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Diagnostic Accuracy of PCR-Based Detection Tests for Helicobacter Pylori in Otitis Media: A Meta-Analysis

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Abstract

Background and objectives: *Helicobacter pylori (H. Pylori)* infection has serious consequences such as peptic ulcers and gastric cancer. Histologic identification of organisms remains the gold standard in the diagnosis of *H. pylori*. This meta-analysis reviewed the overall diagnostic accuracy of polymerase chain reaction (PCR) vs histology of *H. pylori* infection in the patients with otitis media with effusion (OME).

Methods: Medline, Scopus and ISI web of science were systematically searched. Articles meeting the selection criteria were retrieved for the data collection and analysis. Diagnostic odds ratio (DOR) and symmetric summary receiver operating characteristic (sROC) of OME -associated .*H. pylori* infection was estimated for each study. The PCR techniques were compared to the histological tests as the gold standard in .diagnosing *H. pylori* infection.

Results: We included eight relevant studies compromising 259 case of OME. The pooled sensitivity and specificity of PCR compared to the histological diagnosis of *H. Pylori* infection in patient with OME were 71% (95%CI: 61% - 80%, I^2: 0.0%) and 81% (95%CI: 76% - 86%, I^2: 59.9%), respectively. Pooled positive likelihood ratio (PLR) and negative likelihood ratio (NLR) for PCR were 3.61(95%CI: 2.34 – 5.59, I^2: 44.5%) and 0.42 (95%CI: 0.31 – 0.57, I^2: 0.1%), respectively. For DOR analysis, the pooled accuracy of PCR was 10.78 (95%CI: 5.95 – 19.53, I^2: 0.0%) in diagnosing *H. Pylori* infection.

Conclusions: This review showed statistically significant differences in the diagnostic accuracy between the PCR and histological tests. This meta-analysis also suggests a higher sensitivity and specificity of PCR-based molecular diagnostic of *H. Pylori* infection in OME patients compared to the histological tests.

Keywords: Diagnostic accuracy; Meta-analysis; *H. Pylori* infection; Otitis media with effusion (OME); Polymerase chain reaction (PCR); Histology

Introduction

Helicobacter pylori (H. Pylori) infection has serious consequences such as peptic ulcers and gastric cancer [1-3]. Histologic identification remains the gold standard in diagnosing *H. pylori* infection [4]. The urea breath test, polymerase chain reaction (PCR), and CLO are also the most reliable diagnostic techniques for *H. Pylori* infection [5]. Some researchers reported the association between *H. pylori* infection and upper respiratory diseases, including chronic rhino sinusitis, chronic otitis media, and chronic otitis media with effusion [6-12], but little is known about the true colonization and the localization of these bacteria in the upper respiratory tract tissue.

Otitis media with effusion (OME) is a more common condition in persons with poor Eustachian tube function, in which the pathogenesis still remains unknown. Viral or bacterial infections, autoimmunity, allergy, gastro esophageal reflux possibly play a role in the pathogenesis of OME [13]. Recently, the heritability and genetic determinants of OME were also studied [14,15]. Epidemiological evidences have suggested the possible relationship of *H. Pylori* with the OME [16-18]. Over the last decade, several molecular techniques have been developed for targeting various microbial genes [19,20]. Polymerase chain reaction (PCR) is one of the most common molecular techniques used in detecting *H. Pylori* infection [21-23].To the best of our knowledge, the diagnostic accuracy of PCR-based methods for OME-infected patients has not been systematically reviewed and synthesized. Thus, we conducted a meta-analysis and systematic review to summarize the evidence on diagnostic accuracy of PCR-based tests compared to the histological methods in the patients with OME.

