BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062849
Article Type:	Protocol
Date Submitted by the Author:	17-Mar-2022
Complete List of Authors:	Wu, Dan; People' s Hospital of Xinjin District, Chengdu Shi, Anya; Lanzhou University Wang, Haiping; Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine; Lanzhou University First Affiliated Hospital Yu, Xiuzhong; People's Hospital of Xinjin District, Chengdu
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY

A panel of serum biomarkers (GastroPanel) in diagnosis of atrophic gastritis and helicobacter pylori infection: a protocol of systematic review and meta-analysis

Dan Wu [1], Anya Shi [2], Haiping Wang [3,4], Xiuzhong Yu [5,*]

[1]People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China

[2]The Second Clinical Medical Hospital, Lan Zhou University, Lanzhou, Gansu, 730000, China

[3]Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine, Lanzhou, Gansu, 730000, China

[4]The First Hospital of Lanzhou University, Lanzhou, Gansu, 730000, China

[5]People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China

[*]Correspondence:

Xiuzhong Yu

E-mail: yxzhh768019@163.com

People' s Hospital of Xinjin District, NO. 149, Wujin West Road, Chengdu, Sichuan 610500, China

Tel: +86 13608076810

Running title: GastroPanel diagnose atrophic gastritis and helicobacter pylori infection

Count:

Abstract: 247

Text: 2265

Number of figures: 0

Number of tables: 1

E-mail address of all authors

Dan Wu: dan101412@163.com

Anya Shi: shiay18@lzu.edu.cn

Haiping Wang: wanghp2016@hotmail.com

Xiuzhong Yu: yxzhh768019@163.com

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 minimize bias.
- The majority of included studies may be cross-sectional study, which may compromise the results of our study.
- The publication bias is still of concern because this study will be limited to the English- and Chinese-language publications.

ABSTRACT

Introduction The etiology of gastric cancer is still unclear but helicobacter pylori (HP) infection and chronic atrophic gastritis recognized as two major risk factors for gastric cancer. GastroPanel ® test (GP) is the first non-invasive diagnostic tool to detect atrophic gastritis and helicobacter pylori 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 atrophic gastritis (AG) and HP infection. With the objective to estimate the diagnostic performance indices of GP for atrophic gastritis and helicobacter pylori 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 (PRISMA) Protocols statement guidelines. PubMed, Embase, Web of Science, Cochrane Library databases will be systematically searched to identify eligible studies. No language limitations were imposed. The studies will be downloaded into the Endnote 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 conduct risk of bias assessment, resolving disagreement by discussion. Results will be synthesized narratively in summary tables, using a random effect bivariate model and we fit a summary hierarchical receiving operating characteristic (HSROC) curve.

Ethics and dissemination This systematic review will include data extracted form 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.[1] Although the incidence of the GC has decreased constantly over the past five years due to a decreasing prevalence of helicobacter pylori (HP) infection, GC still remains particularly high incidence worldwide.[2] In any case, early gastric cancer is still considered an initial phase of tumor progression with good prognosis, so early detection of these lesions is important for the screening of gastric cancer.[3] International guidelines recommend endoscopic surveillance with chromoendoscopy and guided biopsies to detect early gastric cancer and reduce mortality of subjects with atrophic gastritis, even after HP eradication.[4] However, the methods was invasive diagnostic tests, and was not cost-effective in regions with low incidence of gastric cancer and stepwise- or individualized screening according to the risk factors of gastric cancer.[5] Therefore, novel diagnostic tests were urgently needed to detect early GC.[6]

The etiology of GC is still unclear but is known to involve the complex interplay of host and environment, with HP infection and its associated chronic atrophic gastritis (CAG) were recognized as two major risk factors for gastric cancer.[7-9] The Taipei global consensus supports the proposal that at an individual level, eradication of HP reduces the risk of GC in asymptomatic subjects.[10] Thus, the non-invasive diagnostic test for detection of AG and HP was promising tools for systematic screening of GC risk groups.[11 12] However, it is still a matter that identifying subjects with an underlying atrophic gastritis or HP infection.

