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Accuracy of testing for anti-*Helicobacter pylori* IgG in urine for *H. pylori* infection diagnosis: systematic review and meta-analysis

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Abstract

Objectives：This meta-analysis aims to systematically measure the potential diagnostic value of Anti-H. pylori IgG in urine for infection diagnosis, using all eligible studies published in the English and Chinese language literature.

Design： The random effect model was used to analyse the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative LR (NLR), diagnostic odds ratio (DOR), together with the summary receiver operator characteristic (SROC) curve.

Setting： Literature searches of databases including PubMed, EMBASE, MEDLINE, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Wanfang Databases were performed to retrieve studies evaluating the diagnostic value of urine IgG antiboty for H.pylori infection

Primary outcome measure： Twenty-three studies were included in the current meta-analysis with 4,963 subjects.

Results：The pooled sensitivity, specificity, PLR, NLR, DOR, and AUC were 0.83 (95% CI, 0.82-0.85), 0.89 (95% CI, 0.88-0.90), 8.81 (95% CI, 6.37-12.2), 0.13 (95% CI, 0.09-0.2), 73 (95% CI, 46.45-114.74), and 0.9551, respectively. Subgroup analyses showed that in Asian, healthy or adult population, anti-H.pylori antibody in urine yielded more accurate results and seemed to be more valuable in diagnosing of H.pylori infection.

Conclusions：Anti-H.pylori antibody in urine exerts important function and represent a good marker in diagnosing H.pylori infection. However, further validation based on a larger sample is still required.

Strengths and limitations of this study：

Non-invasive tests for the assessment of *H.pylori* status have become part of the management strategies for individuals. Preliminary studies have explored the diagnostic accuracy for anti-*H.pylori* antibody in urine, but the results are inconclusive. In the present study, we performed a comprehensive databases search for all the eligible studies reported the diagnostic accuracy of anti-*H.pylori* antibody in urine. Our meta-analysis is strengthened by the use of a standard protocol, strict inclusion criteria, standardized data extraction, independent reviewers. To the best of our knowledge, this is the first study assessing the summary predictive value of Anti-*H. pylori* IgG in urine for infection diagnosis.

Several limitations should be acknowledged in this meta-analysis when interpreting the results. First, included documents were not comprehensive enough. The search range was limited to the published studies, however the unpublished research such as conference papers, can not be obtained. This may probably miss some gray literatures. On the other hand, only the studies published in English or Chinese were included in this meta-analysis, which might miss relevant research of other languages. Second, for articles contained different cut-off values within the same study, we selected the cut-off value according to the manufacturer recommendedd. This may lead to the included cutoff value may be not the most appropriate one in the specific area. Third, as a diagnostic test, urine IgG antibody determined with the blinded can minimize the tendency to diagnose. However, most studies did not report whether blinding detect was used, which may increases the possibility of measurement bias.

Introduction

Helicobacter pylori (*H. pylori*) is a bacterium that chronically infects more than half the world's population and plays a causative role in the pathogenesis of chronic gastritis, peptic ulcer diseases, gastric cancer, and mucosa-associated lymphoid tissue lymphoma [1]. The considerable burden of these *H. pylori*-related sequelae means that there is an acute demand for accurate diagnosis of this infection. Several detection methods have been developed, such as culture, histological staining, urea breath test (UBT), and *H. pylori* stool antigen test (HpSA), among which, a simple, non-invasive, and inexpensive but accurate diagnostic test remains the goal.

A number of methods have been developed for non-invasive *H. pylori* infection diagnosis using body fluids. Tests for the detection of anti-*H. pylori* antibodies in serum are widely used because they are relatively straightforward, convenient, and economical. A number of studies have reported the presence of specific antibodies for *H. pylori* in body fluids other than serum [2]. Anti-*H. pylori* IgG in urine is detectable and has been used for the diagnosis of *H. pylori* infection. If sensitive screening for *H. pylori* infection was possible using urine samples, it would not only be more convenient in clinical practice but would also be very useful for mass screening.

In 1993, Alemohammd *et al*. reported that ELISA was both highly sensitive and specific for the detection of anti-*H. pylori* antibodies in urine. These findings were confirmed by another study from Japan [3,4]. The Japanese study laid the groundwork for the development of a urine-based ELISA kit and a rapid immunochromatography assay for *H. pylori* diagnosis. Evaluation of the immunochromatography assay in Japanese asymptomatic adults and patients with gastric disorders showed promising results against UBT (sensitivity: 86.3%–99%; specificity: 91.5%–100%) [4,5]. Studies using ELISA among Japanese children revealed high levels of sensitivity and specificity as well. When compared with ^{13}C-UBT and/or HpSA, sensitivity ranged between 92.3% and 94.4%, and specificity ranged between 76.4% and 96.9% [6,7]. Different findings were recorded, however, for the same kit when compared with gastrointestinal endoscopic testing for *H. pylori*, in line with European multicentre studies. Sensitivity and specificity in adults were 89.4% and 68%, respectively [8]. The corresponding figures in children were 63.2% and 97.3% [9]. Subsequently, the accuracy and usefulness of the immunochromatography assay have been supported by several trials in different geographic areas, including Japan [10], Turkey [11], Hong Kong and Taiwan [12], the United States [13], and Europe [14].

Variations in the sensitivity and specificity of anti-*H. pylori* IgG in urine revealed by the previous trials indicate the need for comprehensive evaluation of the test performance

before wider application. Therefore, this systematic review and meta-analysis was conducted to identify whether anti-*H. pylori* IgG in urine can serve as a valuable test for *H. pylori* diagnosis.

Methods

Literature search strategy

We searched several electronic databases up to January 7, 2016, namely, PubMed, EMBASE, MEDLINE, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Wanfang Databases by two independent researchers to identify relevant studies that evaluated the diagnostic value of urine IgG antiboty for H.pylori infection. The following search terms (in Title, Abstract or keywords fields) were combined using Boolean rules: 'H.pylori', 'Helicobacter pylori', 'urine IgG antibody' ,'urine antibody', with a filter for human studies published in English or Chinese. Two researchers (Yuehua Gong and Qiuping Li) screened all the titles and abstracts; studies including data on H. pylori and urine IgG levels were read in full. The reference lists of the selected papers were hand-searched to identify additional papers. When multiple publications presented results using the same patient cohort, the most recent or the most complete publication was selected for inclusion. Review articles and references from accepted articles were searched for any additional papers.

Literature selection criteria

We included studies that met the following criteria: (1) Anti-H.pylori IgG antibody in urine was determined; (2) Investigation of the diagnostic accuracy of urine IgG of H.pylori compared to culture or histopathology or UBT or HpSA (based on only one or at least two reference methods); (3) Sensitivity, specificity, and cut-off values can be found in identified studies or calculated from the provided data; (4) Publication of full paper in a peer-reviewed scientific journal. While the exclusion criteria were listed as follows: (1) studies with insufficient data to construct the 2*2 table; (2) The reference standard was only serological assay; (3) Reviews, letters, and conference abstracts; and (4) publications were identified as duplicates. Two researchers (Yuehua Gong and Qiuping Li) independently assessed the papers for final selection. If a study fulfilled the eligibility criteria, it was included in the systematic review. Any discrepancies were resolved with discussion.

Data extraction and QUADAS-2 assessment the following variables were extracted from the original studies in a predefined data extraction form (see Table 1): Author, Ethnicity, year

of publication, number of cases, age (adults or children), study population (patients or healthy), reference standard, and assay method (ELISA or IM technique). True positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) with urine IgG antibody diagnose were included. Extraction of studies was done independently by two reviewers. Discrepancies in the interpretation were resolved by consensus. If a study was selected for the systematic review but did not provide data that could be included in the meta-analysis, the authors were contacted via e-mail. If the authors did not reply or did not provide the requested information, then this article would be excluded.

Statistical analysis

The following parameters representing test accuracy were calculated based on the data (TP, FP, FN, and TN) we extracted from each included studies: the pooled sensitivity, specificity, PLR, NLR, DOR, and corresponding 95% confidence intervals (95% CI). Simultaneously, the SROC was also calculated. The heterogeneity was measured by Q test and the inconsistency index (I^2), and a $P < 0.05$ and a $I^2 > 50\%$ indicated significant heterogeneity among studies, the random-effect model (DerSimonian-Laird method) was conducted for the meta-analysis to calculate the pooled sensitivity, specificity, and other related indexes of the studies, and meta-regression was performed to detect the source; otherwise, the fixed-effect model (MantelHaenszel method) was chosen.

In addition, the Spearman correlation coefficient was used to verify if the heterogeneity in meta-analysis could be explained by a threshold effect; a threshold effect was defined as a positive correlation ($P < 0.05$). Subgroup analyses were performed for region, age, study population, and assay method. Deek's Funnel Plot Asymmetry Test was applied to determine the presence of publication bias using STATA 12.1 software (Stata Corp., College Station, Texas, USA.) [15] and a $P < 0.05$ indicated the presence of publication bias. MetaDisc (version 1.4) software [16] was also used to calculate the other parameters of diagnostic accuracy. All P values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Search results

Figure 1 summarizes the search process and numerical selection of the final papers that were included in the systematic review and meta-analysis. A systematic search of biomedical databases resulted in 423 hits, and after excluding duplicates, 246 citations were identified. No unpublished literature relevant to the topic was identified. Forty papers were selected based on their abstracts and titles and were read in full for eligibility. Two eligible studies

referred to the same study group, hence, only one of them was included in the systematic review [6,14]. Twenty-four individual studies fulfilled eligibility criteria and were included in the systematic review [3-5,7,8,10-14],[9,17,18,19]. Twenty-three studies had extractable data after contacting the authors and were included in the meta-analysis [3-5],[7-9,11-14,17,18,20]. A flowchart detailing the process for how studies were selected is shown in Figure 1.

Study characteristics

Baseline characteristics of the eligible studies are summarized in Table 1. A total of 23 studies with 4963 participants were included in the meta-analysis. Among these studies, three were conducted in the United States [3,13,18], two in Europe[8,9], and the remaining 18 in Asia. All eligible studies were published between 2000 and 2014. Sample sizes ranged between 21 and 449. Urinary *H. pylori* IgG was detected using ELISA in nine studies, using immunochromatography in nine studies, and using both assays in five studies. Key data were successfully extracted from all included studies, such as true positives, false positives, false negatives, and true negatives. The number of true positives ranged between 12 and 237, the number of false negatives ranged between 0 and 83, the number of false positives ranged between 0 and 66, and the number of true negatives ranged between 2 and 176.

Quality assessment

Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) summary plots are outlined in Table 2 and Supplemental Figure 1 and show the methodological quality of the selected studies assessed using the QUADAS-2 tool [21]. The majority of studies were ranked as high quality for most domains. A score of 1 for each "yes" and a score of 0 for each "unclear" and "no" was given. Any scoring discrepancies were resolved through discussion.

Diagnostic accuracy and threshold analysis

Spearman's correlation coefficient was first used to examine whether the threshold effect existed, because of it being the important source of heterogeneity. Spearman's correlation coefficient for sensitivity and 1-specificity in the meta-analysis was 0.161, with a *P*-value of 0.413, suggesting no heterogeneity from the threshold effect. Heterogeneity was measured using the Q test and the inconsistency index (I^2) to choose the appropriate calculation model. There was statistically significant heterogeneity in the pooled diagnostic odds ratio (DOR) (DOR = 73, I^2 = 75%, P = 0.0000) (Figure 2). Therefore, the random effects model was used for calculating sensitivity, specificity, positive likelihood ratio (PLR) and DOR.

Based on extracted data on true positives, true negatives, false positives, and false negatives from the included studies that evaluated the diagnostic accuracy of urinary IgG in

H. pylori diagnosis, the following diagnostic quantitative results were obtained. Pooled sensitivity and specificity were 0.83 (95% CI: 0.82–0.85; Figure 3a) and 0.89 (95% CI: 0.88–0.90; Figure 3b), respectively. Pooled PLR and negative likelihood ratio (NLR) were 8.81 (95% CI: 6.37–12.2; Figure 3c) and 0.13 (95% CI: 0.09–0.2; Figure 3d), respectively. The summary receiver operating characteristic (sROC) curve for urinary IgG was positioned near the desirable upper left corner, and the area under the curve (AUC) was 0.9551, indicating that the level of overall accuracy was high (Supplemental Figure 2).

Subgroup analysis

Subgroup analysis was conducted based on age, region, study population, and assay method. Pooled results are shown in Table 3. A random effects model was used because significant heterogeneity was observed (all $I^2 > 50\%$).

Age analysis

Seven studies containing 1047 adults (>17 years of age) were evaluated for diagnostic accuracy of the urine IgG assay for *H. pylori* diagnosis. Pooled sensitivity, specificity, PLR, and NLR were 0.87 (95% CI: 0.84–0.89), 0.91 (95% CI: 0.88–0.94), 8.13 (95% CI: 4.61–14.33), and 0.13 (95% CI: 0.07–0.22), respectively, with a DOR of 85.12 and AUC value of 0.9593. The diagnostic performance of urinary IgG was lower for young persons in the four other studies containing 644 children (≤17 years of age). Pooled sensitivity, specificity, PLR, and NLR were 0.53 (95% CI: 0.48–0.58), 0.96 (95% CI: 0.94–0.97), 17.93 (95% CI: 4.83–62.59), and 0.35 (95% CI: 0.22–0.58), respectively, with a DOR of 61.62 and AUC value of 0.9632. Therefore, the diagnostic accuracy of the urine IgG assay might be more promising in adults than in children.

Region analysis

Of the 23 included studies, five were from Europe or the United States and the remaining 18 were from Asia. For studies from Europe and the United States, analysis showed a pooled sensitivity of 0.80 (95% CI: 0.77–0.82) and a pooled specificity of 0.88 (95% CI: 0.86–0.90). Combined PLR was 12.05 (95% CI: 5.22–27.8) and NLR was 0.16 (95% CI: 0.07–0.38). AUC and DOR were 0.9557 and 73.75, respectively, suggesting moderate diagnostic accuracy. For studies from Asia, performance of the urine IgG assay for the diagnosis of *H. pylori* showed an improvement in accuracy, with a pooled sensitivity of 0.86 (95% CI: 0.84–0.88) and a pooled specificity of 0.9 (95% CI: 0.88–0.92). Combined PLR was 7.74 (95% CI: 5.77–10.39), NLR was 0.12 (95% CI: 0.07–0.2), and DOR was 73.75. AUC was 0.9553, suggesting relatively high diagnostic accuracy. Therefore, the urine IgG assay might be more reliable for Asian populations than for populations from other countries.

Study population analysis

Study population analysis, which included patients and healthy controls, was performed in the systematic review. A total 16 patient studies and five healthy or without significant upper abdominal symptoms studies were evaluated for diagnostic accuracy of the urine IgG assay. In the patient population, pooled sensitivity, specificity, PLR, and NLR were 0.84 (95% CI: 0.82–0.85), 0.87 (95% CI: 0.85–0.89), 7.17 (95% CI: 5.18–9.93), and 0.14 (95% CI: 0.09–0.23), respectively, with a DOR of 54.29 and AUC value of 0.9436. In the healthy population, pooled sensitivity, specificity, PLR, and NLR were 0.75 (95% CI: 0.69–0.80), 0.97 (95% CI: 0.94–0.98), 16.25 (95% CI: 6.94–38.06), and 0.13 (95% CI: 0.03–0.53), respectively, with a DOR of 156.11 and AUC value of 0.98. Except for pooled sensitivity, the diagnostic performance of the urine IgG assay was better for the healthy population than the patient population, suggesting relatively high diagnostic accuracy in the healthy population.

Assay method analysis

In the review, urinary *H. pylori* IgG was detected using ELISA in nine studies, using immunochromatography in nine studies, and using both assays in five studies. For studies that used ELISA, pooled sensitivity was 0.86 (95% CI: 0.84–0.87) and pooled specificity was 0.87 (95% CI: 0.84–0.88). Combined PLR was 7.92 (95% CI: 5.02–12.5) and NLR was 0.12 (95% CI: 0.07–0.23). AUC and DOR were 0.9521 and 67.46, respectively. For studies that used immunochromatography, pooled sensitivity, specificity, PLR, and NLR were 0.81 (95% CI: 0.78–0.83), 0.92 (95% CI: 0.89–0.93), 9.81 (95% CI: 6.28–15.34), and 0.14 (95% CI: 0.07–0.28), respectively, with a DOR of 82.94 and AUC value of 0.9584. Analysis suggested that there was no significant difference between ELISA and immunochromatography in diagnostic performance for the antibody in urine.

Meta-regression analysis

Heterogeneity was found in summary estimates for sensitivity, specificity, PLR, NLR, and DOR. Therefore, meta-regression was conducted to examine the source of heterogeneity based on region, sample size, age, study population, blind design, quality of study, and assay method. The results indicated that study population and quality of study were the important factors contributing to heterogeneity ($P = 0.0189$ and $P = 0.0295$, respectively) (Table 4).

Publication bias

Because publication bias is recognized as an important factor that influences the results of meta-analysis [22], the Deeks' funnel plot asymmetry test was performed to examine publication bias (Supplemental Figure 3). The test returned a *P*-value of 0.124, suggesting

that potential publication bias did not exist among the studies.

Discussion

Non-invasive tests for the assessment of *H. pylori* status have become part of management strategies for individuals[23]. Preliminary studies have explored the diagnostic accuracy of testing for anti-*H. pylori* antibodies in urine, but the results are inconclusive. In the present study, we performed comprehensive database searches for all eligible studies reporting the diagnostic accuracy of testing for anti-*H. pylori* antibodies in urine. Our meta-analysis was strengthened by the use of a standard protocol, strict inclusion criteria, standardized data extraction, and independent reviewers. To the best of our knowledge, this is the first study assessing the summary predictive value of anti-*H. pylori* IgG in urine for infection diagnosis.