Materials and Methods

Literature review

We performed a systematic search without a language limitation in the Medline, Scopus and ISI web of science, covering all published papers up to March 2013, with the following combination of Mesh standardized keywords: ((“Helicobacter pylori"[Mesh]) AND (“Otitis Media"[Mesh] OR "Otitis Media with Effusion"[Mesh] OR "Otitis Media, Suppurative"[Mesh])) OR "Otolaryngology"[Mesh]. We reviewed potentially selected publications through titles and abstract screening and then collected the most related publications for a closer evaluation. Besides, the reference lists of the selected papers were also screened for other potential articles that possibly have been missed in the initial search.

Inclusion and exclusion criteria

The PCR techniques were compared to the histological tests as the gold standard in diagnosing the *H. pylori* infection. Those studies, which concern the association of *H. pylori* infection with OME risk using PCR and histological methods, offer the size of the sample,

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and the information that can help infer the results, were included. Accordingly, the reviews and duplicated publications were excluded.

Data extraction

Full papers of any titles/abstracts that appeared to be relevant were obtained where possible and the relevance of each study independently was assessed according to the aforementioned inclusion and exclusion criteria.

Assessment of study quality

We measured the quality of studies using the Quality Assessment of Studies of Diagnostic Accuracy Approach-QUADAS [24], a 14-item specifically developed tool, to judge the quality of primary studies.

Statistical analysis

The diagnostic odds ratio (DOR) and symmetric summary receiver operating characteristic (sROC) of OME-associated *H. pylori* infection, were estimated for each study. The DOR and its 95% confidence interval (CI) to each study was plotted against the number of participants for detecting any possible sample size biases. The heterogeneity was tested based on the *I*-squared values, with values less than 25%, 25% to 50%, and greater than 50% indicating low, moderate and high heterogeneity, respectively [25]. Using the bivariate method according to Reitsma et al. [26], pooled sensitivity, specificity and 95% confidence intervals were estimated for each diagnostic test. Publication biases were observed, using the relationship between the diagnostic odds ratio (DOR) and the effective sample size (ESS) [27]. Statistical analysis was undertaken using the program STATA 11.0 software. The Meta-Disk was used to calculate individual and pooled diagnostic OR, sensitivity, specificity, negative likelihood ratio, positive likelihood ratio [28]. P <0.05 was considered statistically significant.

Results

From the literature searches, we included eight relevant studies compromising 259 case of OME, which study selection flow is shown in figure 1.Only two studies were stated sensitivity and specificity. Table 1 summarizes the characteristics of eight studies. The quality analysis using QUADAS tool showed that six out of eight studies (75%) fulfilled more than seven criteria. The individual and combined sensitivity and specificity estimations for the PCR test, including all selected studies were assessed (Figure 2). Overall, sensitivity and specificity varied among studies of a given PCR test. The pooled sensitivity and

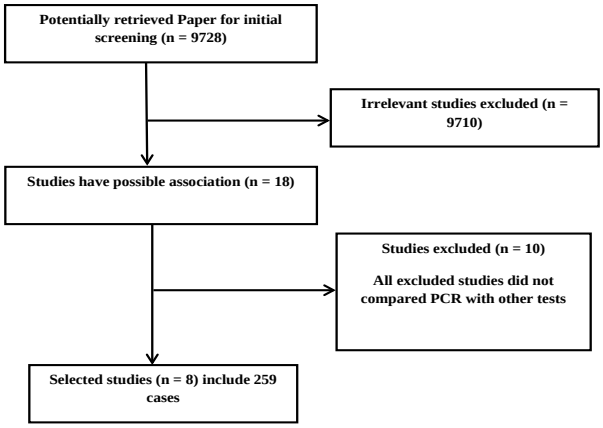

Figure 1: The flow diagram of included/excluded studies.