Gastroscopy and histology are the gold standards for diagnosis of atrophic gastritis, but as a screening test, endoscope is expensive for the majority, especially in low-come countries.[13] Meantime, there were also studies showed that traditional endoscopy cannot reliably diagnose HP gastritis, atrophy or intestinal metaplasia.[14-16] Endoscope is an invasive test, it may make subjects to be uncomfortable and does not have good patient's compliance.[17] For the screening of HP infection, the current non-invasive method is urea breath tests, serology and stool antigen tests, urea breath tests had high

diagnostic accuracy while serology and stool antigen tests were less accurate.[18 19] However the urea breath tests also have some limitations, for instance the ^{14}C-UBTs are radioactive, and people should know the potential risks, so ^{14}C-UBTs cannot be performed in children or pregnant women, and repeated tests should be avoided.[20] The major drawback to use of ^{13}C-UBTs is the cost of the equipment to measure $^{13}CO_2$ in expired breath.[21] Therefore, novel diagnostic measures are urgently needed to allow detection of early AG and HP infection. The novel non-invasive tool alleviates the patients' pain during testing and at the same time improve patient's compliance. In addition, an accurate non-invasive test would be very helpful to improve our knowledge on the epidemiology of atrophic gastritis or HP infection in the general population. The global consensus report has agreed that serological tests (pepsinogen I and II and HP antibody) are useful for identifying individuals at increased risk for gastric cancer and for the diagnosis of chronic gastritis and gastric atrophy.[22] International guidelines and the Maastricht V/Florence Consensus Report also recommend that serological tests may be useful to the patients with HP infection.[4 13]

GastroPanel ® test (GP) is the non-invasive diagnostic tool based on physiology of three biomarkers specific to stomach structure and function, complemented by ELISA (IgG) testing for pepsinogen I and II, Gastrin-17, and HP antibody.[23-25] Over the last decade, GP had been proposed as a non-invasive test for the diagnosis of atrophic gastritis and HP infection.[23 26] 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.[12 27] Two systematic reviews and Meta-analyses were conducted to confirmed the accuracy of GP for diagnosing AG in 2016 and 2017.[25 28] But all the 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, no meta-analysis on diagnostic accuracy of GP for HP infection. New evidence was published for the diagnostic performance indices of GP for both AG and HP infection.[29-32]

OBJECTIVES

This study aims to present a protocol for systematic review and meta-analysis to estimate the diagnostic performance indices of GP for atrophic gastritis 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.[33]

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 with doing biomarker panel GP test for diagnosing AG and HP infection.

Index test

The index test is mainly biomarker panel GP test. The test is a serological test consisting of a panel of stomach-specific biomarkers: Pepsinogens I and II, Gastrin-17, and HP antibodies. Growing demand for non-invasive tests to screen the gastric cancer (GC) risk, GP was designed by Biohit Oyj and used for stomach health as the first serological test.[23-25] Over the last decade, GP has been proposed as a non-invasive test for the diagnosis of atrophic gastritis and HP infection.[23 26]

Reference standards

There is no gold standard for diagnosis of HP infection. Gastroscopy and histology are the gold standard for diagnosis of atrophic gastritis.[13] Therefore we considered only gastroscopy and histology as the reference standard/ gold standard for diagnosis of atrophic gastritis and HP infection.

Target conditions or diseases

Atrophic gastritis (AG), which has two types: a gastric body predominant type in patients with infection of HP, and an autoimmune type, limited to the gastric body and fundus.[34] It is well known that the intestinal-type gastric adenocarcinoma develops in a stepwise manner with a sequence of events that evolves from atrophic gastritis 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.

Type of studies

All applicable studies that evaluate the accuracy of GP in diagnosis of atrophic gastritis and HP infection for the appropriate patient population regardless 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 (alternatively Thesaurus or Subject Headings) for the best possible information retrieval. A search field converting ‘Title’, ‘Abstract’ and ‘Keywords’ will be use 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 medical subject headings 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 references lists from related reviews and studies that were included in our analysis. A complete search update of all databases will be

performed before the references lists that conduct the final analysis and hand screening in the included studies.

Selection of studies

The duplicated 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, two review authors will independently screen the full-text against the eligible criteria. Any disagreement in study selection will be solved by discussion. 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 flowchart.

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:

(1) First author;

(2) Year of publication;

(3) Study design (prospective or retrospective cohort studies, cross-sectional studies or randomized controlled trials);

(4) Population characteristics (age, gender, country, etc.);

(5) Geographic origin of the study;

(6) Inclusion and exclusion criteria for participants;

(7) Whether use of proton pump inhibitors (PPIs) over the last week;

(8) Number of AG and HP infection;

(9) The threshold values used for each test of the panel;

(10) Description of the reference/golden 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 atrophic gastritis (atrophy at any grade of severity or moderate-severe atrophy);

(15) Constructed 2 × 2 tables that contained the precise numbers of true positive (TP), false negative (FN), false positive (FP) and truenegative (TN).