After pooling data, the following summary of diagnostic parameters was obtained. Pooled sensitivity was 0.83 and pooled specificity was 0.89, which represent a good marker for *H. pylori* diagnosis. The sROC curve, which assesses overall test performance by showing the trade-off between sensitivity and specificity, had an AUC of 0.9551, suggesting good accuracy. Another indicator of diagnostic accuracy is DOR, which combines sensitivity and specificity data into a single number ranging from 0 to infinity, with a higher value indicating better discriminatory test performance. Mean DOR in the meta-analysis was 73, suggesting that testing for anti-*H. pylori* antibodies in urine should be helpful in the diagnosis of *H. pylori* infection. We further examined the diagnostic accuracy of anti-*H. pylori* antibody in urine by calculating PLR and NLR, which can be easier to relate to clinical practice than sROC and DOR. Pooled PLR was 8.81 and pooled NLR was 0.13, indicating that the presence of anti-*H. pylori* antibodies in urine has an important function in diagnosing *H. pylori* infection. Substantial heterogeneity was found with meta-analysis, where pooled specificity, PLR, NLR, and DOR were analysed. Therefore, the random-effect model was used to synthesise the above data.

Heterogeneity is an important factor that can affect the results of meta-analysis. Therefore, we used Spearman's correlation coefficient to clarify whether the threshold effect contributed to the source of heterogeneity. Spearman's correlation coefficient was 0.193, with a *P*-value of 0.334, suggesting that heterogeneity among the included studies could not have been induced by the threshold effect. We further used subgroup analysis based on study population, region, age, and assay method to explore heterogeneity.

First, in age subgroup analysis, pooled sensitivity was found to be significantly higher in adults than in children. A previous report suggests a significant positive association between the sensitivity of anti-*H. pylori* antibodies in urine and children's age [24]. A strong

association between the sensitivity of testing using ELISA serum IgG for *H. pylori* and the increasing age of the children studied has been reported [25]. It is possible that the diagnostic accuracy of the urine IgG assay might be because of a higher antibody response in adults than in children.

Second, we found that the urine antibody showed a relatively higher diagnostic accuracy in Asian countries compared with Europe and the United States. This finding may be because the *H. pylori* antigen spectrum is different in Asian strains compared with most European strains. The antigen used in detection kits, which is extracted from *H. pylori* strains isolated in Japan[10,11], might not always react well with anti-*H. pylori* IgG produced by European or American individuals, resulting in a number of false negative cases.

Third, for the study population, subgroup analysis showed that diagnostic performance of the urine IgG assay was better in healthy people than in patients. In meta-analysis, the patient population included dyspeptic, chronic gastritis, and peptic ulcer patients amongst others. It is possible that the disease condition in the stomach may cause a change in *H. pylori* colonization. *H. pylori* IgG is not synchronized with the *H. pylori* infection process, and delayed generation or the disappearance of colonization for several months may affect results. Graham *et al.[18]* reported that urine test results may remain positive for an extended time after successful treatment of the infection. This may be an important factor affecting the accuracy of the antibody test in the diseased population.

Fourth, in assay method subgroup analysis, we did not find any significant difference between ELISA and immunochromatography for the diagnostic performance of urine IgG testing.We conducted meta-regression analysis to investigate sources of heterogeneity. Regression analysis demonstrated that study population was the important factor contributing to heterogeneity, a finding consistent with subgroup analysis. Additionally, regression analysis showed that the quality of included studies was another factor for heterogeneity. In meta-analysis, 23 included studies were qualified using QUADAS-2 assessment, which included a score of 7 for one study, a score of 8 for nine studies, a score of 9 for four studies, and a score of 10 or more for nine studies. According to regression analysis, there was a difference in diagnostic accuracy between low and high scoring studies.

There are several limitations to the meta-analysis that should be borne in mind when interpreting the results. First, the studies included is not an exhaustive list, with the search range being limited to published studies. Unpublished research, such as conference papers, cannot be obtained. It is therefore possible that some literature has been missed. Additionally, only studies published in English or Chinese were included, which means that relevant

research published in other languages has not been included. Second, , for articles that contained different cut-off values within the same study, we selected cut-off values according to the manufacturers' recommendations. This may mean that the included cut-off values may not be the most appropriate ones for specific areas. Third, as a diagnostic test, urinary IgG determined using blinded testing can reduce the tendency to diagnose. However, most studies did not report whether blinded detection was used, which may increase the possibility of measurement bias.

In conclusion, testing for anti-*H. pylori* antibodies in urine has an important function and represents a good marker for the diagnosis of *H. pylori* infection. Sources of heterogeneity were found to come from region, age, quality of the studies included, and especially from study population. The urine IgG assay showed better diagnostic performance in Asian populations compared with European or American, in healthy people compared with patients, and in adults compared with children. Further large-scale, well-designed studies examining different study populations are required to confirm the results of this meta-analysis.

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Acknowledgements

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Author contributions

GYH and YY wrote the main manuscript text and LQP analyzed the data. All authors reviewed the manuscript.

Competing financial interests

The authors declare that they have no competing financial interests.

Data sharing statement

No additional unpublished data are available.

Figure legends

Fig 1. Flow diagram of the literature search.

Fig 2. Forest plots of DOR for or H.pylori diagnosis by urine IgG antibody.

The pooled diagnostic odds ratio was 73(95%CI: 46.45-114.74)

Fig 3. Forest plots of sensitivity, specificity, DLR+, and DLR- for H.pylori diagnosis by urine IgG antibody

(a) The summary sensitivity was 0.83 (95% CI: 0.82–0.85; I2 = 94.4%); (b) The summary specificity 0.89 (95% CI: 0.87–0.90; I2 = 86.1%); (c) The summary PLR was 8.5 (95% CI: 6.27-12.2; I2 = 81.0%); (d) The summary NLR of all articles was 0.13 (95% CI: 0.09–0.20; I2 = 96.3%).

Table 1. Characteristics of the studies included in the meta-analysis

Author	Ethnicity	Year	Region	No. of cases	Age	Diseases	Reference standard	Blind design	Assay method	TP(a)	FP(b)	FN(c)	TN(d)
Mohammad M	American	1993	America	306	MIX	Patient	C,HE,R	N.A.	ELISA	237	6	10	53
Kiyonori Katsuragi	Japanese	1998	Asia	119	N.A.	MIX	U	N.A.	ELISA	69	0	1	49
Hiroto Miwa	Japanese	1999	Asia	132	Adult	Patient	U	Yes	ELISA	63	5	10	54
Mototsugu Kato	Japanese	2000	Asia	189	N.A.	Patient	C,H,R	N.A.	ELISA	127	12	5	45
Soichiro Yamamoto	Japanese	2000	Asia	117	N.A.	mix	H,S	N.A.	IM	81	2	7	27
D. Y. Graham	American	2001	America	104	Adult	healthy	U	Yes	IM	41	2	2	59
Toru Fujisawa	Japanese	2001	Asia	21	Adult	healthy	C,H,R	N.A.	IM	18	1	0	2
Hiroto Miwa	Japanese	2001	Asia	155	Adult	Patient	U	N.A.	IM	93	7	4	51
Kyoichi Adachi	Japanese	2002	Asia	100	MIX	healthy	U	Yes	ELISA	32	2	3	37
									IM	30	1	5	38
W. M. Wong	Chinese	2002	Asia	123	Adult	Patient	R,H	Yes	IM	58	3	2	60
Youke Lu	Chinese	2002	Asia	102	MIX	Patient	C,R,H	N.A.	ELISA	60	4	2	27
A. Leodolter, D. Vaira	European	2003	Europe	449	N.A.	Patient	C,H,R	N.A.	IM	178	34	38	170
									ELISA	193	66	23	140
T Shimizu	Japanese	2003	Asia	68	Children	Patient	U, HpSA	N.A.	ELISA	12	13	1	42
Antone R. Opekun	American	2004	America	188	Adult	Patient	U,S	Yes	IM	72	0	8	87
Fu-Chen Kuo	Chinese	2005	Asia	317	MIX	Patient	C,R,H,U	N.A.	ELISA	211	8	19	79
Francis Megraud	European	2005	Europe	316	Children	Patient	C,H,R	Yes	ELISA	86	4	50	176
									IM	36	2	83	151
Yanfang Gong	Chinese	2005	Asia	215	MIX	Patient	U	Yes	ELISA	80	19	16	100
Chien-Yu Lu	Chinese	2006	Asia	120	NA	Patient	C,HE,R,U	Yes	IM	54	6	8	52
Khitam Muhsen	Israeli Arab	2006	Asia	159	Children	healthy	HpSA	N.A.	ELISA	27	3	52	77
Lam Tung Nguyen	Vietnamese	2010	Asia	148	MIX	Patient	C,IM,S	Yes	IM	66	6	17	59
Demıray Gürbüz E	Turks	2012	Asia	124	Adult	Patient	C,H,R	Yes	IM	61	8	21	34
									ELISA	61	8	21	34
Masumi Okuda	Japanese	2013	Asia	101	Children	healthy	U, HpSA	Yes	ELISA	34	2	3	62
									IM	29	0	7	64
Duc T Quach	Vietnamese	2014	Asia	200	Adult	Patient	R,H	N.A.	IM	94	9	17	80

C:culture, H: histology,R: rapid urease test,IM:immunochromatographic technique, S:serology;

Table 2. Summary of QUADAS-2 assessments of included studies

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quanlity
Mohammad M	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Kiyonri Katsuragi	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Hiroto Miwa	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Mototsugu Kato	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Soichiro Yamamoto	U	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	8
D. Y. Graham	N	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	10
Toru Fujisawa	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Hiroto Miwa	Y	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	10
Kyoichi Adachi	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
W. M. WONG	U	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	10
Youke Lu	Y	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	10
A. LEODOLTER, D. VAIRA	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
T Shimizu	N	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	9
Antone R. Opekun	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	13
Fu-Chen Kuo	N	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	9
Francis Megraud	U	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Chien-Yu Lu	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Yanfang Gong	U	Y	N	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	9
Khitam Muhsen	N	Y	N	Y	U	Y	N	Y	U	N	U	Y	Y	Y	7
Lam Tung Nguyen	N	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	8
Demıray Gürbüz E	N	Y	Y	Y	U	Y	N	Y	Y	N	U	Y	Y	Y	8
Masumi Okuda	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	9
Duc T Quach	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8

Y:Yes;N:No;U:Unclear.

1.Was a consecutive or random sample of patients enrolled?
2.Was a case–control design avoided?
3.Did the study avoid inappropriate exclusions?
4.Are There Concerns That the Included Patients and Setting Do Nt Match the Review Question?
5.Were the index test results interpreted without knwledge of the results of the reference standard?
6.If a threshold was used, was it prespecified?
7.Are There Concerns That the Index Test, Its Conduct, or Its Interpretation Differ From the Review Question?
8. Is the reference standard likely to correctly classify the target condition?
9.Were the reference standard results interpreted without knwledge of the results of the index test?
10.Are There Concerns That the Target Condition as Defined by the Reference Standard Does Nt Match the Question?
11.Was there an appropriate interval between the index test and reference standard?
12.Did all patients receive the same reference standard?
13.Were all patients included in the analysis?
14.Could the patient flow have introduced bias?

Table 3. Group/ subgroup analysis of Pooled estimates with 95 % confidence interval for sensitivity, specificity, and positive and negative likelihood ratios

		Cochrane Q test		Pooled Sensitivity	Pooled Specificity	Pooled Positive LR	Pooled Negative NR	
Group/Subgroup	Spearman P	DOR (95%CI)	P	(95%CI)	(95%CI)	(95%CI)	(95%CI)	AUC
Overall	0.413	73(46.45-114.74)	0.0000	0.83(0.82-0.85)	0.89(0.88-0.90)	8.81(6.37-12.2)	0.13(0.09-0.2)	0.9551
Age								
Children	0.397	61.62(22.16-171.32)	0.0335	0.53(0.48-0.58)	0.96(0.94-0.97)	17.93(4.83-62.59)	0.35(0.22-0.58)	0.9632
Adult	0.732	85.12(29.81-243.06)	0.0000	0.87(0.84-0.89)	0.91(0.88-0.94)	8.13(4.61-14.33)	0.13(0.07-0.22)	0.9593
Region								
Asian	0.724	73.75(43.38-125.38)	0.0000	0.86 (0.84-0.88)	0.9 (0.88-0.92)	7.74(5.77-10.39)	0.12(0.07-0.20)	0.9553
Europe and America	0.645	73.75(29.26-125.38)	0.0000	0.80 (0.77-0.82)	0.88(0.86-0.90)	12.05 (5.22-27.8)	0.16(0.07-0.38)	0.9557
Study population								
Patient	0.616	54.29(34.07-86.51)	0.0000	0.84(0.82-0.85)	0.87(0.85-0.89)	7.17 (5.18-9.93)	0.14 (0.09-0.23)	0.9436
Healthy	0.294	156.11(41.44-588.04)	0.0073	0.75 (0.69-0.80)	0.97(0.94-0.98)	16.25 (6.94-38.06)	0.13 (0.03-0.53)	0.98
Assay method								
IM	0.5940	82.94(41.62-165.29)	0.0000	0.81(0.78-0.83)	0.92(0.90-0.94)	9.81 (6.28-15.34)	0.14 (0.07-0.28)	0.9584
ELISA	0.7820	67.46(35.58-127.9)	0.0000	0.86(0.84-0.87)	0.87(0.84-0.88)	7.92(5.02-12.5)	0.12 (0.07-0.23)	0.9521

Table 4. Meta-regression of potential heterogeneity within the included studies

Variables	Coeff.	Std. Err.	P-value	RDOR	[95%CI]
Cte.	-0.98	3.4737	0.781	----	----
S	0.309	0.1614	0.0706	----	----
Region	-0.459	0.8022	0.574	0.63	(0.12;3.39)
Sample size	-0.001	0.0041	0.8856	1	(0.99;1.01)
Age	-0.093	0.2489	0.7117	0.91	(0.54;1.53)
Study population	1.367	0.5326	0.0189	3.92	(1.29;11.96)
blinded design	0.144	0.6537	0.8282	1.15	(0.29;4.54)
Assay method	0.008	0.4155	0.9841	1.01	(0.42;2.41)
quanlity	0.518	0.22	0.0295	1.68	(1.06;2.66)

Coeff:Constant Coefficient; Std. Err.Stardard Error: RDOR:Reletive diagnostic odd ratio.

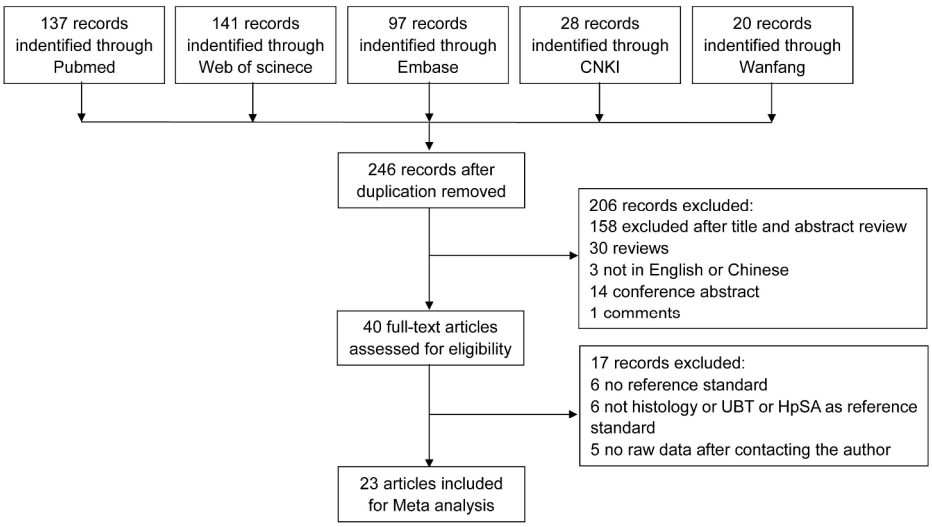

Fig 1. Flow diagram of the literature search.