Author, Year	Country	Number of Cases	Age	Method	HP-Positive
[16]	China	60	19-73 years	PCR	24 (40%)
[38]	Korea	60	2–12 years	PCR	18 (30%)
[39]	USA	45	2–11 years	PCR	14 (32%)
[40]	Turkey	22	2-13 years	PCR	10 (45%)
[41]	Lebanon	18	3-8 years	PCR	0
[42]	Turkey	38	2–12 years	PCR	3 (7.9%)
[43]	Turkey	38	2–12 years	PCR	7 (16.3%)
[40]	Turkey	20	2-13 years	PCR	16 (47%)

PCR, Polymerase Chain Reaction

Table 1: *H. pylori* infection status among OME cases included in the meta-analysis.

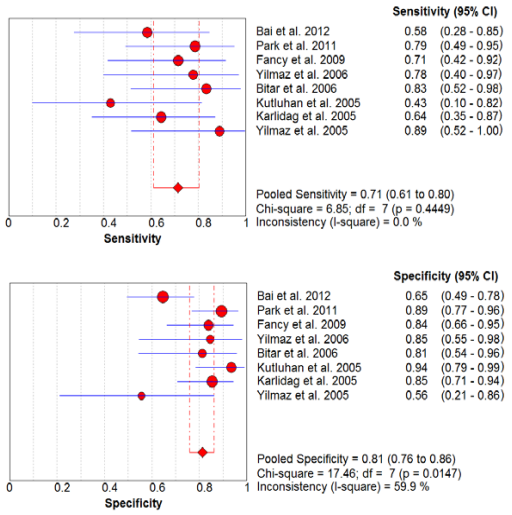

Figure 2: Estimates of sensitivity (Top) and specificity (Bottom) (95% confidence interval) of PCR. Combined results are shown using bothoptions: fixed and random effects model. When both results are similar with low heterogeneity, both can be used.

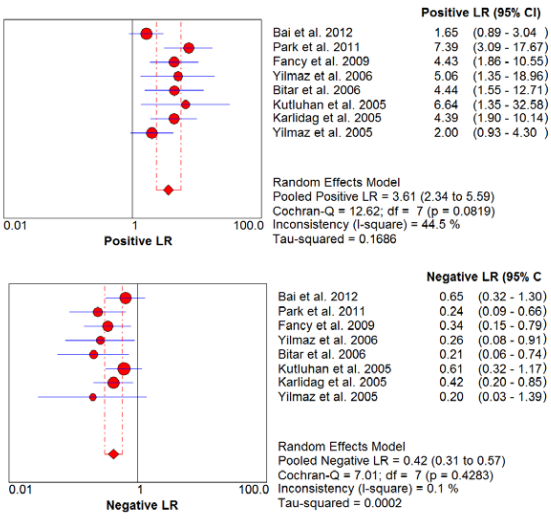

Figure 3: Estimates of positive likelihood ratio (PLR, Top) and negativelikelihood ratio (NLR, Bottom) (95% confidence interval) of PCR. Combined results are shown using both options: fixed and random effects model. When both results are similar with low heterogeneity, both can be used.