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 (QUADAS-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 categorized as “low”, “high”, or “unclear”. Discrepancies in the interpretation were 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 odds ratio (DOR) with 95% confidence intervals (95% CI) using a random effect bivariate model.

We will explore the heterogeneity between studies through visual examination of the hierarchical receiving 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, β (beta), where β=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-analytic model, we used

likelihood ratio tests to assess model fit. Likelihood ratio tests were also used to determine the statistical significance of differences in test accuracy. When heterogeneity was present, the degree was quantified using the I^2 statistic. Values of less than 25% are considered as homogenous and 25% to <50% are considered as having low heterogeneity. For values of 50% or more, significant heterogeneity is assumed. And heterogeneity will also be assumed at significance level of $P< 0.05$ and tested by chi-square.

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 atrophic gastritis and helicobacter pylori infection and adding them as covariates, if appropriate, to a bivariate regression model: country, geographic origin, sample size, time of publication (early, recent), setting, study design.

Besides, for diagnosis of atrophic gastritis, we will perform subgroup analyses and meta-regressions by GC incidence (high-, intermediate-, low-), grade and extent of AG, activity of mucosal inflammation. For diagnosis of HP infection, subgroup analyses and meta regressions will be performed by application of PPIs, nonsteroidal anti-inflammatory drugs and antibiotic 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 analyzed using precision funnel plots and the test statistics.

Patients 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 atrophic gastritis have been recognized as two major risk factors for gastric cancer.[7-9] To identify subjects with an underlying AG and HP infection plays a vital role in preventing and improving the prognosis for GC. The accurate non-invasive tool would be very helpful to identify these subjects, especially in the general population. GP test is the non-invasive diagnostic tool based on physiology of three biomarkers specific to stomach structure and function, complemented by ELISA (IgG) testing for Hp antibodies.[23-25] However, the accuracy of GP is still controversial. And it is necessary to provide a comprehensive review of the relevant studies publish to date. Therefore, we will conduct this systematic review and meta-analysis to provide more supportive evidence in diagnosing atrophic gastritis and HP infection by GastroPanel ®. This study will synthesize the current literature on the diagnostic performance indices of GastroPanel ® for atrophic gastritis and helicobacter pylori infection. However, there will be many limitations for this study. Firstly, the majority of included studies will be cross-sectional study, which might cause bias. Secondly, there may be heterogeneity due to this test combinates four biomarkers which have different evaluation criteria. Thirdly, publication bias is still of concern because this study will be limited to the English- and Chinese-language publications.

ETHICS AND DISSEMINATION

Due to this study as 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 concepted 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.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

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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

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6, 7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7, 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8, 16
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9, 10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9, 10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10, 11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

NA, not applicable.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062849.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Aug-2022
Complete List of Authors:	Wu, Dan; People's Hospital of Xinjin District Chengdu Shi, Anya; Lanzhou University Wang, Haiping; Lanzhou University Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine; Lanzhou University First Affiliated Hospital Yu, Xiuzhong; People's Hospital of Xinjin District Chengdu
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Gastroenterology and hepatology, Diagnostics, Infectious diseases
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY

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Dan Wu [1], Anya Shi [2], Haiping Wang [3,4], Xiuzhong Yu [5, *]

[1]People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China

[2]The Second Clinical Medical Hospital, Lan Zhou University, Lanzhou, Gansu, 730000, China

[3]Lanzhou University Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine, Lanzhou, Gansu, 730000, China

[4]The First Hospital of Lanzhou University, Lanzhou, Gansu, 730000, China

[5]People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China

[*]Correspondence:

Xiuzhong Yu

E-mail: yxzhh768019@163.com

People' s Hospital of Xinjin District, NO. 149, Wujin West Road, Chengdu, Sichuan 610500, China

Tel: +86 13608076810

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Count:

Abstract: 247

Text: 2287

Number of figures: 0

Number of tables: 1

E-mail address of all authors

Dan Wu: dan101412@163.com

Anya Shi: shiay18@lzu.edu.cn

Haiping Wang: wanghp2016@hotmail.com

Xiuzhong Yu: yxzhh768019@163.com

ABSTRACT

Introduction The etiology of gastric cancer is still unclear but helicobacter pylori (HP) infection and chronic atrophic gastritis recognized as two major risk factors for gastric cancer. GastroPanel® test (GP) is the first non-invasive diagnostic tool to detect atrophic gastritis and helicobacter pylori 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 atrophic gastritis (AG) and HP infection. With the objective to estimate the diagnostic performance indices of GP for atrophic gastritis and helicobacter pylori 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 (PRISMA) Protocols statement guidelines. PubMed, Embase, Web of Science, Cochrane Library databases will be systematically searched to identify eligible studies. No language limitations were imposed. The studies will be downloaded into the Endnote 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 conduct risk of bias assessment, resolving disagreement by discussion. Results will be synthesized narratively in summary tables, using a random effect bivariate model and we fit a summary hierarchical receiving operating characteristic (HSROC) curve.

Ethics and dissemination This systematic review will include data extracted form 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.

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 minimize bias.
- The majority of included studies may be cross-sectional study, which may compromise the results of our study.
- The publication bias is still of concern because this study will be limited to the English- and Chinese-language publications.

INTRODUCTION

Gastric cancer (GC) is the sixth most common cancer and the fourth most common cause of cancer-related deaths worldwide in 2020.[1] Although the incidence of GC has decreased steadily over the past five years due to a decreasing prevalence of helicobacter pylori (HP) infection, GC still remains particularly high incidence worldwide.[2] In any case, early gastric cancer is still considered an initial phase of tumor progression with good prognosis, so early detection of these lesions is important for the screening of gastric cancer.[3] International guidelines recommend endoscopic surveillance with chromoendoscopy and guided biopsies to detect early gastric cancer and reduce mortality of subjects with atrophic gastritis, even after HP eradication.[4] However, the method is an invasive test and is not cost-effective in regions with low incidence of gastric cancer and stepwise- or individualized screening according to the risk factors of gastric cancer.[5] Therefore, novel diagnostic tests were urgently needed to detect early GC.[6]

The etiology of GC is still unclear but is known to involve the complex interplay of host and environment, with HP infection and its associated chronic atrophic gastritis (CAG) were recognized as two major risk factors for gastric cancer.[7-9] The Taipei global consensus supports the proposal that at an individual level, eradication of HP reduces the risk of GC in asymptomatic subjects.[10] Thus, the non-invasive diagnostic test for detection of AG and HP is a promising tool for systematic screening of GC risk groups.[11 12] 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 atrophic gastritis, but as a screening test, endoscope is expensive for the majority, especially in low-income countries.[13] Several studies have showed that traditional endoscopy cannot reliably diagnose HP gastritis, atrophy or intestinal metaplasia.[14-16] Endoscopy is an invasive test, which causes much discomfort, thus reducing patient compliance.[17] For the screening of HP infection, the current non-invasive methods are urea breath tests, serology and stool antigen tests. Urea breath tests have to make it have high diagnostic

accuracy while serology and stool antigen tests were less accurate.[18 19] However the urea breath tests also have some limitations, for instance the ^{14}C-UBTs are radioactive, and people should know the potential risks, so ^{14}C-UBTs cannot be performed in children or pregnant women, and repeated tests should be avoided.[20] The major drawback to use of ^{13}C-UBTs is the cost of the equipment to measure $^{13}CO_2$ in expired breath.[21] Therefore, novel diagnostic methods are urgently needed to allow detection of early AG and HP infection. The novel non-invasive tool significantly improves patient's compliance. In addition, an accurate non-invasive test would be very helpful to improve our knowledge of the epidemiology of atrophic gastritis or HP infection in the general population. The global consensus report has agreed that serological tests (pepsinogen I and II and HP antibody) are useful for identifying individuals at increased risk for gastric cancer and for the diagnosis of chronic gastritis and gastric atrophy.[22] International guidelines and the Maastricht V/Florence Consensus Report also recommend that serological tests may be useful to the patients with HP infection.[4 13]

GastroPanel® test (GP) is the non-invasive diagnostic tool based on physiology of three biomarkers specific to stomach structure and function, complemented by ELISA (IgG) testing for pepsinogen I and II, Gastrin-17, and HP antibody.[23-25] Over the last decade, GP had been proposed as a non-invasive test for the diagnosis of atrophic gastritis and HP infection.[23 26] 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.[12 27] Two systematic reviews and Meta-analyses confirmed the accuracy of GP for diagnosing AG in 2016 and 2017.[25 28] 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-analysis 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.[29-32]

OBJECTIVES

This study aims to present a protocol for systematic review and meta-analysis to

estimate the diagnostic performance indices of GP for atrophic gastritis 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.[33]

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 biomarker panel GP test for diagnosing AG and HP infection.

