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ORIGINAL ARTICLE

Esophagogastric Junction Morphology on Hill's Classification Predicts Gastroesophageal Reflux with Good Accuracy and Consistency

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Abstract

Introduction Hill's classification provides a reproducible endoscopic grading system for esophagogastric junction morphology and competence, specifically whether the gastroesophageal flap valve (GEFV) is normal (grade I/II) or abnormal (grades III/IV). However, it is not routinely used in clinical practice. We report a systematic review and meta-analysis to determine association between abnormal GEFV and gastroesophageal reflux disorder (GERD).

Methods A comprehensive literature search of MEDLINE and Scopus databases was conducted to identify studies that reported the association between abnormal GEFV and GERD. The search and quality assessment were performed independently by two authors. Fixed- and random-effects meta-analyses were conducted using symptomatic GERD and erosive esophagitis as outcomes.

Results A total of 11 studies met inclusion criteria that included a total of 5054 patients. In the general population, patients with abnormal GEFV had greater risk of symptomatic GERD compared to patients with a normal GEFV (risk ratio [RR] 1.88, 95% CI 1.57–2.24). Further, in patients with symptomatic GERD, patients with abnormal GEFV had greater risk of erosive esophagitis compared to patients with normal GEFV (RR 2.17, 95% CI 1.40–3.36). Finally, the specificity of abnormal GEFV for symptomatic GERD was 73.3% (95% CI 69.3–77.0%) and 75.7% (95% CI 65.9–83.4%) for erosive esophagitis in symptomatic GERD.

Conclusion Our systematic review and meta-analysis showed consistent association between abnormal GEFV indicated by Hill's classification III/IV and symptomatic GERD and erosive esophagitis. Our recommendation is to include Hill's classification in routine endoscopy reports and workup for GERD.

Keywords Endoscopy · Erosive esophagitis · Gastroesophageal reflux disorder · Gastroesophageal flap valve

Introduction

Gastroesophageal reflux disorder (GERD) is the result of abnormal reflux of gastric contents into the esophagus. The prevalence of GERD is increasing alongside the obesity epidemic [1]. Mechanisms of defense against gastroesophageal reflux (GER) includes a competent esophagogastric junction (EGJ), esophageal peristalsis, buffering from salivary bicarbonate, mucosal integrity, and gravity. The EGJ acts as a multidimensional barrier against GER and consists of the lower esophageal sphincter (LES), crural diaphragm, angle of His, and a gastroesophageal flap valve (GEFV) maintained by the musculature of the gastric cardia. The LES and crural diaphragm provide a barrier by keeping the EGJ closed with a basal LES tone and augmentation with respiration from crural diaphragm, whereas the angle of His and GEFV create a one-way valve [2]. Proximal migration of

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LES (i.e., hiatal hernia) results in losing the barrier provided by angle of His and GEFV as well as augmentation of the LES from the crural diaphragm [2].

Hill's classification provides an endoscopic grading system for EGJ morphology, specifically whether the GEFV is normal (grades I/II) or abnormal (grades III/IV) [3]. Grade I is defined by the tissue ridge or GEFV being snug to the endoscope and extending 3–4 cm along the lesser curvature (Fig. 1, panel A), whereas grade II is defined by the GEFV being less snug to the endoscope and open with respiration, yet closing promptly (Fig. 1, panel B). By contrast, grade III is defined by the loss of GEFV with the EGJ failing to close around the endoscope (Fig. 1, panel C), whereas grade IV is defined by a wide-open diaphragmatic hiatus (i.e., hiatal hernia; Fig. 1, panel D).

Hill's classification has been shown to be a better predictor of GER than EGJ pressure [3]. Further, Hill's classification has shown excellent inter-observer agreement in assessing EGJ morphology [3], which is important considering that endoscopic diagnosis and the length of hiatal hernia have shown poor accuracy and reproducibility, especially with small hiatal hernias [4, 5]. Despite its benefits, Hill's classification is not used regularly in the clinical practice of gastroenterologists; as such, it is not documented routinely as part of the endoscopy report. This may be due, in part, to the fact that it is unknown whether abnormal GEFV defined using Hill's classification can be used as a reliable predictor of GERD or erosive esophagitis. As such, we performed a comprehensive systematic review and meta-analysis to determine association between abnormal GEFV defined using Hill's classification grades III/IV and GERD.

