

# BMJ Open Panel of serum biomarkers (GastroPanel) in diagnosis of atrophic gastritis and *Helicobacter pylori* infection: a protocol of systematic review and meta-analysis

Dan Wu <sup>1</sup>, Anya Shi,<sup>2</sup> Haiping Wang,<sup>3,4</sup> Xiuzhong Yu<sup>1</sup>

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<sup>1</sup>Clinical Laboratory, People's Hospital of Xinjin District Chengdu (Emergency Command Sub-center of Xinjin District, Chengdu), Chengdu, Sichuan, China

<sup>2</sup>The Second Clinical Medical Hospital, Lanzhou University, Lanzhou, Gansu, China

<sup>3</sup>Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine, The first hospital of Lanzhou university, Lanzhou, Gansu, China

<sup>4</sup>The First Clinical Medical School, Lanzhou University, Lanzhou, Gansu, China

## Correspondence to

Xiuzhong Yu;  
yxzh768019@163.com

## ABSTRACT

**Introduction** The aetiology of gastric cancer is still unclear but *Helicobacter pylori* (HP) infection and chronic atrophic gastritis (AG) are recognised as two major risk factors for gastric cancer. GastroPanel (GP) test is the first non-invasive diagnostic tool to detect AG and HP infection. The aim of the study is to conduct a systematic review and meta-analysis to review published literature about the GP test for diagnosing AG and HP infection, with the objective of estimating the diagnostic performance indices of GP for AG and HP infection.

**Methods and analysis** This protocol of systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement guidelines. PubMed, Embase, Web of Science and Cochrane Library databases will be systematically searched from inception to March 2022 for eligible studies. No language limitations were imposed. The studies will be downloaded into the EndNote V.X9 software and duplicates will be removed. Two review authors independently screened the full text against the inclusion criteria, extracted the data from each included study by using a piloted data extraction form and conducted risk of bias assessment, resolving disagreement by discussion. Results will be synthesised narratively in summary tables, using a random-effect bivariate model, and we fit a hierarchical summary receiver operating characteristic curve.

**Ethics and dissemination** This systematic review will include data extracted from published studies, therefore, does not require ethics approval. The results of this study will be submitted to a peer-reviewed journal.

**PROSPERO registration number** CRD42021282616.

## INTRODUCTION

Gastric cancer (GC) is the sixth most common cancer and the fourth most common cause of cancer-related deaths worldwide in 2020.<sup>1</sup> Although the incidence of GC has decreased steadily over the past 5 years due to a decreasing prevalence of *Helicobacter pylori* (HP) infection, GC still remains particularly to have a high incidence worldwide.<sup>2</sup> In any case, early GC is still considered an initial phase of tumour progression

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study will be the first systematic review and meta-analysis to synthetically investigate the diagnostic accuracy of GastroPanel test for *Helicobacter pylori* infection.
- ⇒ This research will be conducted in strict accordance with the relevant methodological guidelines of systematic review and meta-analysis to minimise bias.
- ⇒ The majority of included studies may be cross-sectional studies, which may compromise the results of our study.
- ⇒ The publication bias is still of concern because this study will be limited to the English-language and Chinese-language publications.

with good prognosis, so early detection of lesions is important for the screening of GC.<sup>3</sup> International guidelines recommend endoscopic surveillance with chromoendoscopy and guided biopsies to detect early GC and reduce mortality of subjects with atrophic gastritis (AG), even after HP eradication.<sup>4</sup> However, the method is an invasive test and is not cost-effective in regions with low incidence of GC and stepwise or individualised screening according to the risk factors of GC.<sup>5</sup> Therefore, novel diagnostic tests were urgently needed to detect early GC.<sup>6</sup>

The aetiology of GC is still unclear but is known to involve the complex interplay of host and environment, with HP infection and its associated chronic AG recognised as two major risk factors for GC.<sup>7-9</sup> The Taipei global consensus supports the proposal that at an individual level, eradication of HP reduces the risk of GC in asymptomatic subjects.<sup>10</sup> Thus, a non-invasive diagnostic test for detection of AG and HP is a promising tool for systematic screening of GC risk groups.<sup>11 12</sup> However, the optimal diagnostic test for detection of AG and HP infection is still under discussion.