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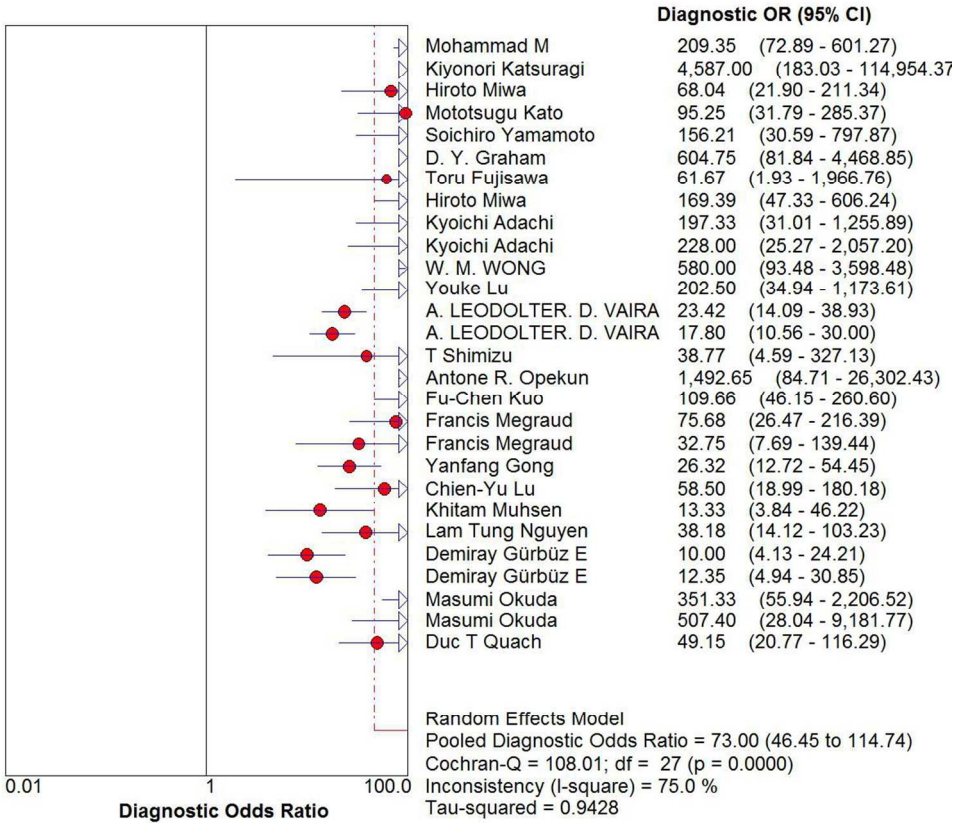

Fig 2. Forest plots of DOR for or H.pylori diagnosis by urine IgG antibody.
The pooled diagnostic odds ratio was 73(95%CI: 46.45-114.74)

433x369mm (72 x 72 DPI)

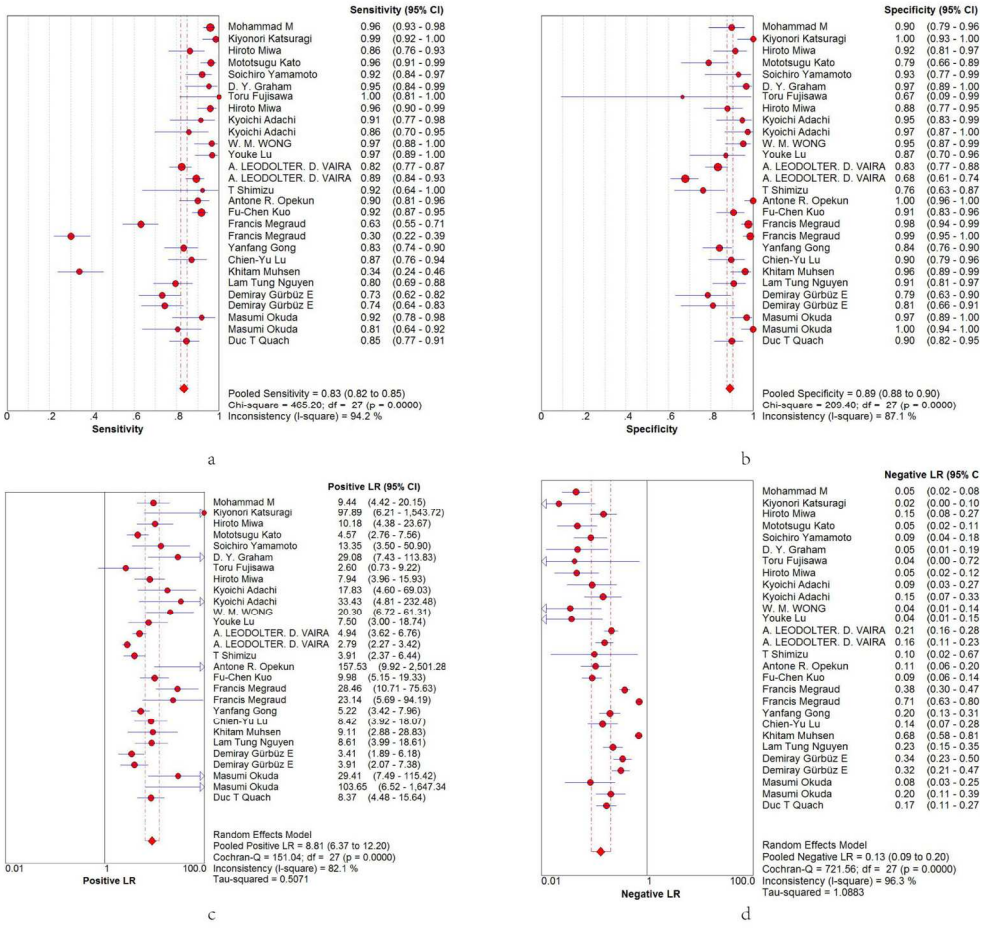

Fig 3. Forest plots of sensitivity, specificity, DLR+, and DLR- for H.pylori diagnosis by urine IgG antibody (a) The summary sensitivity was 0.83 (95% CI: 0.82–0.85; I2 = 94.4%); (b) The summary specificity was 0.89 (95% CI: 0.87–0.90; I2 = 86.1%); (c) The summary PLR was 8.5 (95% CI: 6.27-12.2; I2 = 81.0%); (d) The summary NLR of all articles was 0.13 (95% CI: 0.09–0.20; I2 = 96.3%).

150x140mm (300 x 300 DPI)

Accuracy of testing for anti-*Helicobacter pylori* IgG [1]in urine for *H. pylori* infection diagnosis: systematic review and meta-analysis

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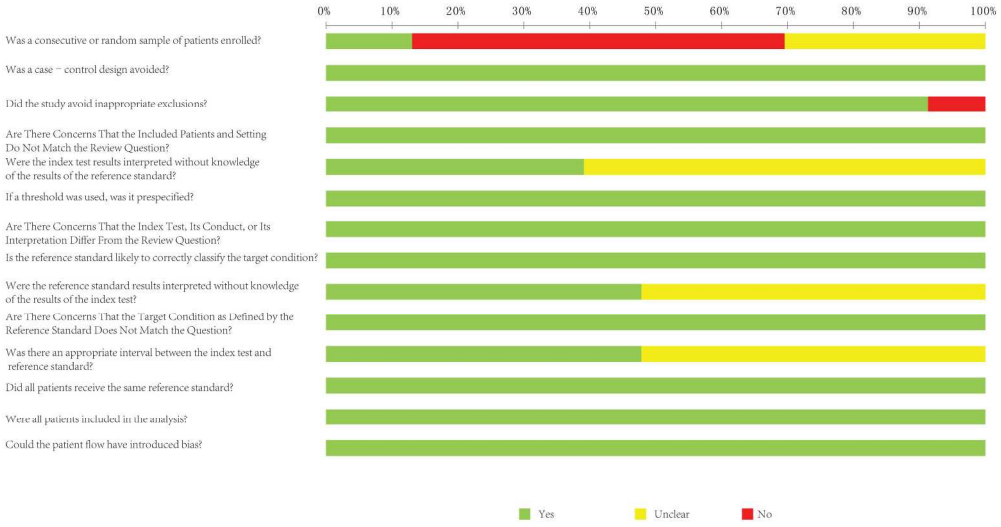
Supplemental Figure legends

Figure 1. Summary of QUADAS-2 assessments of included studies.

Fig 2. Summary receiver operating characteristic (SROC) curves and confidence interval for the diagnosis of *H.pylori* infection using IgG antibody in urine

Fig 3. Deek's funnel plot to assess the likelihood of publication bias. The statistically non-significant P-value of 0.124 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias



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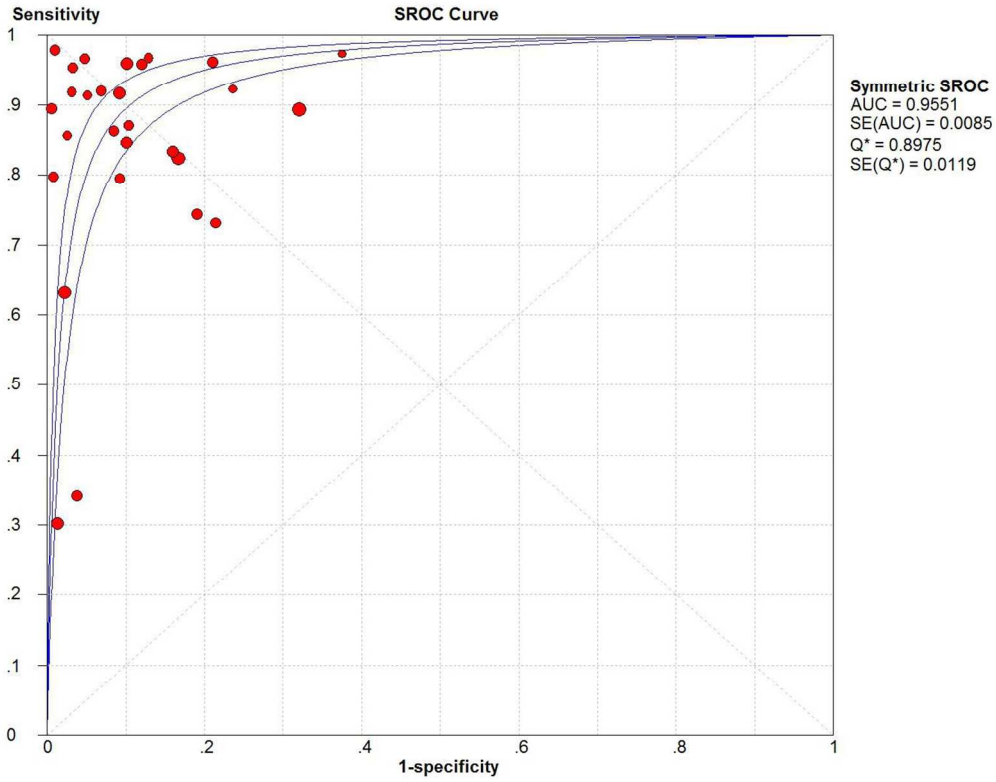

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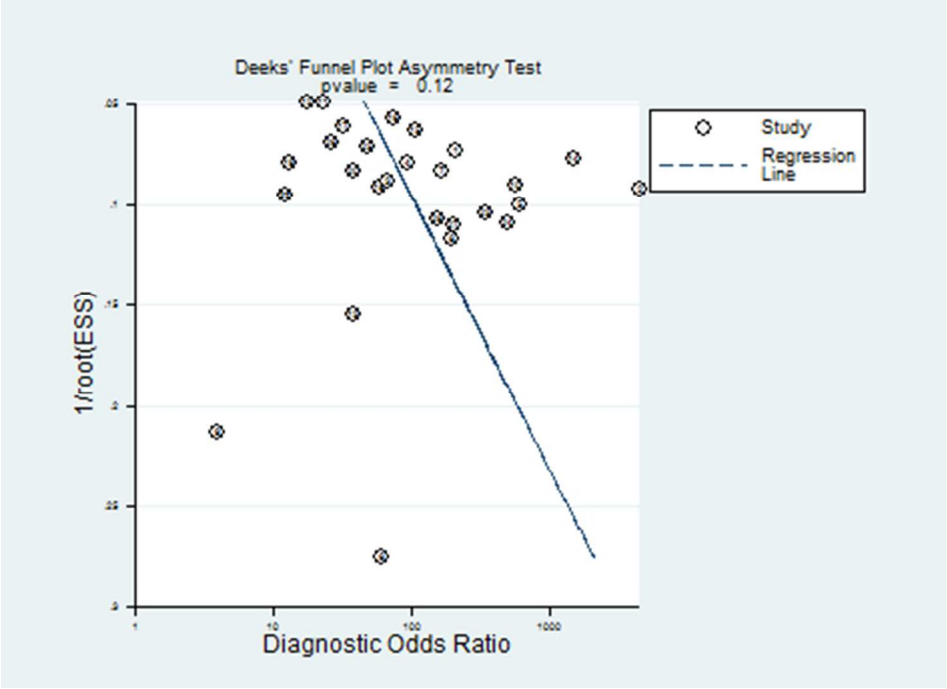

166x121mm (72 x 72 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2,3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3,4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3,4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3,4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4-5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Accuracy of testing for anti-Helicobacter pylori IgG in urine for H. pylori infection diagnosis: systematic review and meta-analysis

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Infectious diseases, Gastroenterology and hepatology
Keywords:	H.pylori, urine IgG antibody, diagnosis, Meta analysis

Accuracy of testing for anti-*Helicobacter pylori* IgG in urine for *H. pylori* infection diagnosis: a systematic review and meta-analysis

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Abstract

Objectives： This meta-analysis aims to systematically measure the potential diagnostic value of anti-*H. pylori* IgG in urine for infection diagnosis, using all eligible studies published in English and Chinese language.

Design： The random effect model was used to analyze the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative LR (NLR), diagnostic odds ratio (DOR), together with the summary receiver operator characteristic (SROC) curve.

Setting： Literature searches of databases including PubMed, EMBASE, MEDLINE, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Wanfang Databases were performed to retrieve studies evaluating the diagnostic value of urine IgG antiboty for *H.pylori* infection.

Primary outcome measure： Twenty-three studies with 4,963 subjects were included in the current meta-analysis.

Results： The pooled sensitivity, specificity, PLR, NLR, DOR, and AUC were 0.83 (95% CI, 0.82-0.85), 0.89 (95% CI, 0.88-0.90), 8.81 (95% CI, 6.37-12.2), 0.13 (95% CI, 0.09-0.2), 73 (95% CI, 46.45-114.74), and 0.9551, respectively. Subgroup analyses showed that diagnostic accuracy of the urine IgG assay was different in the study population.

Conclusions： Anti-*H.pylori* antibody in urine might serve as a good marker in diagnosing H.pylori infection. However, further validation based on a larger sample is still required.

Strengths and limitations of this study

1. A comprehensive search of literature databases was performed to identify all eligible studies that reported the diagnostic performance of an anti-*Helicobacter pylori* antibody in urine.
2. The systematic meta-analysis used a standard protocol, strict inclusion criteria, standardized data extraction, and independent reviewers.
3. We first assessed the summary predictive value of anti-*H. pylori* IgG in urine for infection diagnosis, and additional subgroup analyses based on study population, region, age, and assay method were used to explore heterogeneity.
4. Unpublished research such as conference papers and studies published in languages other than English or Chinese were not included in this meta-analysis, so some relevant research may have been missed.
5. We selected the cut-off value according to the manufacturer's recommendations, but this may not have been the most appropriate for specific areas.

Introduction

Helicobacter pylori (*H. pylori*) is a bacterium that chronically infects more than half of the world's population and plays a causative role in the pathogenesis of chronic gastritis, peptic ulcer diseases, gastric cancer, and mucosa-associated lymphoid tissue lymphoma [1-4]. The considerable burden of these *H. pylori*-related outcomes means that there is an acute demand for accurate diagnosis of this infection. Several detection methods have already been developed, such as culture, histological staining, the urea breath test (UBT), and the *H. pylori* stool antigen test (HpSA), but a simple, non-invasive, inexpensive, and accurate diagnostic test remains the goal.

A number of methods have been developed for non-invasive *H. pylori* infection diagnosis using body fluids. Tests for the detection of serum anti-*H. pylori* antibodies are widely used because they are relatively straightforward, convenient, and economical. Several studies have also reported the presence of specific anti-*H. pylori* antibodies in body fluids other than serum [5,6]. For example, anti-*H. pylori* immunoglobulin (Ig)G is detectable in urine and has been used for the diagnosis of *H. pylori* infection. If urine samples could be used for the sensitive screening of *H. pylori* infection, this would be more convenient both for clinical practice and mass screening.

In 1993, Alemohammd *et al*. reported that the enzyme-linked immunosorbent assay (ELISA) was both highly sensitive and specific for the detection of anti-*H. pylori* antibodies in urine. This was confirmed by another study from Japan [7]. These studies laid the groundwork for the development of a urine-based ELISA kit and a rapid immunochromatography (IM) assay for *H. pylori* diagnosis[8]. Evaluation of the IM assay in Japanese asymptomatic adults and patients with gastric disorders showed promising results compared with UBT (sensitivity: 86.3%–99%; specificity: 91.5%–100%) [8,9]. The use of ELISA to detect *H. pylori* in Japanese children also revealed high levels of sensitivity and specificity. When compared with ^{13}C-UBT and/or HpSA, the ELISA sensitivity ranged from 92.3%–94.4%, and specificity from 76.4%–96.9% [10,11]. Different findings were recorded, however, for the same kit when compared with gastrointestinal endoscopic testing for *H. pylori*, in line with European multicentre studies. Sensitivity and specificity in adults were 89.4% and 68%, respectively [12], and the corresponding figures in children were 63.2% and 97.3%, respectively [13]. Subsequently, the accuracy and usefulness of the IM assay have been supported by several trials in different geographic areas, including Japan [14], Turkey [15], Hong Kong and Taiwan [16], the United States [17], and Europe [18].

These variations in the sensitivity and specificity of anti-*H. pylori* IgG urine testing

indicate the need for a comprehensive evaluation of the test performance before wider application. Therefore, this systematic review and meta-analysis was conducted to identify whether anti-*H. pylori* IgG in urine can serve as a valuable test for *H. pylori* diagnosis.

Methods

Literature search strategy

Literatures of electronic databases including PubMed, EMBASE, MEDLINE, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Wanfang Databases were searched by two independent researchers to identify relevant studies that evaluate the diagnostic value of urine IgG antiboty for *H.pylori* infection. The last search date was January 7, 2016. The following search terms (in Title, Abstract or keywords fields) were combined using Boolean rules: '*H.pylori*', '*Helicobacter pylori*', 'urine IgG antibody', 'urine antibody' （Supplemental Figure 1）, with a filter for human studies published in English or Chinese. Two researchers (Yuehua Gong and Qiuping Li) screened all the titles and abstracts; studies including data on *H. pylori* and urine IgG levels were read in full text. The reference lists of the selected papers were hand-searched to identify additional available papers. When multiple publications presented results using the same patient cohort, the most recent or the most complete publication was selected for inclusion. Review articles and references of the accepted articles were searched for additional papers.