Methods

We followed the reporting guidelines of Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements [6, 7]. No IRB oversight

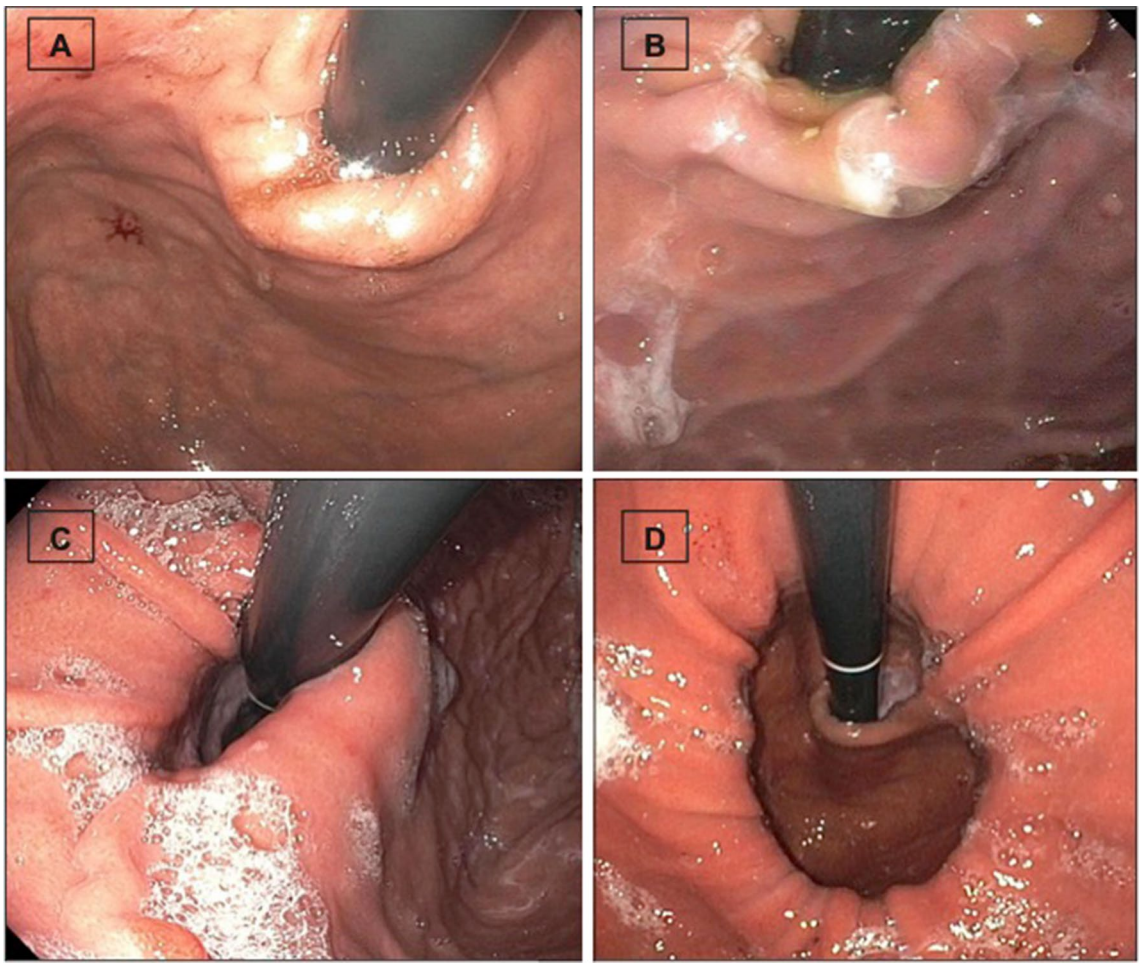

Fig. 1 Hill's classification of esophagogastric junction: Grade I has the tissue ridge or gastroesophageal flap valve (GEFV) being snug to the endoscope and extending 3–4 cm along the lesser curvature (**a**), grade II has the GEFV being less snug to the endoscope and open with respiration, yet closing promptly (**b**), grade III has loss of GEFV with the EGJ failing to close around the endoscope (**c**), and grade IV has a wide-open diaphragmatic hiatus (**d**)

was required given the systematic review, and meta-analysis was based on previously published studies without identifiable patient data.