Gastroscopy and histology are the gold standards for diagnosis of AG, but as a screening

test, endoscopy is expensive for the majority, especially in low-income countries.<sup>13</sup> Several studies have shown that traditional endoscopy cannot reliably diagnose HP gastritis, atrophy or intestinal metaplasia.<sup>14–16</sup> Endoscopy is an invasive test, which causes much discomfort, thus reducing patient compliance.<sup>17</sup> For the screening of HP infection, the current non-invasive methods are urea breath tests (UBTs), serology and stool antigen tests. UBTs have high diagnostic accuracy, while serology and stool antigen tests were less accurate.<sup>18–19</sup> However, the UBTs also have some limitations, for instance, the <sup>14</sup>C-UBTs are radioactive, and people should know the potential risks, so <sup>14</sup>C-UBTs cannot be performed in children or pregnant women, and repeated tests should be avoided.<sup>20</sup> The major drawback to using <sup>13</sup>C-UBTs is the cost of the equipment to measure <sup>13</sup>CO<sub>2</sub> in expired breath.<sup>21</sup> Therefore, novel diagnostic methods are urgently needed to allow detection of early AG and HP infection. A novel non-invasive tool will significantly improve patients' compliance. In addition, an accurate non-invasive test would be very helpful to improve our knowledge of the epidemiology of AG or HP infection in the general population. The global consensus report has agreed that serological tests (pepsinogens I and II and HP antibody) are useful for identifying individuals at increased risk of GC and for the diagnosis of chronic gastritis and AG.<sup>22</sup> International guidelines and the Maastricht V/Florence Consensus Report also recommend that serological tests may be useful to the patients with HP infection.<sup>4 13</sup>

The GastroPanel (GP) test is a non-invasive diagnostic tool based on the physiology of three biomarkers specific to stomach structure and function, complemented by ELISA (IgG) testing for pepsinogens I and II, gastrin-17 and HP antibody.<sup>23–25</sup> Over the last decade, GP had been proposed as a non-invasive test for the diagnosis of AG and HP infection.<sup>23 26</sup> Moreover, recent original studies showed that this test is a useful non-invasive diagnostic tool in an individual patient, and as a population screening and surveillance tool.<sup>12 27</sup> Two systematic reviews and meta-analyses confirmed the accuracy of GP for diagnosing AG in 2016 and 2017.<sup>25 28</sup> Previous meta-analyses were limited by the few studies with a small sample size for assessing the reliability of the test for the diagnosis. The limited number of studies also eroded the power of the subgroup analysis. To our knowledge, there are no meta-analyses on diagnostic accuracy of GP for HP infection. New evidence has been published for the diagnostic performance indices of GP for both AG and HP infection.<sup>29–32</sup>

## Objectives

This study aims to present a protocol for systematic review and meta-analysis to estimate the diagnostic performance indices of GP for AG and HP infection.

## METHODS AND ANALYSIS

### Study registration

This protocol of systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols statement guidelines.<sup>33</sup>

This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) database. PROSPERO registration number is CRD42021282616.

## Criteria for study selection

### Population

Population who had a biomarker panel GP test for diagnosing AG and HP infection.

### Index test

The index test is mainly the biomarker panel GP test. The test is a serological test consisting of a panel of gastric-specific biomarkers: pepsinogens I and II, gastrin-17 and HP antibodies. There is a growing demand for non-invasive tests to screen the GC risk. GP was designed by Biohit Oyj and used for stomach health as the first serological test.<sup>23–25</sup> Over the last decade, GP has been proposed as a non-invasive test for the diagnosis of AG and HP infection.<sup>23 26</sup>

### Reference standards

Compared with other HP detection methods, histology is the gold standard. Gastroscopy and histology are the gold standard for the diagnosis of AG.<sup>13</sup> Therefore, we considered only gastroscopy and histology as the reference standard/gold standard for diagnosis of AG and HP infection.

### Target conditions or diseases

There are two types of AG: a gastric body-predominant type in patients with infection of HP, and an autoimmune type, limited to the gastric body and fundus.<sup>34</sup> It is well known that the intestinal-type gastric adenocarcinoma develops in a stepwise manner with a sequence of events that evolves from AG and intestinal metaplasia to dysplasia and carcinoma.