Literature selection criteria

We included studies that met the following criteria: (1) Anti-*H.pylori* IgG antibody in urine was detected; (2) Investigation of the diagnostic accuracy of urine IgG of *H.pylori* compared to culture or histopathology or UBT or HpSA (based on only one or at least two reference methods); (3) Sensitivity, specificity, and cut-off values can be found in identified studies or calculated from the provided data; (4) Publication with full text in a peer-reviewed scientific journal. While the exclusion criteria were listed as follows: (1) studies with insufficient data to construct the 2*2 table; (2) Reviews, letters, and conference abstracts; and (3) publications identified as duplicates. If a study fulfilled the eligibility criteria, it was included in the systematic review. Any discrepancies were resolved with discussion.

Data extraction and Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 assessment

The following variables were extracted from the original studies in a predefined data extraction form (see Table 1): author, ethnicity, year of publication, number of cases, age (adults or children), study population (patients or healthy), reference standard, and assay method (ELISA or IM technique). True positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) for urine IgG antibody diagnose were included. Extraction of studies was performed independently by two reviewers (Yuehua Gong and Qiuping Li). Discrepancies were discussed with the third researcher (Yuan Yuan) and agreement was eventually reached. If a study was selected for the systematic review but did not provide data that could be included in the meta-analysis, the authors were contacted via e-mail. If the authors did not reply or did not provide the requested information, then this article would be excluded. QUADAS-2 summary plots were outlined in Table 2 and Supplemental Figure 2 [19].

Statistical analysis

The following parameters representing test accuracy were calculated based on the data (TP, FP, FN, and TN) we extracted from each included studies: the pooled sensitivity, specificity, PLR, NLR, DOR, and corresponding 95% confidence intervals (95% CI). Simultaneously, the SROC was also assessed. The heterogeneity was measured by Q test and the inconsistency index (I^2), and $P < 0.05$ and $I^2 > 50\%$ indicated significant heterogeneity among studies. The random-effect model (DerSimonian-Laird method) was conducted for the meta-analysis to calculate the pooled sensitivity, specificity, and other related indexes of the studies, and meta-regression was performed to detect the source of the heterogeneity; otherwise, the fixed-effect model (MantelHaenszel method) was chosen.

In addition, the Spearman correlation coefficient was used to verify if the heterogeneity in meta-analysis could be explained by a threshold effect, which was defined as a positive correlation ($P < 0.05$). Subgroup analyses were performed for region, age, study population and assay method. The differences between subgroups were compared by Z test. The formula was Z=|AUC1 – AUC2|/SQRT（$SE1^2$+$SE2^2$）. Deek's Funnel Plot Asymmetry Test was applied to determine the presence of publication bias using STATA 12.1 software (Stata Corp., College Station, Texas, USA.) [20]. MetaDisc (version 1.4) software [21] was also used to calculate other parameters of diagnostic performance. All P values were two-sided, and $P <$ 0.05 was considered statistically significant.

Results

Search results

This meta-analysis was organized according to the PRISMA statement (Supplemental file 1). Figure 1 summarizes the search process and numerical selection of the final papers that were included in the systematic review and meta-analysis. A systematic search of biomedical databases resulted in 423 hits, and after excluding duplicates, 246 citations were identified. No unpublished literature relevant to the topic was identified. Forty papers were selected based on their abstracts and titles and were read in full for eligibility. Two eligible studies referred to the same study group; hence, only one of these was included in the systematic review [10,18]. Twenty-four individual studies fulfilled the eligibility criteria and were included in the systematic review [7-9,11,12,14-18],[13,22-31]. Of these, 23 studies had extractable data after contacting the authors and were included in the meta-analysis [7-9],[11-13,15-18,22-24,26,28,30-33]. A flowchart detailing the study selection process is shown in Figure 1.

Study characteristics

Baseline characteristics of the eligible studies are summarized in Table 1. A total of 23 studies with 4963 participants were included in the meta-analysis. Of these, three were conducted in the United States [7,17,23], two in Europe [12,13], and the remaining 18 in Asia. All eligible studies were published between 2000 and 2014. Sample sizes ranged from 21–449. Urinary *H. pylori* IgG was detected using ELISA in nine studies, using IM in nine studies, and using both assays in five studies. Key data were successfully extracted from all studies, including TPs, FPs, FNs, and TNs. The number of TPs ranged from 12–237, FNs from 0–83, FPs from 0–66, and TNs from 2–176.

Diagnostic accuracy and threshold analysis

Spearman's correlation coefficient was first used to determine the existence of the threshold effect because it is an important source of heterogeneity. The Spearman's correlation coefficient for sensitivity and 1-specificity in the meta-analysis was 0.161, with a *P*-value of 0.413, suggesting no heterogeneity from the threshold effect. Heterogeneity was measured using the Q test and the inconsistency index (I^2) to choose the appropriate calculation model. Significant heterogeneity was detected in the pooled diagnostic odds ratio (DOR) (DOR = 73, I^2 = 75%, P = 0.0000) (Figure 2). Therefore, the random effects model was used to calculate sensitivity, specificity, the positive likelihood ratio (PLR), and DOR.

Based on TP, TN, FP, and FN data extracted from the included studies, we evaluated the diagnostic accuracy of urinary IgG in *H. pylori* diagnosis from the following quantitative parameters: pooled sensitivity and specificity were 0.83 (95% CI: 0.82–0.85; Figure 3a) and 0.89 (95% CI: 0.88–0.90; Figure 3b), respectively; pooled PLR and negative likelihood ratio (NLR) were 8.81 (95% CI: 6.37–12.2; Figure 3c) and 0.13 (95% CI: 0.09–0.2; Figure 3d), respectively. The summary receiver operating characteristic (sROC) curve for urinary IgG was positioned near the desirable upper left corner, and the area under the curve (AUC) was 0.9551, indicating that the level of overall accuracy was high (Supplemental Figure 3).

Subgroup analysis

Subgroup analysis was conducted based on age, region, study population, and assay method. Pooled results are shown in Table 3. A random effects model was used because significant heterogeneity was observed (all $I^2 > 50\%$). A two-sample Z-test was conducted to evaluate significant differences in AUC values between any two subgroups.

Age analysis

Seven studies containing 1047 adults (>17 years of age) were evaluated. Pooled sensitivity, specificity, PLR, and NLR were 0.87 (95% CI: 0.84–0.89), 0.91 (95% CI: 0.88–0.94), 8.13 (95% CI: 4.61–14.33), and 0.13 (95% CI: 0.07–0.22), respectively, with a DOR of 85.12 and an AUC value of 0.9593. The diagnostic performance of urinary IgG was evaluated for young people in the four other studies containing 644 children (≤17 years of age). Pooled sensitivity, specificity, PLR, and NLR were 0.53 (95% CI: 0.48–0.58), 0.96 (95% CI: 0.94–0.97), 17.93 (95% CI: 4.83–62.59), and 0.35 (95% CI: 0.22–0.58), respectively, with a DOR of 61.62 and an AUC value of 0.9632. There was no significant difference in the AUC values between adults and children ($P>0.05$).

Regional analysis

Of the 23 included studies, five were from Europe or the United States and the remaining 18 were from Asia. For studies from Europe and the United States, the analysis showed a pooled sensitivity of 0.80 (95% CI: 0.77–0.82) and a pooled specificity of 0.88 (95% CI: 0.86–0.90). Combined PLR was 12.05 (95% CI: 5.22–27.8), NLR was 0.16 (95% CI: 0.07–0.38), and AUC and DOR were 0.9557 and 73.75, respectively. For studies from Asia, the pooled sensitivity was 0.86 (95% CI: 0.84–0.88) and the pooled specificity was 0.9 (95% CI: 0.88–0.92). Combined PLR was 7.74 (95% CI: 5.77–10.39), NLR was 0.12 (95% CI:

0.07–0.2), DOR was 73.75, and AUC was 0.9553. There was no significant difference in the AUC values between Europe or the United States and Asia (P>0.05).

Study population analysis

Study population analysis, of both patients and healthy controls, was performed in the systematic review. A total of 16 patient studies and five studies of healthy controls or individuals with no upper abdominal symptoms were evaluated. In the patient population, pooled sensitivity, specificity, PLR, and NLR were 0.84 (95% CI: 0.82–0.85), 0.87 (95% CI: 0.85–0.89), 7.17 (95% CI: 5.18–9.93), and 0.14 (95% CI: 0.09–0.23), respectively, with a DOR of 54.29 and AUC value of 0.9436. In the healthy population, pooled sensitivity, specificity, PLR, and NLR were 0.75 (95% CI: 0.69–0.80), 0.97 (95% CI: 0.94–0.98), 16.25 (95% CI: 6.94–38.06), and 0.13 (95% CI: 0.03–0.53), respectively, with a DOR of 156.11 and AUC value of 0.98. Except for pooled sensitivity, the diagnostic performance of the urine IgG assay was better for the healthy population than the patient population. Furthermore, there was a significant difference in AUC values between patients and controls (P<0.05), suggesting that relatively high diagnostic accuracy can be achieved in the healthy population.

Assay method analysis

Of all studies included, urinary *H. pylori* IgG was detected using ELISA in nine, IM in nine, and both assays in five. For studies that used ELISA, the pooled sensitivity was 0.86 (95% CI: 0.84–0.87) and pooled specificity was 0.87 (95% CI: 0.84–0.88). Combined PLR was 7.92 (95% CI: 5.02–12.5), NLR was 0.12 (95% CI: 0.07–0.23), and AUC and DOR were 0.9521 and 67.46, respectively. For studies that used IM, pooled sensitivity, specificity, PLR, and NLR were 0.81 (95% CI: 0.78–0.83), 0.92 (95% CI: 0.89–0.93), 9.81 (95% CI: 6.28–15.34), and 0.14 (95% CI: 0.07–0.28), respectively, with a DOR of 82.94 and AUC value of 0.9584. No significant difference was detected between ELISA and IM for the diagnostic accuracy of urine antibody detection.

Meta-regression analysis

Heterogeneity was found in summary estimates for sensitivity, specificity, PLR, NLR, and DOR. Therefore, meta-regression was conducted to examine the source of heterogeneity based on region, sample size, age, study population, blind design, quality of study, and assay method. The results indicated that study population and quality of study were the important factors contributing to heterogeneity (P = 0.0189 and P = 0.0295, respectively) (Table 4).

Publication bias

Because publication bias is recognized as an important factor that influences the results of meta-analyses [34], the Deeks' funnel plot asymmetry test was performed to examine publication bias (Supplemental Figure 4). The test returned a *P*-value of 0.124, suggesting no significant publication bias was found in the pooled analysis of the studies.

Discussion

Non-invasive tests for the assessment of *H. pylori* status have become part of patient management strategies [35-37]. Preliminary studies have explored the diagnostic accuracy of testing for anti-*H. pylori* antibodies in urine, but the results are inconclusive. In the present study, we performed comprehensive database searches for all eligible studies reporting the diagnostic accuracy of testing for anti-*H. pylori* antibodies in urine. Our meta-analysis was strengthened by the use of a standard protocol, strict inclusion criteria, standardized data extraction, and independent reviewers. To the best of our knowledge, this is the first study assessing the summary predictive value of anti-*H. pylori* IgG in urine for infection diagnosis.

Anti-*H. pylori* IgG in urine is detectable and has been used for the diagnosis of *H. pylori* infection, but a comprehensive evaluation of the test performance is needed before its wider application. After pooling data, we obtained a pooled sensitivity of 0.83 and a pooled specificity of 0.89, which represent good markers for *H. pylori* diagnosis. The sROC curve, which assesses overall test performance by showing the trade-off between sensitivity and specificity [38,39], had an AUC of 0.9551, suggesting a good level of accuracy. Another indicator of diagnostic accuracy is DOR, which combines sensitivity and specificity data into a single number ranging from 0 to infinity, with higher values indicating better discriminatory test performances [40]. The mean DOR in the meta-analysis was 73, suggesting that testing for anti-*H. pylori* antibodies in urine should be helpful in the diagnosis of *H. pylori* infection. We further examined the diagnostic accuracy of an anti-*H. pylori* antibody in urine by calculating the PLR and NLR, which can be easier to relate to clinical practice than sROC and DOR. The pooled PLR was 8.81 and the pooled NLR was 0.13, indicating that the presence of anti-*H. pylori* antibodies in urine has an important function in diagnosing *H. pylori* infection. Substantial heterogeneity was found with meta-analysis, so the random effects model was used to synthesize the above data. Our results show that anti-*H. pylori* IgG represents a good marker for the diagnosis of *H. pylori* infection.

Heterogeneity is an important factor that can affect the results of meta-analysis. Therefore, we used the Spearman's correlation coefficient to clarify whether the threshold effect contributed to the source of heterogeneity. The Spearman's correlation coefficient was 0.193, with a *P*-value of 0.334, suggesting that heterogeneity among the included studies could not have been induced by the threshold effect. We further used subgroup analysis based on study population, region, age, and assay method to explore heterogeneity. No significant difference in age, region, or assay method was detected, but subgroup analysis for the study population revealed a significant difference in AUC values between patients and controls, suggesting a relatively high level of diagnostic accuracy in the healthy population. In meta-analysis, the patient population included dyspeptic, chronic gastritis, and peptic ulcer patients amongst others. It is possible that the disease condition in the stomach may cause a change in *H. pylori* colonization [41]. On the other hand, *H. pylori* IgG is not synchronized with the *H. pylori* infection process, so the delayed generation or disappearance of *H. pylori* colonization for several months may affect the level of anti-*H. pylori* IgG in the urine [42]. Indeed, Graham *et al*. [23] reported that urine tests may remain positive for an extended time after successful treatment of the infection. This may be an important factor affecting the accuracy of the antibody test in the diseased population. The meta-regression analysis also demonstrated that study population was an important factor contributing to heterogeneity, which is consistent with subgroup analysis. These findings indicate that *H. pylori* infection diagnosis by anti-*H. pylori* IgG in the urine requires extra caution in diseased populations.

The QUADAS tool was developed and evaluated by Whiting et al. [43] and is recommended by the Cochrane diagnostic accuracy systematic reviews [44] to provide a methodological assessment of the quality of diagnostic accuracy studies. Experience, reports from users, and feedback from the Cochrane Collaboration suggested the potential for improvements; therefore, QUADAS-2 was developed [19] and has been shown to be a considerable improvement over the original tool. The responses to QUADAS-2 signalling questions are assessed in terms of risk of bias or concerns regarding applicability. In the present meta-analysis, 23 of the included studies were qualified using QUADAS-2 assessment, which included a score of 7 for one study, a score of 8 for nine studies, a score of 9 for four studies, and a score of 10 or more for nine studies. Meta-regression analysis showed that the quality of included studies was another factor for heterogeneity. Therefore, a difference in diagnostic accuracy was present between low and high scoring studies according to regression analysis. This indicates that meta-analyses should include as many high-quality articles as possible to improve their accuracy.

There are several limitations to our meta-analysis that should be borne in mind when interpreting the results. First, the studies included are not an exhaustive list because the search range was limited to published studies. Unpublished research, such as conference papers, cannot be obtained so it is possible that some relevant literature has been missed. Additionally, only studies published in English or Chinese were included. Second, for articles that contained different cut-off values within the same study, we selected cut-off values according to the manufacturers' recommendations. However, these may not be the most appropriate values for specific areas.

In conclusion, testing for anti-*H. pylori* antibodies in urine appears to have an important function and represents a good marker for the diagnosis of *H. pylori* infection. Sources of heterogeneity were found to come from the quality of the studies included, and especially from the study population. The urine IgG assay also showed a higher level of diagnostic accuracy in healthy individuals compared with patients. Further large-scale, well-designed studies examining different study populations are required to confirm the results of this meta-analysis.

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Author contributions

GYH and YY wrote the main manuscript text and LQP analyzed the data. All authors reviewed the manuscript.

Competing financial interests

The authors declare that they have no competing financial interests.

Data sharing statement

No additional unpublished data are available.

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Figure legends

Figure 1. Flow diagram of the literature search.

Figure 2. Forest plots of DOR for *H. pylori* diagnosis by urine IgG antibody. The pooled diagnostic odds ratio was 73 (95%CI: 46.45–114.74).

Figure 3. Forest plots of sensitivity, specificity, PLR, and NLR for H. pylori diagnosis by urine IgG (a) The summary sensitivity was 0.83 (95% CI: 0.82–0.85; $I^2 = 94.4\%$). (b) The summary specificity was 0.89 (95% CI: 0.87–0.90; $I^2 = 86.1\%$). (c) The summary PLR was 8.5 (95% CI: 6.27–12.2; $I^2 = 81.0\%$). (d) The summary NLR of all articles was 0.13 (95% CI: 0.09–0.20; $I^2 = 96.3\%$).