Search Strategy and Study Selection

A comprehensive search of MEDLINE and Scopus was performed in October 2018 without time restriction to identify all studies reporting EGJ morphology based on Hill's classification and GERD as either typical symptoms (e.g., heartburn and regurgitation) or erosive esophagitis. Inclusion required that the study reports Hill's classification based on upper endoscopy, measures GERD as typical symptoms or erosive esophagitis, reports the association between Hill's classification and GERD, and includes at least 20 patients, and that the data be published as a peer-reviewed manuscript. Two investigators (AO and MA) independently screened the titles and abstracts of all identified records. Excluded studies were not relevant, review articles, case reports, those that did not use original data, and/or had sample sizes with fewer than 20 patients. When duplicate publication was indicated, we retained the study that included the greatest number of patients. We obtained the complete manuscript when either reviewer believed that the study should be eligible for inclusion, after which two investigators (AO and MA) independently assessed the eligibility of each study. All the disagreements in study selection were resolved via consensus after review with the senior author (SC). In addition, we reviewed the reference lists of all eligible articles to identify additional studies not identified by our initial database search. The detailed database search is provided in the online-only appendix.

Quality Assessment

The methodological quality of each eligible study was assessed independently by two investigators (AO and MA). The quality assessment criteria were chosen to minimize selection and observer bias, and were adopted from the Newcastle–Ottawa scale [8]. Assessment criteria included that patients be selected in an unbiased fashion (i.e., as consecutive patients or as a random sample; patients undergoing surgical treatment were considered biased), that the patients were representative of a wide spectrum of EGJ morphology by including at least 25% patients with Hill's classification grades I/II and at least 25% patients with grades III/IV, that the EGJ morphology was assessed without knowledge of the outcomes GERD or erosive esophagitis, likewise that GERD or erosive esophagitis were assessed without knowledge of EGJ morphology, that GERD be indicated using the Montreal definition [9], and that the patients were not receiving proton pump inhibitors as these medications can heal erosive esophagitis. Each criterion was assessed as yes, no, or not reported, with one point assigned when meeting a given criterion (i.e., yes). Points were then summed with any study scoring less than three considered to be of poor methodological quality and therefore excluded from the meta-analysis.

Data Extraction

Data extraction was performed independently by two reviewers (AO and MA). Collected data included study inclusion and exclusion criteria, study design, Hill's classification, presence of GERD, presence of erosive esophagitis, and the country in which the study was conducted, as well as data for patient age and biological sex. Data were entered into a predefined data collection sheet in Microsoft Excel.

Statistical Analysis

Cohen's kappa was used to measure the chance-corrected agreement between reviewers within the initial screening phase and when evaluating eligibility based on full text. Pooled prevalence, sensitivity, specificity, and predictive values were calculated using the logit link of the study-specific values (e.g., prevalence) with standard errors calculated by taking the square root of: $[1/k + 1/(n-k)]$, in which k is the numerator and n is the denominator used when calculating the study-specific value. For reporting, software-outputted odds ratios (OR) and 95% confidence limits were then inverse-linked onto the probability scale as: $\mathrm{OR}/(1+\mathrm{OR})$. For the meta-analysis, effect sizes are risk ratios (RRs), stratified by the presence of abnormal GEFV (i.e., Hill's classification III/IV vs. I/II, respectively). A planned sensitivity analysis was conducted stratifying by Hill's classification grade III vs. I/II. When calculating pooled estimates in the meta-analysis, heterogeneity was quantified using I^2 and tau-squared. The fixed-effects approach was used when pooling estimates based on fewer than three studies. Meta-analysis results are reported using forest plots. No funnel plots are presented following random-effects meta-analysis given they are inappropriate in the presence of heterogeneity. Cohen's kappa was estimated using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA, 2017), whereas the pooled estimates and meta-analyses were conducted using RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Search

The comprehensive literature search identified 211 records, of which 63 were removed as duplicates (Fig. 2). In the

screening phase, 124 records were excluded as not relevant, review articles, or case reports, whereas others were excluded because they did not use original data or had sample sizes with fewer than 20 patients. These exclusions resulted in 24 studies for which full text was requested. Inter-observer agreement in this initial screening phase was substantial (kappa 0.73, 95% CI 0.57–0.90). Upon review of full text, a total of 11 studies were identified as eligible for inclusion in the systematic review (kappa 0.49, 95% CI 0.14–0.84).

