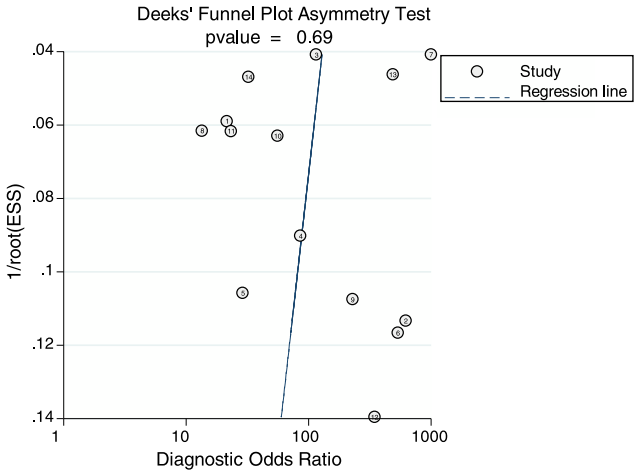

Figure 4 Publication bias evaluation for RAC sign in diagnosing non-Hp infection.

further prospective studies, the model for the prediction and treatment of HP infections can be improved.

Our article is the first to systematically evaluate the value of the sign in predicting a *Helicobacter pylori*-negative stomach. However, the limitations of our study should be recognized. First, we excluded conference abstracts, which may have led to some bias. Second, some detailed descriptions were not found, leading to an ''unclear'' assessment in QUADAS-II. Third, given the limited information, including multiple age groups and some other factors were not analyzed. Further studies should focus on the patient-relevant characteristics with or without the RAC and whether this sign is associated with gastric cancer.

Conclusions

The RAC is a valuable sign for predicting patients without an Hp infection. No significant differences were found between ethnicities and ages with regard to the predictive ability of the RAC.

Conflict of interest

They are no conflict of interest.

Acknowledgements

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