HP infection remains one of the most prevalent infections worldwide, especially in low-resource countries. HP infection has been clearly correlated with gastric carcinogenesis.<sup>35</sup>

### Type of studies

All applicable studies that evaluate the accuracy of GP in diagnosis of AG and HP infection for the appropriate patient population regardless of whether data were collected prospectively or retrospectively. However, letters, meeting abstracts, notes, comments, editorials, protocols, guidelines, case reports and case series will be excluded. Case-control studies will also be excluded, because these are prone to bias.

### Search strategy

A systematic search of PubMed, Embase, Web of Science and Cochrane Library will be performed. We will use a combination of the search field 'Title/Abstract' and MeSH (Medical Subject Headings) (alternatively Thesaurus or Subject Headings) for the best possible information retrieval. A search field converting 'Title',

**Table 1** Search strategy used in PubMed

Number	Search terms
1	“helicobacter pylori”[MeSH Terms]
2	“helicobacter nemestrinae”[Title/Abstract]
3	“helicobacter infections”[Title/Abstract]
4	“Helicobacter”[Title/Abstract]
5	“pylori”[Title/Abstract]
6	“H.Pylori”[Title/Abstract]
7	“Campylobacter”[Title/Abstract]
8	“campylobacter pylori”[Title/Abstract]
9	1 or 2–9
10	“gastritis, atrophic”[MeSH Terms]
11	“atrophic gastritides”[Title/Abstract]
12	“atrophic gastritis”[Title/Abstract]
13	10 or 11–12
14	“GastroPanel”[Title/Abstract]
15	“serum biomarkers”[Title/Abstract]
16	“panels”[Title/Abstract]
17	“pepsinogens”[MeSH Terms]
18	“pepsinogen i”[Title/Abstract]
19	“pepsinogen ii”[Title/Abstract]
20	“pepsinogen i ii”[Title/Abstract]
21	“Gastrin-17”[Title/Abstract]
22	“helicobacter pylori antibodies”[Title/Abstract]
23	14 or 15–22
24	9 and 13 and 23

‘Abstract’ and ‘Keywords’ will be used in the absence of a MeSH, Thesaurus or Subject Headings.

We identified eligible studies by searching PubMed, Embase, Web of Science and Cochrane Library databases from inception to March 2022. The MeSH and keywords searched consisted of ‘atrophic gastritis’, ‘helicobacter pylori’, ‘gastric cancer’, ‘GastroPanel’. The detailed search strategy for PubMed is shown in [table 1](#). Deduplication and screening details will be reported in a PRISMA flow diagram. No language or publication date limitations were imposed. To identify additional studies, we examined reference lists from related reviews and studies that were included in our analysis. A complete search update of all databases will be performed before the reference lists that conduct the final analysis and hand screening in the included studies.

### Selection of studies

The duplicate studies will be removed, and then two independent review authors will screen the title and abstract to identify relevant studies. The full text for identified relevant studies will be obtained, thereafter, two review authors will independently screen the full text against the eligible criteria. Any disagreement in study selection will be resolved by consensus. We will attempt to contact study

authors if there were doubts about the eligibility of a study. Primary reasons for exclusion will be documented in a PRISMA flow chart.

### Data extraction and management

Two review authors will extract the data from each included study independently, using a data extraction form. Any disagreement in study selection will be solved by discussion. Extracted data should include the following:

1. First author.
2. Year of publication.
3. Study design (prospective or retrospective cohort studies, cross-sectional studies or randomised controlled trials).
4. Population characteristics (age, gender, country, etc).
5. Geographical origin of the study.
6. Inclusion and exclusion criteria for participants.
7. Whether use of proton pump inhibitors (PPIs) over the last 2 weeks.
8. Number of AG and HP infections.
9. The threshold values used for each test of the panel.
10. Description of the reference/gold standard.
11. Description of the index test.
12. The indications for endoscopy.
13. The number and site of gastric biopsy specimens used for defining the target condition.
14. Grade of severity of AG (atrophy at any grade of severity or moderate-severe atrophy).
15. Constructed 2×2 tables that contained the precise numbers of true positive, false negative, false positive and true negative.
16. Recent antibiotic ingestion.
17. Alcohol ingestion.
18. Bile salts.
19. Time lag between taking the samples and analysis.
20. Whether the samples were transported to a laboratory for analysis, and under what conditions.

If we suspected an overlap of participants between multiple reports, we will identify multiple reports of the same study using the information provided in the reports. We sought further information from study authors, if necessary.