Index test

The index test is mainly 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. Growing demand for non-invasive tests to screen the gastric cancer (GC) risk. GP was designed by Biohit Oyj and used for stomach health as the first serological test.[23-25] Over the last decade, GP has been proposed as a non-invasive test for the diagnosis of atrophic gastritis and HP infection.[23 26]

Reference standards

Compared with other Hp detection methods, histology is the gold standard. Gastroscopy and histology are the gold standard for diagnosis of atrophic gastritis.[13] Therefore we considered only gastroscopy and histology as the reference standard/ gold standard for diagnosis of atrophic gastritis and HP infection.

Target conditions or diseases

There are two types of atrophic gastritis (AG): a gastric body predominant type in

patients with infection of HP, and an autoimmune type, limited to the gastric body and fundus.[34] It is well known that the intestinal-type gastric adenocarcinoma develops in a stepwise manner with a sequence of events that evolves from atrophic gastritis 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.[35]

Type of studies

All applicable studies that evaluate the accuracy of GP in diagnosis of atrophic gastritis and HP infection for the appropriate patient population regardless 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 (alternatively Thesaurus or Subject Headings) for the best possible information retrieval. A search field converting 'Title', 'Abstract' and 'Keywords' will be use 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 medical subject headings 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 references lists from related reviews and studies that were included in our analysis. A complete search update of all databases will be performed before the references lists that conduct the final analysis and hand screening

in the included studies.

Selection of studies

The duplicated 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 flowchart.

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:

(1) First author;

(2) Year of publication;

(3) Study design (prospective or retrospective cohort studies, cross-sectional studies or randomized controlled trials);

(4) Population characteristics (age, gender, country, etc.);

(5) Geographic origin of the study;

(6) Inclusion and exclusion criteria for participants;

(7) Whether use of proton pump inhibitors (PPIs) over the last two weeks;

(8) Number of AG and HP infection;

(9) The threshold values used for each test of the panel;

(10) Description of the reference/golden 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 atrophic gastritis (atrophy at any grade of severity or moderate-severe atrophy);

(15) Constructed 2 × 2 tables that contained the precise numbers of true positive (TP), false negative (FN), false positive (FP) and truenegative (TN);

(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 lab 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 (QUADAS-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 categorized as “low”, “high”, or “unclear”. Discrepancies in the interpretation were 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 odds ratio (DOR) with 95% confidence intervals (95% CI) using a random effect bivariate model.

We will explore the heterogeneity between studies through visual examination of the

hierarchical receiving 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, β (beta), where β=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-analytic 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 homogenous and 25% to <50% are considered as having low heterogeneity. For values of 50% or more, significant heterogeneity is assumed. And heterogeneity will also be assumed at significance level of $P< 0.05$ and tested by chi-square.

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 atrophic gastritis and helicobacter pylori infection and adding them as covariates, if appropriate, to a bivariate regression model: country, geographic origin, sample size, time of publication (early, recent), setting, study design.

Besides, for diagnosis of atrophic gastritis, we will perform subgroup analyses and meta-regressions by GC incidence (high-, intermediate-, low-), grade and extent of AG, activity of mucosal inflammation. For diagnosis of HP infection, subgroup analyses and meta regressions will be performed by application of PPIs, nonsteroidal anti-inflammatory drugs and antibiotic 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 analyzed using precision funnel plots and the test statistics.

Patients 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 atrophic gastritis have been recognized as two major risk factors for gastric cancer.[7-9] To identify subjects with an underlying AG and HP infection plays a vital role in preventing and improving the prognosis for GC. The accurate non-invasive tool would be very helpful to identify these subjects, especially in the general population. GP test is the non-invasive diagnostic tool based on physiology of three biomarkers specific to stomach structure and function, complemented by ELISA (IgG) testing for Hp antibodies.[23-25] 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 atrophic gastritis and HP infection by GastroPanel ®. This study will synthesize the current literature on the diagnostic performance indices of GastroPanel ® for atrophic gastritis and helicobacter pylori infection. However, there will be many limitations for this study. Firstly, the majority of included studies will be cross-sectional study, which might cause bias. Secondly, there may be heterogeneity with because this test combines four biomarkers which have different evaluation criteria. Thirdly, publication bias is still of concern because this study will be limited to the English- and Chinese-language publications.