Study Characteristics and Quality Assessment

The 11 studies included in the systematic review had a total of 5054 patients from nine different countries (Table 1). Reported descriptive statistics varied between studies, with mean/median age ranging between 36 and 55 years of age; the proportion of males ranged from 39 to 61%. The methodological quality assessment is summarized in Table 2. Two studies had biased patient selection, whereas one study did not include patients with wide-spectrum EGJ morphology; only two studies excluded patients on PPIs. None of the studies assessed the outcome without knowledge of EGJ morphology or vice versa. In total, two studies were excluded from the meta-analysis due to insufficient study methodology [10, 11].

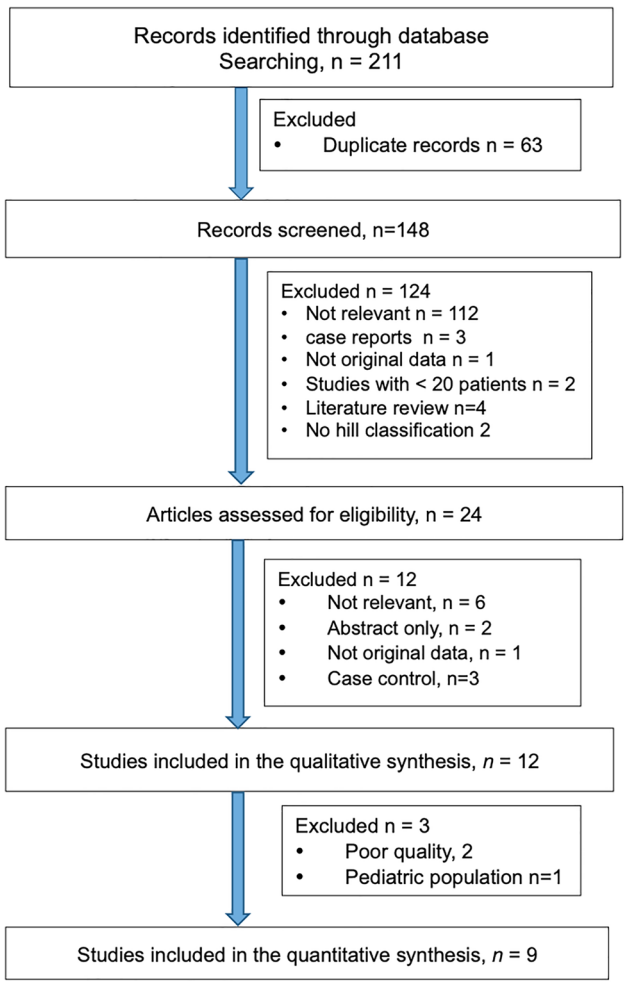

Fig. 2 Flowchart of study selection

Abnormal GEFV and GERD in the General Population

Two studies reported prevalence of GERD symptoms in general population, which included a total of 840 patients [4, 12]. In the 276 patients with abnormal GEFV (defined as Hill's classification grades III/IV), the estimated pooled prevalence of symptomatic GERD was 49.0% (95% CI 42.9–55.0%). Patients with abnormal GEFV had statistically greater risk of symptomatic GERD compared to patients with normal GEFV (RR 1.88, 95% CI 1.57–2.24, $p < .001$). Further, when detecting symptomatic GERD in the general population, abnormal GEFV had a sensitivity of 45.7% (95% CI 40.1–51.5%) and specificity of 73.3% (95% CI 69.3–77.0%). Table 3 presents the diagnostic accuracy and predictive values of abnormal GEFV to identify symptomatic GERD.

EGJ Morphology and Erosive Esophagitis in Symptomatic GERD

Seven studies reported the prevalence of erosive esophagitis in patients with symptomatic GERD, which included a total of 3914 patients [13–19]. In these patients, the pooled prevalence of erosive esophagitis was 27.0% (95% CI 18.0–37.9%). Patients with abnormal GEFV (Hill's classification grades III/IV) had significantly greater risk of erosive esophagitis compared to patients with normal GEFV (RR 2.17, 95% CI 1.40–3.36, $p < .001$; Fig. 3, Panel A). As shown in Table 3, when detecting erosive esophagitis in symptomatic GERD, the presence of abnormal GEFV had a sensitivity of 54.8% (95% CI 37.9–70.3%) and specificity of 75.7% (95% CI 65.9–83.4%). Finally, after excluding 327 patients with Hill's classification grade IV, in addition to the 1507 patients from Keskin et al. [15] who did not differentiate grade III from grade IV, patients with Hill's classification grade III had statistically greater risk of erosive esophagitis compared to patients with normal GEFV (RR 1.87, 95% CI 1.04–3.34, $p = .040$; Fig. 3, Panel B).