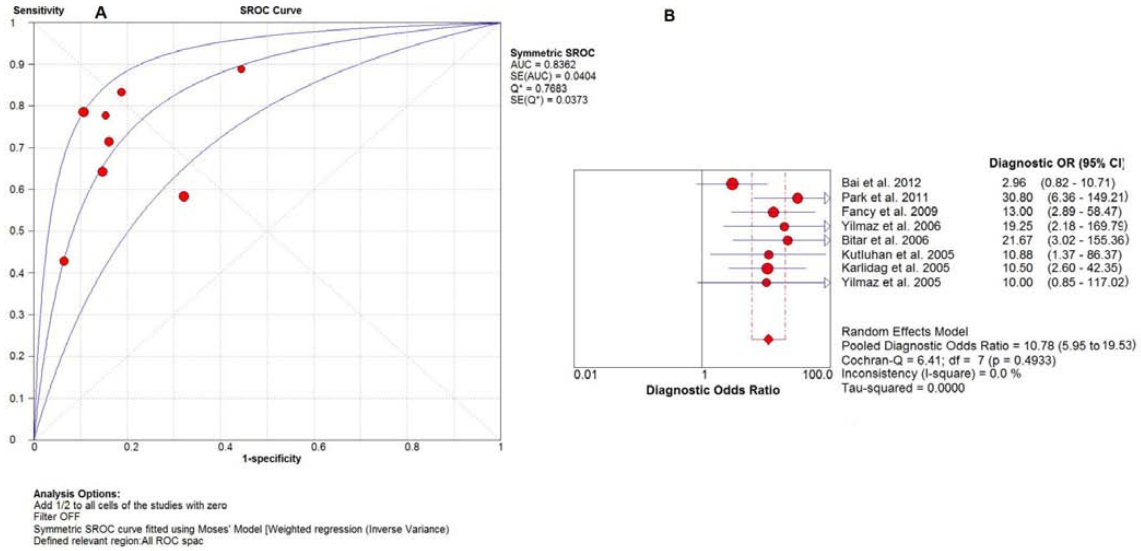

Figure 4: A, sROC curve for PCR in patient with OME; B, DOR of individual and combined studies.

specificity of PCR test in diagnosing *H. Pylori* infection in patient with OME were 71% (95%CI: 61%-80%, I^2: 0.0%) and 81% (95%CI: 76% - 86%,I^2: 59.9%), respectively. Pooled positive likelihood ratio (PLR) and negative likelihood ratio (NLR) for PCR were 3.61(95%CI: 2.34 – 5.59, I^2: 44.5%) and 0.42 (95%CI: 0.31 – 0.57, I^2: 0.1%), respectively (Figure 3).The sROC plots of eight selected studies and estimated DOR (95% confidence interval) are shown in figure 4A. For DOR analysis, the pooled accuracy of PCR was 10.78 (95%CI: 5.95 – 19.53, I^2: 0.0%) in diagnosing *H. Pylori infection* in patient with OME (Figure 4B). Egger's test 2-sided p-value was larger than 0.05, suggesting absence of publication bias for all tests.

Discussion

The *H. Pylori* infection diagnosis usually relies on the serology and histologic identification in the past [4]. However, the serology and histologic identification are not fast and reliable enough [29-33].The PCR-based molecular diagnostic techniques have been used for testing *H. Pylori* infections for about a decade [34,35]. Our meta-analysis revealed some concerns using the available evidences, which basically reflects the experience with PCR-based molecular diagnosis of *H. Pylori* infection among patient with OME, including the limitation of available evidences and a considerable variability among the available studies. Furthermore, the accuracy of molecular methods such as PCR is great enough, although specificity was generally high, and there is unpredictably variation in specificity among studies evaluating the same test.

Several limitations have been introduced for PCR-based molecular diagnostic, including presence false-negative and false-positive results due to the PCR inhibitors in the samples and easy contamination, and a difficulty in obtaining the worthy samples. Diagnostic accuracy of PCR may decrease at seven days after onset of the disease compared to the histologic identification and serology [36,37].

This meta-analysis addressed a moderate heterogeneity that likely was due to the differences between studies in the design (test protocol, definition of a positive result), geographical location (diverse *H. Pylori* infection prevalence, local strain dominance) and ethnicity (Asian and American).

This meta-analysis also showed that PCR-based molecular diagnostic method may generate consistent result with high and more variable specificity than sensitivity. Possible descriptions for these differences may include the standard control of PCR and threshold, types of the subjects and time point for sampling. Because of the absence of relative limited high quality studies and small number of published papers, this systematic review and meta-analysis have limitations, which need to be cited with cautious. Furthermore, because of only eight studies included in this review, this meta-analysis could not give strong enough evidence; thus, the findings should to be addressed in further and additional research.

Conclusion

This review showed statistically significant differences in the diagnostic accuracy between the PCR and histological tests. This meta-analysis also suggests a higher sensitivity and specificity of PCR-based molecular diagnostic method for *H. Pylori* infection in OME patients compared to the histological tests.

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