Table 1. Characteristics of the studies included in the meta-analysis

Author	Ethnicity	Year	Region	No. of cases	Age	Diseases	Reference standard	Blind design	Assay method	TP(a)	FP(b)	FN(c)	TN(d)
Mohammad M	American	1993	America	306	MIX	Patient	C,HE,R	N.A.	ELISA	237	6	10	53
Kiyonori Katsuragi	Japanese	1998	Asia	119	N.A.	MIX	U	N.A.	ELISA	69	0	1	49
Hiroto Miwa	Japanese	1999	Asia	132	Adult	Patient	U	Yes	ELISA	63	5	10	54
Mototsugu Kato	Japanese	2000	Asia	189	N.A.	Patient	C,H,R	N.A.	ELISA	127	12	5	45
Soichiro Yamamoto	Japanese	2000	Asia	117	N.A.	mix	H,S	N.A.	IM	81	2	7	27
D. Y. Graham	American	2001	America	104	Adult	healthy	U	Yes	IM	41	2	2	59
Toru Fujisawa	Japanese	2001	Asia	21	Adult	healthy	C,H,R	N.A.	IM	18	1	0	2
Hiroto Miwa	Japanese	2001	Asia	155	Adult	Patient	U	N.A.	IM	93	7	4	51
Kyoichi Adachi	Japanese	2002	Asia	100	MIX	healthy	U	Yes	ELISA	32	2	3	37
									IM	30	1	5	38
W. M. Wong	Chinese	2002	Asia	123	Adult	Patient	R,H	Yes	IM	58	3	2	60
Youke Lu	Chinese	2002	Asia	102	MIX	Patient	C,R,H	N.A.	ELISA	60	4	2	27
A. Leodolter, D. Vaira	European	2003	Europe	449	N.A.	Patient	C,H,R	N.A.	IM	178	34	38	170
									ELISA	193	66	23	140
T Shimizu	Japanese	2003	Asia	68	Children	Patient	U, SA	N.A.	ELISA	12	13	1	42
Antone R. Opekun	American	2004	America	188	Adult	Patient	U,S	Yes	IM	72	0	8	87
Fu-Chen Kuo	Chinese	2005	Asia	317	MIX	Patient	C,R,H,U	N.A.	ELISA	211	8	19	79
Francis Megraud	European	2005	Europe	316	Children	Patient	C,H,R	Yes	ELISA	86	4	50	176
									IM	36	2	83	151
Yanfang Gong	Chinese	2005	Asia	215	MIX	Patient	U	Yes	ELISA	80	19	16	100
Chien-Yu Lu	Chinese	2006	Asia	120	NA	Patient	C,HE,R,U	Yes	IM	54	6	8	52
Khitam Muhsen	Israeli Arab	2006	Asia	159	Children	healthy	SA	N.A.	ELISA	27	3	52	77
Lam Tung Nguyen	Vietnamese	2010	Asia	148	MIX	Patient	C,IM,S	Yes	IM	66	6	17	59
Demıray Gürbüz E	Turks	2012	Asia	124	Adult	Patient	C,H,R	Yes	IM	61	8	21	34
									ELISA	61	8	21	34
Masumi Okuda	Japanese	2013	Asia	101	Children	healthy	U, SA	Yes	ELISA	34	2	3	62
									IM	29	0	7	64
Duc T Quach	Vietnamese	2014	Asia	200	Adult	Patient	R,H	N.A.	IM	94	9	17	80

C: culture, HE: hematoxylin and eosin, H: histology, R: rapid urease test, U: urea breath test, SA: stool, IM: immunochromatographic technique, S: serology.

Table 2. Summary of QUADAS-2 assessments of included studies

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quanlity
Mohammad M	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Kiyonri Katsuragi	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Hiroto Miwa	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Mototsugu Kato	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Soichiro Yamamoto	U	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	8
D. Y. Graham	N	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	10
Toru Fujisawa	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Hiroto Miwa	Y	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	10
Kyoichi Adachi	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
W. M. WONG	U	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	10
Youke Lu	Y	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	10
A. LEODOLTER, D. VAIRA	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
T Shimizu	N	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	9
Antone R. Opekun	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	13
Fu-Chen Kuo	N	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	9
Francis Megraud	U	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Chien-Yu Lu	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Yanfang Gong	U	Y	N	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	9
Khitam Muhsen	N	Y	N	Y	U	Y	N	Y	U	N	U	Y	Y	Y	7
Lam Tung Nguyen	N	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	8
Demıray Gürbüz E	N	Y	Y	Y	U	Y	N	Y	Y	N	U	Y	Y	Y	8
Masumi Okuda	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	9
Duc T Quach	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8

Y: Yes, N: No, U: Unclear.

1. Was a consecutive or random sample of patients enrolled?
2. Was a case–control design avoided?
3. Did the study avoid inappropriate exclusions?
4. Are there concerns that the included patients and setting do not match the review question?
5. Were the index test results interpreted without knowledge of the results of the reference standard?
6. If a threshold was used, was it prespecified?
7. Are there concerns that the index test, its conduct, or its interpretation differ from the review question?
8. Is the reference standard likely to correctly classify the target condition?
9. Were the reference standard results interpreted without knowledge of the results of the index test?
10. Are there concerns that the target condition as defined by the reference standard does not match the question?
11. Was there an appropriate interval between the index test and reference standard?
12. Did all patients receive the same reference standard?
13. Were all patients included in the analysis?
14. Could the patient flow have introduced bias?

Table 3. Group/subgroup analysis of pooled estimates with 95 % confidence interval for sensitivity, specificity, and positive and negative likelihood ratios

Group/Subgroup	Spearman P	Cochrane Q test DOR (95%CI)	Cochrane Q test P	Pooled Sensitivity (95%CI)	Pooled Specificity (95%CI)	Pooled Positive LR (95%CI)	Pooled Negative NR (95%CI)	AUC	*P* (AUC)
Overall	0.413	73(46.45-114.74)	0.0000	0.83(0.82-0.85)	0.89(0.88-0.90)	8.81(6.37-12.2)	0.13(0.09-0.2)	0.96	
Age									
Children	0.397	61.62(22.16-171.32)	0.0335	0.53(0.48-0.58)	0.96(0.94-0.97)	17.93(4.83-62.59)	0.35(0.22-0.58)	0.96	>0.05
Adult	0.732	85.12(29.81-243.06)	0.0000	0.87(0.84-0.89)	0.91(0.88-0.94)	8.13(4.61-14.33)	0.13(0.07-0.22)	0.96	
Region									
Asian	0.724	73.75(43.38-125.38)	0.0000	0.86 (0.84-0.88)	0.9(0.88-0.92)	7.74(5.77-10.39)	0.12(0.07-0.20)	0.96	>0.05
Europe and America	0.645	73.75(29.26-125.38)	0.0000	0.80 (0.77-0.82)	0.88(0.86-0.90)	12.05(5.22-27.8)	0.16(0.07-0.38)	0.96	
Study population									
Patient	0.616	54.29(34.07-86.51)	0.0000	0.84(0.82-0.85)	0.87(0.85-0.89)	7.17(5.18-9.93)	0.14 (0.09-0.23)	0.94	<0.05
Healthy	0.294	156.11(41.44-588.04)	0.0073	0.75 (0.69-0.80)	0.97(0.94-0.98)	16.25(6.94-38.06)	0.13 (0.03-0.53)	0.98	
Assay method									
IM	0.5940	82.94(41.62-165.29)	0.0000	0.81(0.78-0.83)	0.92(0.90-0.94)	9.81 (6.28-15.34)	0.14 (0.07-0.28)	0.96	>0.05
ELISA	0.7820	67.46(35.58-127.9)	0.0000	0.86(0.84-0.87)	0.87(0.84-0.88)	7.92(5.02-12.5)	0.12 (0.07-0.23)	0.95	

Table 4. Meta-regression of potential heterogeneity within the included studies

Variables	Coeff.	Std. Err.	P-value	RDOR	[95%CI]
Cte.	-0.98	3.4737	0.781	----	----
S	0.309	0.1614	0.0706	----	----
Region	-0.459	0.8022	0.574	0.63	(0.12;3.39)
Sample size	-0.001	0.0041	0.8856	1	(0.99;1.01)
Age	-0.093	0.2489	0.7117	0.91	(0.54;1.53)
Study population	1.367	0.5326	0.0189	3.92	(1.29;11.96)
blinded design	0.144	0.6537	0.8282	1.15	(0.29;4.54)
Assay method	0.008	0.4155	0.9841	1.01	(0.42;2.41)
quanlity	0.518	0.22	0.0295	1.68	(1.06;2.66)

Cte: Constant coefficient, S: Statistic, Coeff: Constant coefficient, Std. Err: Standard error, RDOR: Relative diagnostic odd ratio.

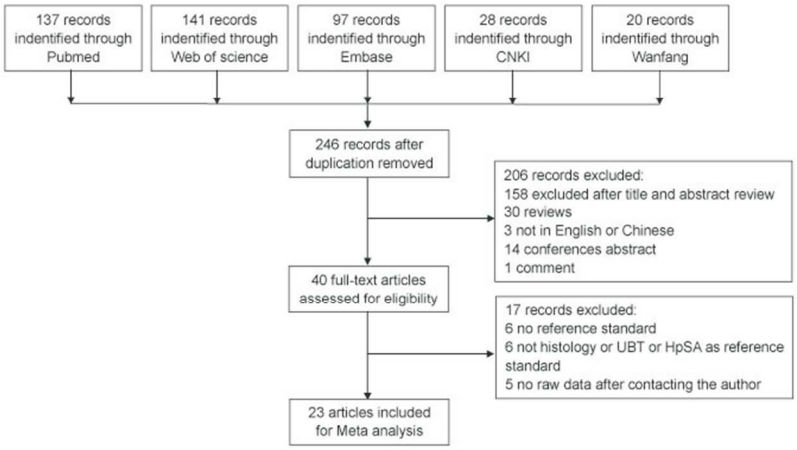

Figure 1. Flow diagram of the literature search.

71x50mm (300 x 300 DPI)

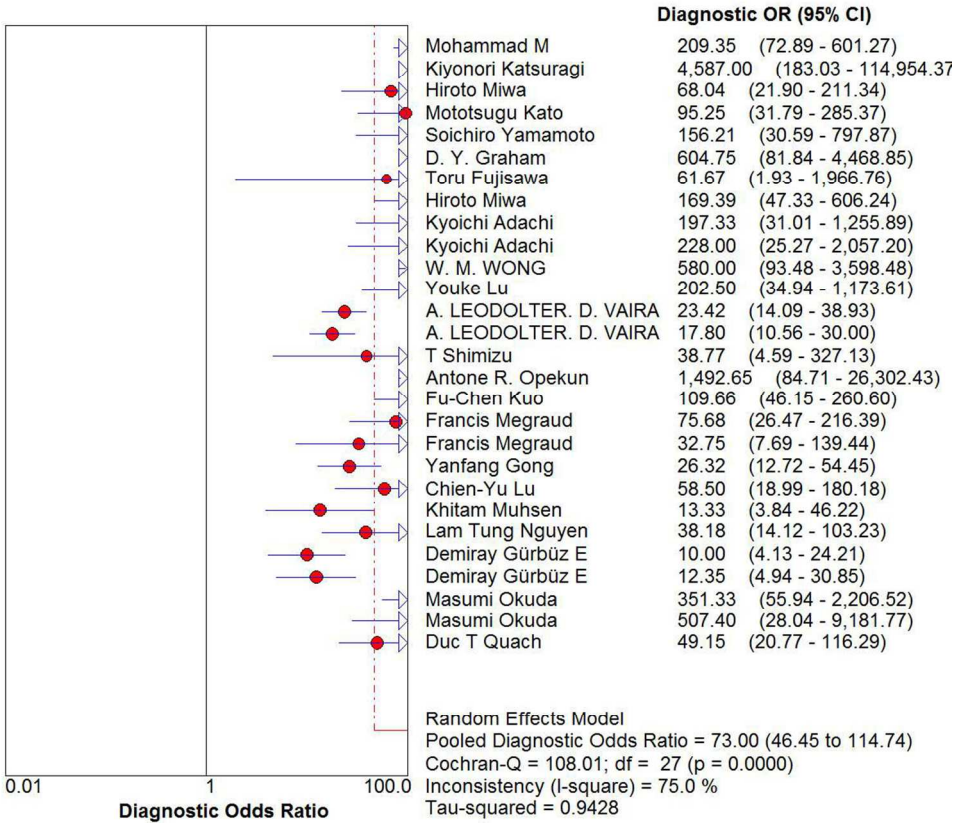

Figure 2. Forest plots of DOR for H. pylori diagnosis by urine IgG antibody. The pooled diagnostic odds ratio was 73 (95%CI: 46.45–114.74).

103x88mm (300 x 300 DPI)

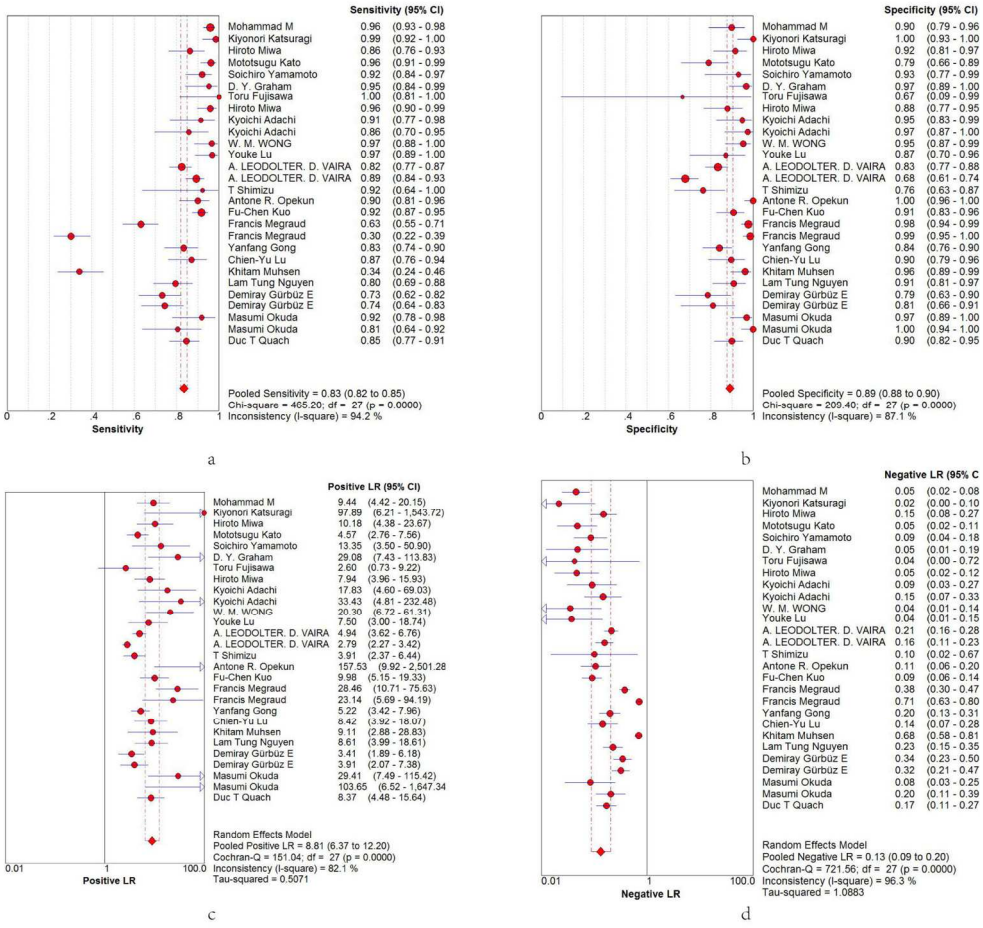

Figure 3. Forest plots of sensitivity, specificity, PLR, and NLR for H. pylori diagnosis by urine IgG antibody. (a) The summary sensitivity was 0.83 (95% CI: 0.82–0.85; I2 = 94.4%). (b) The summary specificity was 0.89 (95% CI: 0.87–0.90; I2 = 86.1%). (c) The summary PLR was 8.5 (95% CI: 6.27–12.2; I2 = 81.0%). (d) The summary NLR of all articles was 0.13 (95% CI: 0.09–0.20; I2 = 96.3%).

150x140mm (300 x 300 DPI)

Accuracy of testing for anti-*Helicobacter pylori* IgG [1]in urine for *H. pylori* infection diagnosis: systematic review and meta-analysis

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Supplemental Figure legends

Fig 1. Detail of search strategy as performed in Pubmed.

Fig 2. Summary of QUADAS-2 assessments of included studies.

Fig 3. Summary receiver operating characteristic (SROC) curves and confidence interval for the diagnosis of *H.pylori* infection using IgG antibody in urine.

Fig 4. Deek's funnel plot to assess the likelihood of publication bias. The statistically non-significant P-value of 0.124 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias

#1 H.pylori
Search details:
"helicobacter pylori"[MeSH Terms] OR ("helicobacter"[All Fields] AND "pylori"[All Fields]) OR "helicobacter pylori"[All Fields] OR "h pylori"[All Fields]
#2 Helicobacter pylori
#3 #1 OR #2
#4 urine IgG antibody
Search details:
("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) AND IgG[All Fields] AND ("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields])
#5 urine antibody
#6 #4 OR #5
#7 #3 AND #6

Fig 1. Detail of search strategy as performed in Pubmed.