Table 1 Characteristics of included cohort studies

Author	Year	Country	*N*	Age	Male	Study design	Patient selection	Exclusion criteria	Outcomes
Hansdotter	2016	Sweden	334	54.8	171 (51.2)	P	General population	Angina pectoris, MI in last 6 months, CHD, severe lung or liver disease, varices, anticoagulation, GE surgery, need for anesthesia for EGD, age > 80 years, or have symptoms < weekly	1. GERD was defined by the presence of heartburn and/or regurgitation at least once a week, and/or erosive esophagitis or Barrett's esophagus
Lin	2006	Taiwan	506	50.8	301 (59.5)	P	Consecutive patients undergoing routine health check up	None	1. Erosive esophagitis 2. Nonerosive reflux disease (NERD), normal endoscopy, but typical symptoms 3. GERD = erosive esophagitis and or typical symptoms
Quach	2018	Vietnam	331	36.4–39.7	159 (48.0)	P	All the adult patients with upper GI symptoms who underwent EGD.	On PPIs, GE surgery/malignancy	1. GERD (GERDQ ≥ 8), 2. NERD (GERDQ ≥ 8 without reflux esophagitis), 3. Erosive esophagitis
Keskin	2017	Turkey	1507	49 [15–88]	620 (41.2)	P	Consecutive patients referred for elective EGD.	On PPIs, GE surgery/malignancy	1. GERD 2. Erosive esophagitis
Xie	2017	China	83	45.2–51.6	48 (57.8)	P	Consecutive patients with heartburn and/or regurgitation for at least 3 months, > 2 days a week.	GE surgery/malignancy, peptic ulcer, motility abnormalities, varices or severe comorbidities, and functional GERD.	1. NERD 2. Erosive esophagitis, 3. Reflux hypersensitivity
Kaplan	2014	Turkey	257	50.2	150 (58.7)	P	Consecutive patients with typical GERD symptoms for at least 6 months	GE surgery, upper respiratory symptoms/infection.	Reflux esophagitis
Kayaoglu	2014	Turkey	453	37.7–44.1	178 (39.2)		Patients referred for GERD symptoms	None	1. Erosive esophagitis 2. Abnormal PH test
Navarathne	2010	Sri Lanka	1150	50.4 ± 23.7	690 (60.0)	P	Adults with GERD symptoms for > 3 months	Dyspepsia, on antiplatelets, NSAIDs, bisphosphonates, PPIs in last 2 weeks, dysphagia, overt GI bleeding, ischemic heart disease, or abnormal EKG.	Erosive esophagitis
Inoue	2007	Japan	122	52.3 ± 12.5	Not available	P	Consecutive patients who underwent eradication treatment for symptomatic H. pylori infection	Prior reflux esophagitis or known GEFV status	Erosive esophagitis
Oberg	1999	Sweden	268	51	150 (56.0)	P	Consecutive patients with GERD symptoms	Motility disorder and GE surgery	1. Erosive esophagitis, 2. Barrett's esophagus 3. Abnormal esophageal acid exposure (> 4%)

Table 1 (continued)

Author	Year	Country	*N*	Age	Male	Study design	Patient selection	Exclusion criteria	Outcomes
Koch	2013	Austria	43	49.9 ± 13.8	28 (65.1)	R	All the patients who underwent fundoplication for GERD (> 6 months symptoms despite PPI, decreased QOL and abnormal pH study), documented pH testing, esophageal manometry, and Hill's classification. PPIs were stopped 7 days prior	Missing data	1. Erosive esophagitis 2. Abnormal acid exposure (> 73 episodes in 24 h or DeMeester > 14.7 or positive symptoms index with at least three symptoms 3. Gastrointestinal Quality of Life Index

Age presented as mean ± SD, median [inter-quartile range], or as single or range of means. Age for Oberg (1999) is median. For study design, P = prospective and R = retrospective

Discussion

Esophagogastroduodenoscopy (EGD) is a widely performed procedure with GERD symptoms being the most common indication [20]. EGD can identify complications of GERD (e.g., erosive esophagitis, esophageal cancer) and also assess the integrity of the EGJ. However, the EGD documentation specific to EGJ morphology is typically limited to the presence or absence of hiatal hernia, which is a quality indicator for EGD [21]. Hill's classification includes hiatal hernia (i.e., grade IV) and has been shown to be a more objective in identifying pathological GER than GERD symptoms as more than a third of patients with GERD symptoms do not have underlying pathological GER [3, 22].