### Risk of bias assessment

Two reviewers will independently assess the quality of included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 instrument. This instrument consists of four key domains that include patient selection, index test, reference standard, and flow of patients through the study and timing of the index and reference standard test. Each domain will be assessed in terms of risk of bias, and the first three domains will also be assessed in terms of applicability. Using this instrument, the risk of bias may be categorised as ‘low’, ‘high’ or ‘unclear’. Discrepancies in the interpretation will be resolved by consensus between the two reviewers, if necessary, arbitration by a third reviewer.



### Data synthesis and analysis

Using 2×2 tables, we will calculate summary estimates of sensitivity and specificity, positive and negative likelihood ratio and diagnostic OR (DOR) with 95% CIs using a random-effect bivariate model.

We will explore the heterogeneity between studies through visual examination of the hierarchical summary receiver operating characteristic (HSROC) curve. Heterogeneity across the studies will be determined by correlation coefficient between logit-transformed sensitivity and specificity by bivariate model and asymmetry parameter,  $\beta$  (beta), where  $\beta=0$  corresponds to a symmetric ROC curve in which the DOR does not vary along the curve by HSROC model. To determine the final meta-analytical model, we will use likelihood ratio tests to assess model fit. Likelihood ratio tests will also be used to determine the statistical significance of differences in test accuracy. When heterogeneity is present, the degree will be quantified using the  $I^2$  statistic. Values of less than 25% are considered as homogeneous and 25%–<50% are considered as having low heterogeneity. For values of 50% or more, significant heterogeneity is assumed. Heterogeneity will also be assumed at significance level of  $p<0.05$  and tested by  $X^2$ .

### Subgroup analysis

If we extract sufficient data, we will perform subgroup analyses for any covariates that showed a statistically significant association with the summary estimates. We will explore the following sources of heterogeneity for the diagnosis of AG and HP infection and adding them as covariates, if appropriate, to a bivariate regression model: country, geographical origin, sample size, time of publication (early, recent), setting, study design.

Moreover, for diagnosis of AG, we will perform subgroup analyses and meta-regressions by GC incidence (high, intermediate, low), grade and extent of AG and activity of mucosal inflammation. For diagnosis of HP infection, subgroup analyses and meta-regressions will be performed by application of PPIs, non-steroidal anti-inflammatory drugs and antibiotics to identify the reasons for heterogeneity.

### Sensitivity analysis and publication bias

Sensitivity analysis will be performed to assess the stability of the meta-analytical results, using the one-by-one study removal and evaluated by descriptively comparing the magnitude and precision of the random-effects summary effect sizes. Publication bias will be analysed using precision funnel plots and the test statistics.

### Patient and public involvement

This protocol will use previously published data. No patients or members of public will be included in this study.

### DISCUSSION

HP infection and AG have been recognised as two major risk factors for GC.<sup>7–9</sup> To identify subjects with an underlying AG and HP infection plays a vital role in preventing and improving the prognosis for GC. An accurate non-invasive tool would be very helpful to identify these subjects, especially in the general population. GP test is a non-invasive diagnostic tool based on the physiology of three biomarkers specific to stomach structure and function, complemented by ELISA (IgG) testing for HP antibodies.<sup>23–25</sup> However, the accuracy of GP is still controversial, and it is necessary to provide a comprehensive review of the relevant studies published to date. Therefore, we will conduct this systematic review and meta-analysis to provide more supportive evidence in diagnosing AG and HP infection by GP. This study will synthesise the current literature on the diagnostic performance indices of GP for AG and HP infection. However, there will be many limitations for this study. First, the majority of included studies will be cross-sectional studies, which might cause bias. Second, there may be heterogeneity because this test combines four biomarkers which have different evaluation criteria. Third, publication bias is still of concern because this study will be limited to the English-language and Chinese-language publications.

### Ethics and dissemination

Because this study is a systematic review, ethics approval is not necessary as we are not directly targeting individuals or extracting data without privacy. The results of this study will be submitted to a peer-reviewed journal.

**Contributors** XY and DW conceptualised and designed the study. HW critically revised the design. AS and DW drafted the manuscript. DW, AS, HW and XY critically revised and edited the manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

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### ORCID iD

Dan Wu <http://orcid.org/0000-0002-6494-4380>

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