144x76mm (300 x 300 DPI)

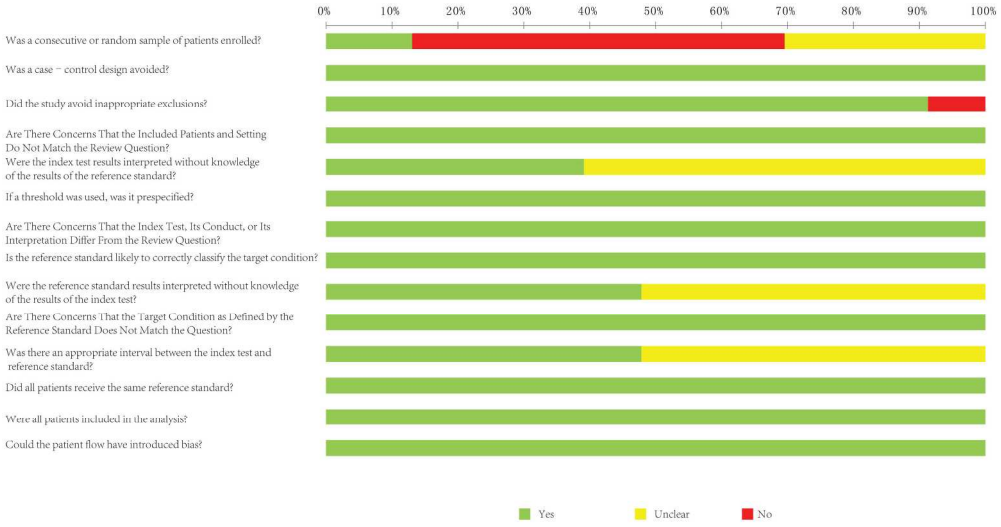

Fig 2. Summary of QUADAS-2 assessments of included studies.

216x112mm (300 x 300 DPI)

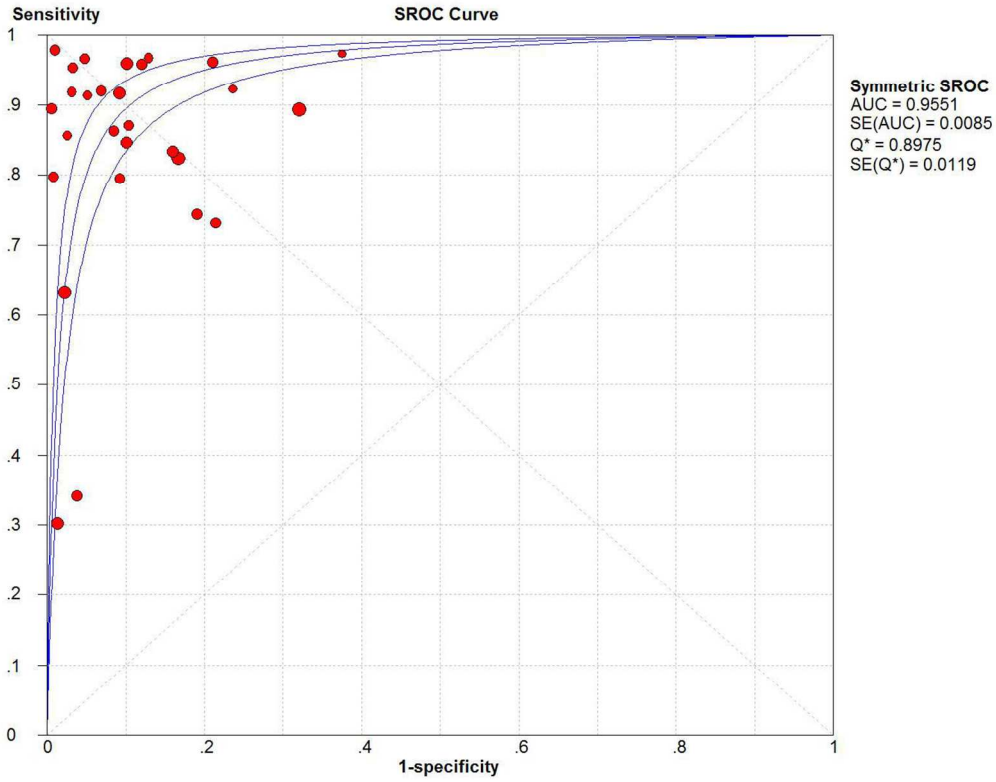

Fig 3. Summary receiver operating characteristic (SROC) curves and confidence interval for the diagnosis of H.pylori infection using IgG antibody in urine.

113x90mm (300 x 300 DPI)

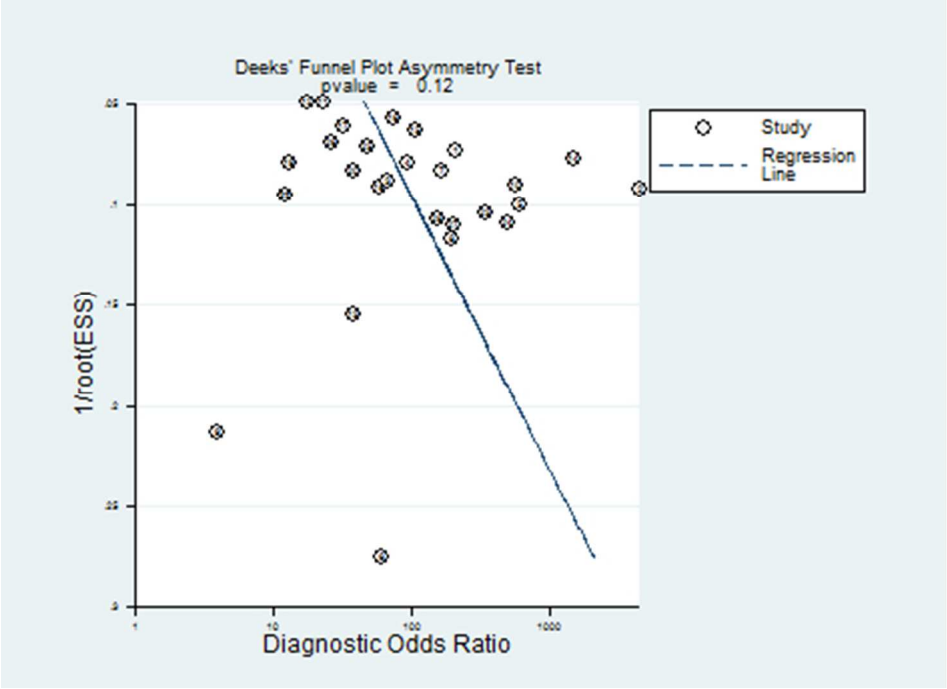

Fig 4. Deek's funnel plot to assess the likelihood of publication bias. The statistically non- significant P-value of 0.124 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias

39x29mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3,4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4,5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4,5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4,5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Accuracy of testing for anti-Helicobacter pylori IgG in urine for H. pylori infection diagnosis: a systematic review and meta-analysis

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Infectious diseases, Gastroenterology and hepatology
Keywords:	H.pylori, urine IgG antibody, diagnosis, Meta analysis

Accuracy of testing for anti-*Helicobacter pylori* IgG in urine for *H. pylori* infection diagnosis: a systematic review and meta-analysis

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Abstract

Objectives： This meta-analysis aims to systematically measure the potential diagnostic value of anti-*H. pylori* IgG in urine for infection diagnosis, using all eligible studies published in English and Chinese language.

Design： The random effect model was used to analyze the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative LR (NLR), diagnostic odds ratio (DOR), together with the summary receiver operator characteristic (SROC) curve.

Setting： Literature searches of databases including PubMed, EMBASE, MEDLINE, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Wanfang Databases were performed to retrieve studies evaluating the diagnostic value of urine IgG antiboty for *H.pylori* infection.

Primary outcome measure： Twenty-three studies with 4,963 subjects were included in the current meta-analysis.

Results： The pooled sensitivity, specificity, PLR, NLR, DOR, and AUC were 0.83 (95% CI, 0.82-0.85), 0.89 (95% CI, 0.88-0.90), 8.81 (95% CI, 6.37-12.2), 0.13 (95% CI, 0.09-0.2), 73 (95% CI, 46.45-114.74), and 0.9551, respectively. Subgroup analyses showed that diagnostic accuracy of the urine IgG assay was no different in age, region, study population and assay method.

Conclusions： Anti-*H.pylori* antibody in urine might serve as a good marker in diagnosing H.pylori infection. However, further validation based on a larger sample is still required.

Strengths and limitations of this study

1. A comprehensive search of literature databases was performed to identify all eligible studies that reported the diagnostic performance of an anti-*Helicobacter pylori* antibody in urine.
2. The systematic meta-analysis used a standard protocol, strict inclusion criteria, standardized data extraction, and independent reviewers.
3. We first assessed the summary predictive value of anti-*H. pylori* IgG in urine for infection diagnosis, and additional subgroup analyses based on study population, region, age, and assay method were used to explore heterogeneity.
4. Unpublished research such as conference papers and studies published in languages other than English or Chinese were not included in this meta-analysis, so some relevant research may have been missed.
5. We selected the cut-off value according to the manufacturer's recommendations, but this may not have been the most appropriate for specific areas.

Introduction

Helicobacter pylori (*H. pylori*) is a bacterium that chronically infects more than half of the world's population and plays a causative role in the pathogenesis of chronic gastritis, peptic ulcer diseases, gastric cancer, and mucosa-associated lymphoid tissue lymphoma [1-4]. The considerable burden of these *H. pylori*-related outcomes means that there is an acute demand for accurate diagnosis of this infection. Several detection methods have already been developed, such as culture, histological staining, the urea breath test (UBT), and the *H. pylori* stool antigen test (HpSA), but a simple, non-invasive, inexpensive, and accurate diagnostic test remains the goal.

A number of methods have been developed for non-invasive *H. pylori* infection diagnosis using body fluids. Tests for the detection of serum anti-*H. pylori* antibodies are widely used because they are relatively straightforward, convenient, and economical. Several studies have also reported the presence of specific anti-*H. pylori* antibodies in body fluids other than serum [5,6]. For example, anti-*H. pylori* immunoglobulin (Ig)G is detectable in urine and has been used for the diagnosis of *H. pylori* infection. If urine samples could be used for the sensitive screening of *H. pylori* infection, this would be more convenient both for clinical practice and mass screening.

In 1993, Alemohammd *et al*. reported that the enzyme-linked immunosorbent assay (ELISA) was both highly sensitive and specific for the detection of anti-*H. pylori* antibodies in urine. This was confirmed by another study from Japan [7]. These studies laid the groundwork for the development of a urine-based ELISA kit and a rapid immunochromatography (IM) assay for *H. pylori* diagnosis[8]. Evaluation of the IM assay in Japanese asymptomatic adults and patients with gastric disorders showed promising results compared with UBT (sensitivity: 86.3%–99%; specificity: 91.5%–100%) [8,9]. The use of ELISA to detect *H. pylori* in Japanese children also revealed high levels of sensitivity and specificity. When compared with ^{13}C-UBT and/or HpSA, the ELISA sensitivity ranged from 92.3%–94.4%, and specificity from 76.4%–96.9% [10,11]. Different findings were recorded, however, for the same kit when compared with gastrointestinal endoscopic testing for *H. pylori*, in line with European multicentre studies. Sensitivity and specificity in adults were 89.4% and 68%, respectively [12], and the corresponding figures in children were 63.2% and 97.3%, respectively [13]. Subsequently, the accuracy and usefulness of the IM assay have been supported by several trials in different geographic areas, including Japan [14], Turkey [15], Hong Kong and Taiwan [16], the United States [17], and Europe [18].

These variations in the sensitivity and specificity of anti-*H. pylori* IgG urine testing

indicate the need for a comprehensive evaluation of the test performance before wider application. Therefore, this systematic review and meta-analysis was conducted to identify whether anti-*H. pylori* IgG in urine can serve as a valuable test for *H. pylori* diagnosis.

Methods

Literature search strategy

Literatures of electronic databases including PubMed, EMBASE, MEDLINE, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Wanfang Databases were searched by two independent researchers to identify relevant studies that evaluate the diagnostic value of urine IgG antiboty for *H.pylori* infection. The last search date was January 7, 2016. The following search terms (in Title, Abstract or keywords fields) were combined using Boolean rules: '*H.pylori*', '*Helicobacter pylori*', 'urine IgG antibody', 'urine antibody' （Supplemental Figure 1）, with a filter for human studies published in English or Chinese. Two researchers (Yuehua Gong and Qiuping Li) screened all the titles and abstracts; studies including data on *H. pylori* and urine IgG levels were read in full text. The reference lists of the selected papers were hand-searched to identify additional available papers. When multiple publications presented results using the same patient cohort, the most recent or the most complete publication was selected for inclusion. Review articles and references of the accepted articles were searched for additional papers.

Literature selection criteria

We included studies that met the following criteria: (1) Anti-*H.pylori* IgG antibody in urine was detected; (2) Investigation of the diagnostic accuracy of urine IgG of *H.pylori* compared to culture or histopathology or UBT or HpSA (based on only one or at least two reference methods); (3) Sensitivity, specificity, and cut-off values can be found in identified studies or calculated from the provided data; (4) Publication with full text in a peer-reviewed scientific journal. While the exclusion criteria were listed as follows: (1) studies with insufficient data to construct the 2*2 table; (2) Reviews, letters, and conference abstracts; and (3) publications identified as duplicates. If a study fulfilled the eligibility criteria, it was included in the systematic review. Any discrepancies were resolved with discussion.

Data extraction and Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 assessment

The following variables were extracted from the original studies in a predefined data extraction form (see Table 1): author, ethnicity, year of publication, number of cases, age (adults or children), study population (patients or healthy), reference standard, and assay method (ELISA or IM technique). True positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) for urine IgG antibody diagnose were included. Extraction of studies was performed independently by two reviewers (Yuehua Gong and Qiuping Li). Discrepancies were discussed with the third researcher (Yuan Yuan) and agreement was eventually reached. If a study was selected for the systematic review but did not provide data that could be included in the meta-analysis, the authors were contacted via e-mail. If the authors did not reply or did not provide the requested information, then this article would be excluded. QUADAS-2 summary plots were outlined in Table 2 and Supplemental Figure 2 [19].

Statistical analysis

The following parameters representing test accuracy were calculated based on the data (TP, FP, FN, and TN) we extracted from each included studies: the pooled sensitivity, specificity, PLR, NLR, DOR, and corresponding 95% confidence intervals (95% CI). Simultaneously, the SROC was also assessed. The heterogeneity was measured by Q test and the inconsistency index (I^2), and $P < 0.05$ and $I^2 > 50\%$ indicated significant heterogeneity among studies. The random-effect model (DerSimonian-Laird method) was conducted for the meta-analysis to calculate the pooled sensitivity, specificity, and other related indexes of the studies, and meta-regression was performed to detect the source of the heterogeneity; otherwise, the fixed-effect model (MantelHaenszel method) was chosen.

In addition, the Spearman correlation coefficient was used to verify if the heterogeneity in meta-analysis could be explained by a threshold effect, which was defined as a positive correlation ($P < 0.05$). Subgroup analyses were performed for region, age, study population and assay method. Deek's Funnel Plot Asymmetry Test was applied to determine the presence of publication bias using STATA 12.1 software (Stata Corp., College Station, Texas, USA.) [20]. MetaDisc (version 1.4) software [21] was also used to calculate other parameters of diagnostic performance. All P values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Search results

This meta-analysis was organized according to the PRISMA statement (Supplemental file 1). Figure 1 summarizes the search process and numerical selection of the final papers that were included in the systematic review and meta-analysis. A systematic search of biomedical databases resulted in 423 hits, and after excluding duplicates, 246 citations were identified. No unpublished literature relevant to the topic was identified. Forty papers were selected based on their abstracts and titles and were read in full for eligibility. Two eligible studies referred to the same study group; hence, only one of these was included in the systematic review [10,18]. Twenty-four individual studies fulfilled the eligibility criteria and were included in the systematic review [7-9,11,12,14-18],[13,22-31]. Of these, 23 studies had extractable data after contacting the authors and were included in the meta-analysis [7-9],[11-13,15-18,22-24,26,28,30-33]. A flowchart detailing the study selection process is shown in Figure 1.

Study characteristics

Baseline characteristics of the eligible studies are summarized in Table 1. A total of 23 studies with 4963 participants were included in the meta-analysis. Of these, three were conducted in the United States [7,17,23], two in Europe [12,13], and the remaining 18 in Asia. All eligible studies were published between 2000 and 2014. Sample sizes ranged from 21–449. Urinary *H. pylori* IgG was detected using ELISA in nine studies, using IM in nine studies, and using both assays in five studies. Key data were successfully extracted from all studies, including TPs, FPs, FNs, and TNs. The number of TPs ranged from 12–237, FNs from 0–83, FPs from 0–66, and TNs from 2–176.

Diagnostic accuracy and threshold analysis

Spearman's correlation coefficient was first used to determine the existence of the threshold effect because it is an important source of heterogeneity. The Spearman's correlation coefficient for sensitivity and 1-specificity in the meta-analysis was 0.161, with a *P*-value of 0.413, suggesting no heterogeneity from the threshold effect. Heterogeneity was measured using the Q test and the inconsistency index (I^2) to choose the appropriate calculation model. Significant heterogeneity was detected in the pooled diagnostic odds ratio (DOR) (DOR = 73, I^2 = 75%, P = 0.0000) (Figure 2). Therefore, the random effects model was used to calculate sensitivity, specificity, the positive likelihood ratio (PLR), and DOR.

Based on TP, TN, FP, and FN data extracted from the included studies, we evaluated the diagnostic accuracy of urinary IgG in *H. pylori* diagnosis from the following quantitative

parameters: pooled sensitivity and specificity were 0.83 (95% CI: 0.82–0.85; Figure 3a) and 0.89 (95% CI: 0.88–0.90; Figure 3b), respectively; pooled PLR and negative likelihood ratio (NLR) were 8.81 (95% CI: 6.37–12.2; Figure 3c) and 0.13 (95% CI: 0.09–0.2; Figure 3d), respectively. The summary receiver operating characteristic (sROC) curve for urinary IgG was positioned near the desirable upper left corner, and the area under the curve (AUC) was 0.9551, indicating that the level of overall accuracy was high (Supplemental Figure 3).