The results of our systematic review and meta-analysis indicated a consistent association between EGJ morphology defined by Hill's classification and GERD in general population as well as between EGJ morphology and erosive esophagitis in patients with symptomatic GERD. In a sensitivity analysis, results indicated that these associations were not solely due to the presence of hiatal hernia (i.e., Hill's classification grade IV) as loss of GEFV (grade III) was also associated with pathological GER and erosive esophagitis. Taken together, results indicated that it is not sufficient to solely document the presence of hiatal hernia following EGD for GERD symptoms. More detailed diagnostic information specific to EGJ morphology can be provided by Hill's classification grades, which could better quantify GERD severity to better inform the prognosis of various treatment options, e.g., abnormal EGJ morphology is known to be associated with decreased responsiveness to proton pump inhibitors [23].

We also found that Hill's classification had suboptimal sensitivity for both GERD and erosive esophagitis, suggesting that pathological GER is a multifactorial process, of which an incompetent EGJ is only one of the contributors alongside others such as increased abdominal pressure in central obesity or late dinner and naps right immediately following meals [16].

Despite being recognized as important indicator of EGJ competency, Hill's classification has not been adopted in clinical practice by gastroenterologists. This is likely result from gastroenterologist not performing EGJ augmentation performance. Given that surgeons perform most antireflux procedures, most of the data on Hill's classification are found in surgical journals.

Although our systematic review was exhaustive, further study is required to provide additional insight into the strengths and weaknesses of Hill's classification. One of the factors preventing additional study is documentation, particularly for the gastroenterologist. Because assessing EGJ morphology using Hill's classification does not require

Table 2 Quality assessment of included studies

First author	Unbiased patient selection	Wide spectrum of EGJ morphology	Patients on PPIs excluded	EGJ morphology assessed without knowledge of the outcome	Outcome assessed without knowledge of EGJ morphology	Well-defined outcomes	Total quality assessment score
Hansdotter [4]	Yes	Yes	No	No	No	Yes	3
Lin [12]	Yes	Yes	No	No	No	Yes	3
Quach [18]	Yes	Yes	Yes	No	No	Yes	4
Keskin [15]	Yes	Yes	Yes	No	No	Yes	4
Xie [19]	Yes	Yes	No	No	No	Yes	3
Kaplan [10]	No	No	No	No	No	Yes	1
Kayaoglu [14]	Yes	Yes	No	No	No	Yes	3
Navarathne [16]	Yes	Yes	No	No	No	Yes	3
Inoue [13]	Yes	Yes	No	No	No	Yes	3
Oberg [17]	Yes	Yes	No	No	No	Yes	3
Koch [11]	No	Yes	No	No	No	Yes	2

Table 3 Accuracy, sensitivity, specificity, and predictive values for abnormal EGJ morphology

	Symptomatic GERD[a] % [95% CI]	Erosive esophagitis[b] % [95% CI]
Diagnostic accuracy	64.2 [60.9–67.3]	68.7 [60.6–75.6]
Sensitivity	45.7 [40.1–51.5]	54.8 [37.9–70.3]
Specificity	73.3 [69.3–77.0]	75.7 [65.9–83.4]
Positive predictive value	49.0 [42.9–55.0]	49.5 [32.0–67.0]
Negative predictive value	70.8 [66.8–74.4]	82.2 [72.6–89.0]

[a]Based on data from two population-based studies [4, 12]

[b]Based on data from symptomatic GERD patients [14–19]

additional time and effort, we suggest incorporating Hill's classification into endoscopy documentation to provide data available for further study.