Subgroup analysis

Subgroup analysis was conducted based on age, region, study population, and assay method. Pooled results are shown in Table 3. A random effects model was used because significant heterogeneity was observed (all $I^2 > 50\%$). The differences between subgroups were conclusions based on whether there was the overlap of the 95% CI for each AUCs.

Age analysis

Seven studies containing 1047 adults (>17 years of age) were evaluated. Pooled sensitivity, specificity, PLR, and NLR were 0.87 (95% CI: 0.84–0.89), 0.91 (95% CI: 0.88–0.94), 8.13 (95% CI: 4.61–14.33), and 0.13 (95% CI: 0.07–0.22), respectively, with a DOR of 85.12 and an AUC value of 0.9593(95% CI: 0.92-1.0). The diagnostic performance of urinary IgG was evaluated for young people in the four other studies containing 644 children (≤17 years of age). Pooled sensitivity, specificity, PLR, and NLR were 0.53 (95% CI: 0.48–0.58), 0.96 (95% CI: 0.94–0.97), 17.93 (95% CI: 4.83–62.59), and 0.35 (95% CI: 0.22–0.58), respectively, with a DOR of 61.62 and an AUC value of 0.9632(95% CI: 0.91-1.01). There was no significant difference in the AUC values between adults and children.

Regional analysis

Of the 23 included studies, five were from Europe or the United States and the remaining 18 were from Asia. For studies from Europe and the United States, the analysis showed a pooled sensitivity of 0.80 (95% CI: 0.77–0.82) and a pooled specificity of 0.88 (95% CI: 0.86–0.90). Combined PLR was 12.05 (95% CI: 5.22–27.8), NLR was 0.16 (95% CI: 0.07–0.38), and AUC and DOR were 0.9557(95% CI: 0.91-1.0) and 73.75, respectively. For studies from Asia, the pooled sensitivity was 0.86 (95% CI: 0.84–0.88) and the pooled specificity was 0.9 (95% CI: 0.88–0.92). Combined PLR was 7.74 (95% CI: 5.77–10.39), NLR was 0.12 (95% CI: 0.07–0.2), DOR was 73.75, and AUC was 0.9553(95% CI: 0.94-0.97). There was no significant difference in the AUC values between Europe or the United States and Asia.

Study population analysis

Study population analysis, of both patients and healthy controls, was performed in the systematic review. A total of 16 patient studies and five studies of healthy controls or individuals with no upper abdominal symptoms were evaluated. In the patient population, pooled sensitivity, specificity, PLR, and NLR were 0.84 (95% CI: 0.82–0.85), 0.87 (95% CI: 0.85–0.89), 7.17 (95% CI: 5.18–9.93), and 0.14 (95% CI: 0.09–0.23), respectively, with a DOR of 54.29 and AUC value of 0.9436(95% CI: 0.92-0.96). In the healthy population, pooled sensitivity, specificity, PLR, and NLR were 0.75 (95% CI: 0.69–0.80), 0.97 (95% CI: 0.94–0.98), 16.25 (95% CI: 6.94–38.06), and 0.13 (95% CI: 0.03–0.53), respectively, with a DOR of 156.11 and AUC value of 0.98(95% CI: 0.96-1.0). Except for pooled sensitivity, the diagnostic performance of the urine IgG assay was better for the healthy population than the patient population. However, there was no significant difference in AUC values between patients and controls.

Assay method analysis

Of all studies included, urinary *H. pylori* IgG was detected using ELISA in nine, IM in nine, and both assays in five. For studies that used ELISA, the pooled sensitivity was 0.86 (95% CI: 0.84–0.87) and pooled specificity was 0.87 (95% CI: 0.84–0.88). Combined PLR was 7.92 (95% CI: 5.02–12.5), NLR was 0.12 (95% CI: 0.07–0.23), and AUC and DOR were 0.9521 and 67.46, respectively. For studies that used IM, pooled sensitivity, specificity, PLR, and NLR were 0.81 (95% CI: 0.78–0.83), 0.92 (95% CI: 0.89–0.93), 9.81 (95% CI: 6.28–15.34), and 0.14 (95% CI: 0.07–0.28), respectively, with a DOR of 82.94 and AUC value of 0.9584. No significant difference was detected between ELISA and IM for the diagnostic accuracy of urine antibody detection.

Meta-regression analysis

Heterogeneity was found in summary estimates for sensitivity, specificity, PLR, NLR, and DOR. Therefore, meta-regression was conducted to examine the source of heterogeneity based on region, sample size, age, study population, blind design, quality of study, and assay method. The results indicated that study population and quality of study were the important factors contributing to heterogeneity ($P = 0.0189$ and $P = 0.0295$, respectively) (Table 4).

Publication bias

Because publication bias is recognized as an important factor that influences the results of meta-analyses [34], the Deeks' funnel plot asymmetry test was performed to examine publication bias (Supplemental Figure 4). The test returned a *P*-value of 0.124, suggesting no significant publication bias was found in the pooled analysis of the studies.

Discussion

Non-invasive tests for the assessment of *H. pylori* status have become part of patient management strategies [35-37]. Preliminary studies have explored the diagnostic accuracy of testing for anti-*H. pylori* antibodies in urine, but the results are inconclusive. In the present study, we performed comprehensive database searches for all eligible studies reporting the diagnostic accuracy of testing for anti-*H. pylori* antibodies in urine. Our meta-analysis was strengthened by the use of a standard protocol, strict inclusion criteria, standardized data extraction, and independent reviewers. To the best of our knowledge, this is the first study assessing the summary predictive value of anti-*H. pylori* IgG in urine for infection diagnosis.

Anti-*H. pylori* IgG in urine is detectable and has been used for the diagnosis of *H. pylori* infection, but a comprehensive evaluation of the test performance is needed before its wider application. After pooling data, we obtained a pooled sensitivity of 0.83 and a pooled specificity of 0.89, which represent good markers for *H. pylori* diagnosis. The sROC curve, which assesses overall test performance by showing the trade-off between sensitivity and specificity [38,39], had an AUC of 0.9551, suggesting a good level of accuracy. Another indicator of diagnostic accuracy is DOR, which combines sensitivity and specificity data into a single number ranging from 0 to infinity, with higher values indicating better discriminatory test performances [40]. The mean DOR in the meta-analysis was 73, suggesting that testing for anti-*H. pylori* antibodies in urine should be helpful in the diagnosis of *H. pylori* infection. We further examined the diagnostic accuracy of an anti-*H. pylori* antibody in urine by calculating the PLR and NLR, which can be easier to relate to clinical practice than sROC and DOR. The pooled PLR was 8.81 and the pooled NLR was 0.13, indicating that the presence of anti-*H. pylori* antibodies in urine has an important function in diagnosing *H. pylori* infection. Substantial heterogeneity was found with meta-analysis, so the random effects model was used to synthesize the above data. Our results show that anti-*H. pylori* IgG represents a good marker for the diagnosis of *H. pylori* infection.

Heterogeneity is an important factor that can affect the results of meta-analysis. Therefore, we used the Spearman's correlation coefficient to clarify whether the threshold effect

contributed to the source of heterogeneity. The Spearman's correlation coefficient was 0.193, with a *P*-value of 0.334, suggesting that heterogeneity among the included studies could not have been induced by the threshold effect. We further used subgroup analysis based on study population, region, age, and assay method to explore heterogeneity. No significant difference in age, region, or assay method was detected, but subgroup analysis for the study population revealed a little difference in AUC values between patients and controls, suggesting a relatively high level of diagnostic accuracy in the healthy population, although there was the overlap of the 95% CI for each AUCs of study population subgroup. In meta-analysis, the patient population included dyspeptic, chronic gastritis, and peptic ulcer patients amongst others. It is possible that the disease condition in the stomach may cause a change in *H. pylori* colonization [41]. On the other hand, *H. pylori* IgG is not synchronized with the *H. pylori* infection process, so the delayed generation or disappearance of *H. pylori* colonization for several months may affect the level of anti-*H. pylori* IgG in the urine [42]. Indeed, Graham *et al*. [23] reported that urine tests may remain positive for an extended time after successful treatment of the infection. This may be an important factor affecting the accuracy of the antibody test in the diseased population. The meta-regression analysis also demonstrated that study population was an important factor contributing to heterogeneity, which is consistent with subgroup analysis. These findings indicate that *H. pylori* infection diagnosis by anti-*H. pylori* IgG in the urine requires extra caution in diseased populations.

The QUADAS tool was developed and evaluated by Whiting et al. [43] and is recommended by the Cochrane diagnostic accuracy systematic reviews [44] to provide a methodological assessment of the quality of diagnostic accuracy studies. Experience, reports from users, and feedback from the Cochrane Collaboration suggested the potential for improvements; therefore, QUADAS-2 was developed [19] and has been shown to be a considerable improvement over the original tool. The responses to QUADAS-2 signalling questions are assessed in terms of risk of bias or concerns regarding applicability. In the present meta-analysis, 23 of the included studies were qualified using QUADAS-2 assessment, which included a score of 7 for one study, a score of 8 for nine studies, a score of 9 for four studies, and a score of 10 or more for nine studies. Meta-regression analysis showed that the quality of included studies was another factor for heterogeneity. Therefore, a difference in diagnostic accuracy was present between low and high scoring studies according to regression analysis. This indicates that meta-analyses should include as many high-quality articles as possible to improve their accuracy.

There are several limitations to our meta-analysis that should be borne in mind when

interpreting the results. First, the studies included are not an exhaustive list because the search range was limited to published studies. Unpublished research, such as conference papers, cannot be obtained so it is possible that some relevant literature has been missed. Additionally, only studies published in English or Chinese were included. Second, for articles that contained different cut-off values within the same study, we selected cut-off values according to the manufacturers' recommendations. However, these may not be the most appropriate values for specific areas.

In conclusion, testing for anti-*H. pylori* antibodies in urine appears to have an important function and represents a good marker for the diagnosis of *H. pylori* infection. Sources of heterogeneity were found to come from the quality of the studies included, and from the study population. Further large-scale, well-designed studies examining different study populations are required to confirm the results of this meta-analysis.

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Author contributions

GYH and YY wrote the main manuscript text and LQP analyzed the data. All authors reviewed the manuscript.

Competing financial interests

The authors declare that they have no competing financial interests.

Data sharing statement

No additional unpublished data are available.

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Figure legends

Figure 1. Flow diagram of the literature search.

Figure 2. Forest plots of DOR for *H. pylori* diagnosis by urine IgG antibody. The pooled diagnostic odds ratio was 73 (95%CI: 46.45–114.74).

Figure 3. Forest plots of sensitivity, specificity, PLR, and NLR for H. pylori diagnosis by urine IgG (a) The summary sensitivity was 0.83 (95% CI: 0.82–0.85; $I^2 = 94.4\%$). (b) The summary specificity was 0.89 (95% CI: 0.87–0.90; $I^2 = 86.1\%$). (c) The summary PLR was 8.5 (95% CI: 6.27–12.2; $I^2 = 81.0\%$). (d) The summary NLR of all articles was 0.13 (95% CI: 0.09–0.20; $I^2 = 96.3\%$).

Table 1. Characteristics of the studies included in the meta-analysis

Author	Ethnicity	Year	Region	No. of cases	Age	Diseases	Reference standard	Blind design	Assay method	TP(a)	FP(b)	FN(c)	TN(d)
Mohammad M	American	1993	America	306	MIX	Patient	C,HE,R	N.A.	ELISA	237	6	10	53
Kiyonori Katsuragi	Japanese	1998	Asia	119	N.A.	MIX	U	N.A.	ELISA	69	0	1	49
Hiroto Miwa	Japanese	1999	Asia	132	Adult	Patient	U	Yes	ELISA	63	5	10	54
Mototsugu Kato	Japanese	2000	Asia	189	N.A.	Patient	C,H,R	N.A.	ELISA	127	12	5	45
Soichiro Yamamoto	Japanese	2000	Asia	117	N.A.	mix	H,S	N.A.	IM	81	2	7	27
D. Y. Graham	American	2001	America	104	Adult	healthy	U	Yes	IM	41	2	2	59
Toru Fujisawa	Japanese	2001	Asia	21	Adult	healthy	C,H,R	N.A.	IM	18	1	0	2
Hiroto Miwa	Japanese	2001	Asia	155	Adult	Patient	U	N.A.	IM	93	7	4	51
Kyoichi Adachi	Japanese	2002	Asia	100	MIX	healthy	U	Yes	ELISA	32	2	3	37
									IM	30	1	5	38
W. M. Wong	Chinese	2002	Asia	123	Adult	Patient	R,H	Yes	IM	58	3	2	60
Youke Lu	Chinese	2002	Asia	102	MIX	Patient	C,R,H	N.A.	ELISA	60	4	2	27
A. Leodolter, D. Vaira	European	2003	Europe	449	N.A.	Patient	C,H,R	N.A.	IM	178	34	38	170
									ELISA	193	66	23	140
T Shimizu	Japanese	2003	Asia	68	Children	Patient	U, SA	N.A.	ELISA	12	13	1	42
Antone R. Opekun	American	2004	America	188	Adult	Patient	U,S	Yes	IM	72	0	8	87
Fu-Chen Kuo	Chinese	2005	Asia	317	MIX	Patient	C,R,H,U	N.A.	ELISA	211	8	19	79
Francis Megraud	European	2005	Europe	316	Children	Patient	C,H,R	Yes	ELISA	86	4	50	176
									IM	36	2	83	151
Yanfang Gong	Chinese	2005	Asia	215	MIX	Patient	U	Yes	ELISA	80	19	16	100
Chien-Yu Lu	Chinese	2006	Asia	120	NA	Patient	C,HE,R,U	Yes	IM	54	6	8	52
Khitam Muhsen	Israeli Arab	2006	Asia	159	Children	healthy	SA	N.A.	ELISA	27	3	52	77
Lam Tung Nguyen	Vietnamese	2010	Asia	148	MIX	Patient	C,IM,S	Yes	IM	66	6	17	59
Demıray Gürbüz E	Turks	2012	Asia	124	Adult	Patient	C,H,R	Yes	IM	61	8	21	34
									ELISA	61	8	21	34
Masumi Okuda	Japanese	2013	Asia	101	Children	healthy	U, SA	Yes	ELISA	34	2	3	62
									IM	29	0	7	64
Duc T Quach	Vietnamese	2014	Asia	200	Adult	Patient	R,H	N.A.	IM	94	9	17	80

C: culture, HE: hematoxylin and eosin, H: histology, R: rapid urease test, U: urea breath test, SA: stool, IM: immunochromatographic technique, S: serology.

Table 2. Summary of QUADAS-2 assessments of included studies

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quanlity
Mohammad M	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Kiyonri Katsuragi	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Hiroto Miwa	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Mototsugu Kato	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Soichiro Yamamoto	U	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	8
D. Y. Graham	N	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	10
Toru Fujisawa	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
Hiroto Miwa	Y	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	10
Kyoichi Adachi	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
W. M. WONG	U	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	10
Youke Lu	Y	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	10
A. LEODOLTER, D. VAIRA	N	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8
T Shimizu	N	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	9
Antone R. Opekun	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	13
Fu-Chen Kuo	N	Y	Y	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	9
Francis Megraud	U	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Chien-Yu Lu	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	11
Yanfang Gong	U	Y	N	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	9
Khitam Muhsen	N	Y	N	Y	U	Y	N	Y	U	N	U	Y	Y	Y	7
Lam Tung Nguyen	N	Y	Y	Y	Y	Y	N	Y	Y	N	U	Y	Y	Y	8
Demıray Gürbüz E	N	Y	Y	Y	U	Y	N	Y	Y	N	U	Y	Y	Y	8
Masumi Okuda	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	9
Duc T Quach	U	Y	Y	Y	U	Y	N	Y	U	N	U	Y	Y	Y	8

Y: Yes, N: No, U: Unclear.

1. Was a consecutive or random sample of patients enrolled?
2. Was a case–control design avoided?
3. Did the study avoid inappropriate exclusions?
4. Are there concerns that the included patients and setting do not match the review question?
5. Were the index test results interpreted without knowledge of the results of the reference standard?
6. If a threshold was used, was it prespecified?
7. Are there concerns that the index test, its conduct, or its interpretation differ from the review question?
8. Is the reference standard likely to correctly classify the target condition?
9. Were the reference standard results interpreted without knowledge of the results of the index test?
10. Are there concerns that the target condition as defined by the reference standard does not match the question?
11. Was there an appropriate interval between the index test and reference standard?
12. Did all patients receive the same reference standard?
13. Were all patients included in the analysis?
14. Could the patient flow have introduced bias?