The strengths of our systematic review include a robust and well-defined methodology. We searched major databases of biomedical publications and supplemented this search by manually reviewing the reference lists of potentially eligible publications. Study selection, quality assessment, and data gathering were performed independently by two investigators; sufficient inter-observer agreement was observed throughout the study selection process. The primary limitation of this systematic review is the relatively small number of available studies as well as the heterogeneity between study results. Overall, our systematic review included data from 11 studies conducted within nine countries that included data from 5054 patients. Results derived from such diverse patient cohorts provide increased external validity evidence.

Conclusion

Results of the meta-analysis indicated a consistent association between abnormal EGJ morphology (as measured by Hill's classification grades III/IV) and GERD symptoms as well as erosive esophagitis in patients with symptomatic GERD. Further, Hill's classification of EGJ morphology was shown to have good specificity when identifying patients at risk of pathological GER or erosive esophagitis. Considering assessment of EGJ morphology using Hill's classification can be performed by gastroenterologists without additional time and effort during routine endoscopy, we recommend that Hill's classification be included in EGD documentation.

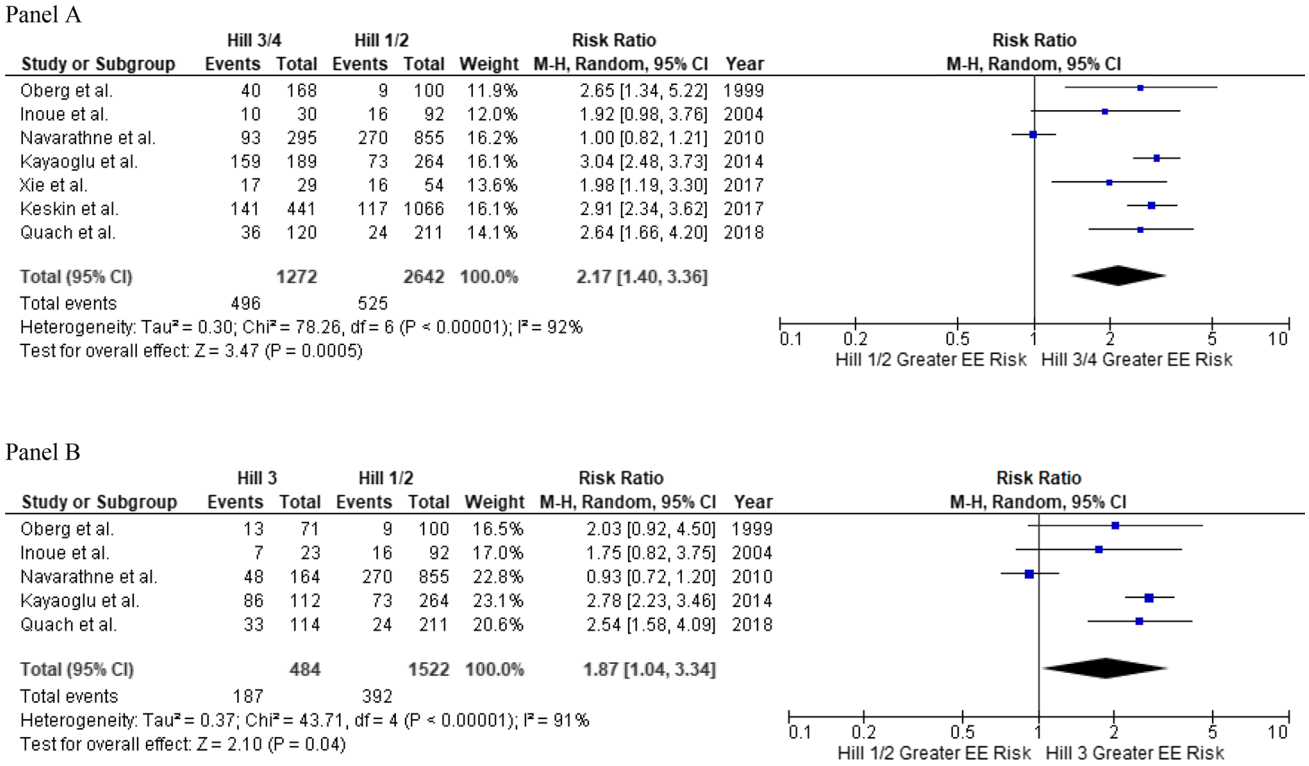

Fig. 3 Forest plot of risk ratios. **a** Erosive esophagitis in Hill's class 3–4 versus 1–2. **b** Erosive esophagitis in Hill's class 3 versus 1–2

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