Table 3. Group/subgroup analysis of pooled estimates with 95 % confidence interval for sensitivity, specificity, and positive and negative likelihood ratios

Group/Subgroup	Spearman P	Cochrane Q test DOR (95%CI)	Cochrane Q test P	Pooled Sensitivity (95%CI)	Pooled Specificity (95%CI)	Pooled Positive LR (95%CI)	Pooled Negative NR (95%CI)	AUC (95%CI)
Overall	0.413	73(46.45-114.74)	0.0000	0.83(0.82-0.85)	0.89(0.88-0.90)	8.81(6.37-12.2)	0.13(0.09-0.2)	0.96 (0.94-0.97)
Age								
Children	0.397	61.62(22.16-171.32)	0.0335	0.53(0.48-0.58)	0.96(0.94-0.97)	17.93(4.83-62.59)	0.35(0.22-0.58)	0.96 (0.91-1.01)
Adult	0.732	85.12(29.81-243.06)	0.0000	0.87(0.84-0.89)	0.91(0.88-0.94)	8.13(4.61-14.33)	0.13(0.07-0.22)	0.96 (0.92-1.0)
Region								
Asian	0.724	73.75(43.38-125.38)	0.0000	0.86 (0.84-0.88)	0.9(0.88-0.92)	7.74(5.77-10.39)	0.12(0.07-0.20)	0.96 (0.94-0.97)
Europe and America	0.645	73.75(29.26-125.38)	0.0000	0.80 (0.77-0.82)	0.88(0.86-0.90)	12.05(5.22-27.8)	0.16(0.07-0.38)	0.96 (0.91-1.0)
Study population								
Patient	0.616	54.29(34.07-86.51)	0.0000	0.84(0.82-0.85)	0.87(0.85-0.89)	7.17(5.18-9.93)	0.14 (0.09-0.23)	0.94 (0.92-0.96)
Healthy	0.294	156.11(41.44-588.04)	0.0073	0.75 (0.69-0.80)	0.97(0.94-0.98)	16.25(6.94-38.06)	0.13 (0.03-0.53)	0.98 (0.96-1.0)
Assay method								
IM	0.5940	82.94(41.62-165.29)	0.0000	0.81(0.78-0.83)	0.92(0.90-0.94)	9.81 (6.28-15.34)	0.14 (0.07-0.28)	0.96 (0.93-0.98)
ELISA	0.7820	67.46(35.58-127.9)	0.0000	0.86(0.84-0.87)	0.87(0.84-0.88)	7.92(5.02-12.5)	0.12 (0.07-0.23)	0.95 (0.93-0.98)

Table 4. Meta-regression of potential heterogeneity within the included studies

Variables	Coeff.	Std. Err.	P-value	RDOR	[95%CI]
Cte.	-0.98	3.4737	0.781	----	----
S	0.309	0.1614	0.0706	----	----
Region	-0.459	0.8022	0.574	0.63	(0.12;3.39)
Sample size	-0.001	0.0041	0.8856	1	(0.99;1.01)
Age	-0.093	0.2489	0.7117	0.91	(0.54;1.53)
Study population	1.367	0.5326	0.0189	3.92	(1.29;11.96)
blinded design	0.144	0.6537	0.8282	1.15	(0.29;4.54)
Assay method	0.008	0.4155	0.9841	1.01	(0.42;2.41)
quanlity	0.518	0.22	0.0295	1.68	(1.06;2.66)

Cte: Constant coefficient, S: Statistic, Coeff: Constant coefficient, Std. Err: Standard error, RDOR: Relative diagnostic odd ratio.

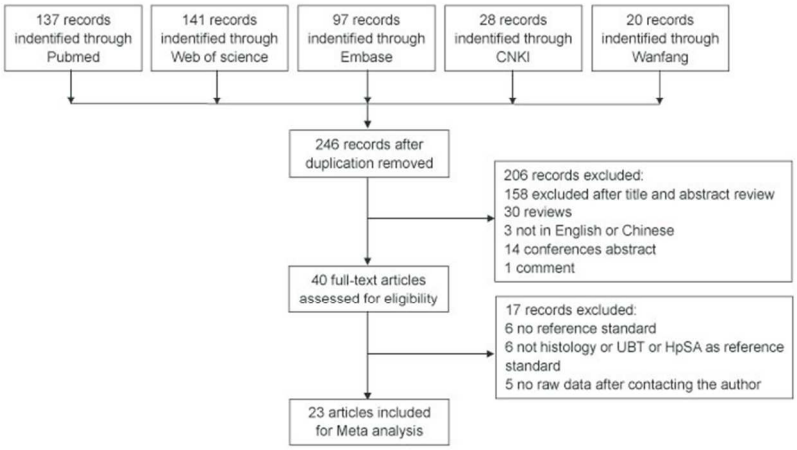


Figure 1. Flow diagram of the literature search.

71x50mm (300 x 300 DPI)

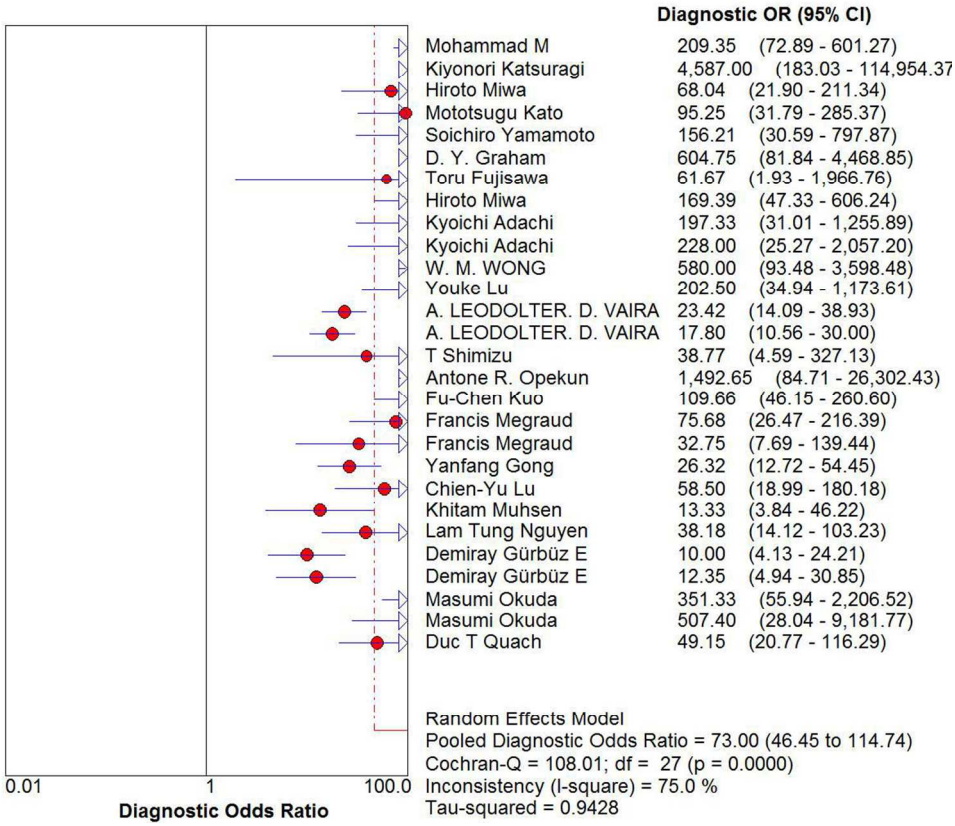


Figure 2. Forest plots of DOR for H. pylori diagnosis by urine IgG antibody. The pooled diagnostic odds ratio was 73 (95%CI: 46.45–114.74).

103x88mm (300 x 300 DPI)

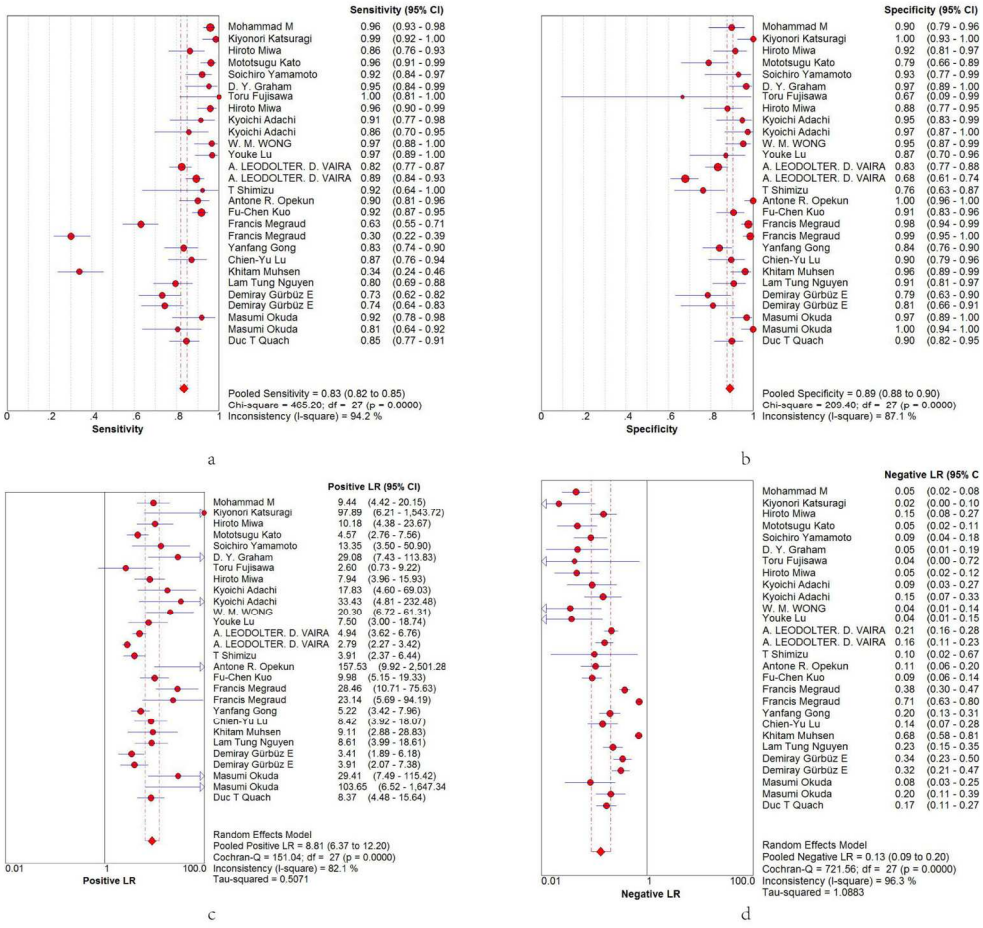


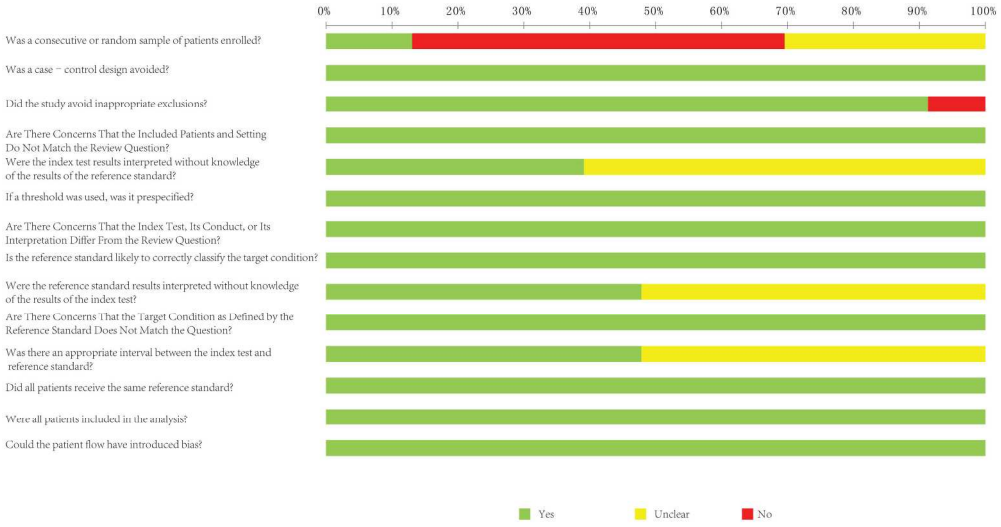
Figure 3. Forest plots of sensitivity, specificity, PLR, and NLR for H. pylori diagnosis by urine IgG antibody. (a) The summary sensitivity was 0.83 (95% CI: 0.82–0.85; I2 = 94.4%). (b) The summary specificity was 0.89 (95% CI: 0.87–0.90; I2 = 86.1%). (c) The summary PLR was 8.5 (95% CI: 6.27–12.2; I2 = 81.0%). (d) The summary NLR of all articles was 0.13 (95% CI: 0.09–0.20; I2 = 96.3%).

150x140mm (300 x 300 DPI)

#1 H.pylori
Search details:
"helicobacter pylori"[MeSH Terms] OR ("helicobacter"[All Fields] AND "pylori"[All Fields]) OR "helicobacter pylori"[All Fields] OR "h pylori"[All Fields]
#2 Helicobacter pylori
#3 #1 OR #2
#4 urine IgG antibody
Search details:
("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) AND IgG[All Fields] AND ("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields])
#5 urine antibody
#6 #4 OR #5
#7 #3 AND #6

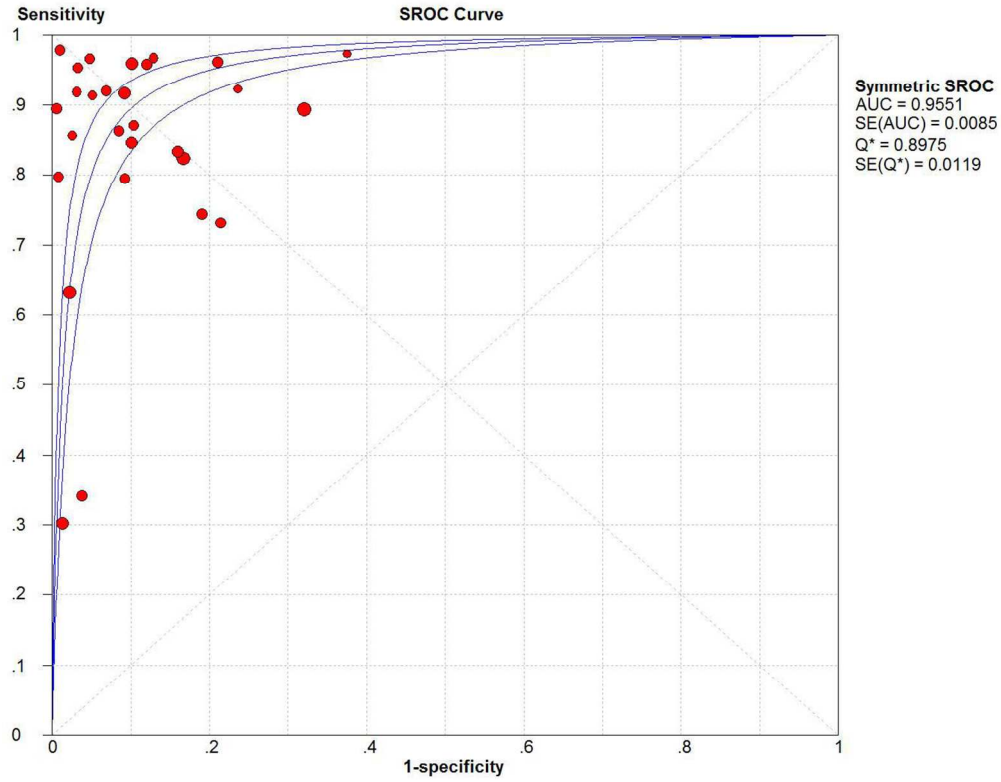
Supplemental Figure 1. Detail of search strategy as performed in Pubmed.

144x76mm (300 x 300 DPI)



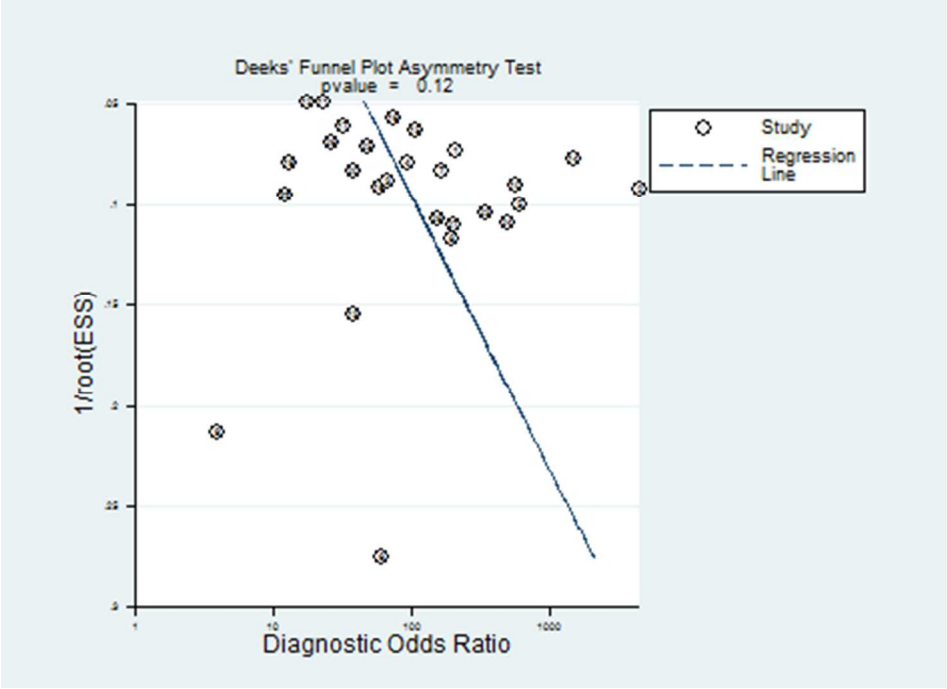
Supplemental Figure 2. Summary of QUADAS-2 assessments of included studies.

216x112mm (300 x 300 DPI)



Supplemental Figure 3. Summary receiver operating characteristic (SROC) curves and confidence interval for the diagnosis of H.pylori infection using IgG antibody in urine.

113x90mm (300 x 300 DPI)



Supplemental Figure 4. Deek's funnel plot to assess the likelihood of publication bias. The statistically non-significant P-value of 0.124 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias

39x29mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3,4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4,5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4,5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4,5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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