ETHICS AND DISSEMINATION

Due to this study as 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 concepted 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.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

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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

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6, 7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7, 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8, 16
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9, 10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9, 10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10, 11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

NA, not applicable.

BMJ Open

A panel of serum biomarkers (GastroPanel) in diagnosis of atrophic gastritis and helicobacter pylori infection: a protocol of systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-062849.R2
Article Type:	Protocol
Date Submitted by the Author:	08-Sep-2022
Complete List of Authors:	Wu, Dan; People's Hospital of Xinjin District Chengdu Shi, Anya; Lanzhou University Wang, Haiping; Lanzhou University Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine; Lanzhou University First Affiliated Hospital Yu, Xiuzhong; People's Hospital of Xinjin District Chengdu
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Gastroenterology and hepatology, Diagnostics, Infectious diseases
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY

A panel of serum biomarkers (GastroPanel) in diagnosis of atrophic gastritis and helicobacter pylori infection: a protocol of systematic review and meta-analysis

Dan Wu [1], Anya Shi [2], Haiping Wang [3,4], Xiuzhong Yu [5, *]

[1]People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China

[2]The Second Clinical Medical Hospital, Lan Zhou University, Lanzhou, Gansu, 730000, China

[3]Lanzhou University Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine, Lanzhou, Gansu, 730000, China

[4]The First Hospital of Lanzhou University, Lanzhou, Gansu, 730000, China

[5]People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China

[*]Correspondence:

Xiuzhong Yu

E-mail: yxzhh768019@163.com

People' s Hospital of Xinjin District, NO. 149, Wujin West Road, Chengdu, Sichuan 610500, China

Tel: +86 13608076810

Running title: GastroPanel diagnose atrophic gastritis and helicobacter pylori infection

Count:

Abstract: 250

Text: 2282

Number of figures: 0

Number of tables: 1

E-mail address of all authors

Dan Wu: dan101412@163.com

Anya Shi: shiay18@lzu.edu.cn

Haiping Wang: wanghp2016@hotmail.com

Xiuzhong Yu: yxzhh768019@163.com

ABSTRACT

Introduction The etiology of gastric cancer is still unclear but helicobacter pylori (HP) infection and chronic atrophic gastritis recognized as two major risk factors for gastric cancer. GastroPanel® test (GP) is the first non-invasive diagnostic tool to detect atrophic gastritis and helicobacter pylori 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 atrophic gastritis (AG) and HP infection. With the objective to estimate the diagnostic performance indices of GP for atrophic gastritis and helicobacter pylori 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 (PRISMA) Protocols statement guidelines. PubMed, Embase, Web of Science, 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 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 conduct risk of bias assessment, resolving disagreement by discussion. Results will be synthesized narratively in summary tables, using a random effect bivariate model and we fit a summary hierarchical receiving operating characteristic (HSROC) curve.

Ethics and dissemination This systematic review will include data extracted form 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.

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 minimize bias.
- The majority of included studies may be cross-sectional study, which may compromise the results of our study.
- The publication bias is still of concern because this study will be limited to the English- and Chinese-language publications.

INTRODUCTION

Gastric cancer (GC) is the sixth most common cancer and the fourth most common cause of cancer-related deaths worldwide in 2020.[1] Although the incidence of GC has decreased steadily over the past five years due to a decreasing prevalence of helicobacter pylori (HP) infection, GC still remains particularly high incidence worldwide.[2] In any case, early gastric cancer is still considered an initial phase of tumor progression with good prognosis, so early detection of these lesions is important for the screening of gastric cancer.[3] International guidelines recommend endoscopic surveillance with chromoendoscopy and guided biopsies to detect early gastric cancer and reduce mortality of subjects with atrophic gastritis, even after HP eradication.[4] However, the method is an invasive test and is not cost-effective in regions with low incidence of gastric cancer and stepwise- or individualized screening according to the risk factors of gastric cancer.[5] Therefore, novel diagnostic tests were urgently needed to detect early GC.[6]

The etiology of GC is still unclear but is known to involve the complex interplay of host and environment, with HP infection and its associated chronic atrophic gastritis (CAG) were recognized as two major risk factors for gastric cancer.[7-9] The Taipei global consensus supports the proposal that at an individual level, eradication of HP reduces the risk of GC in asymptomatic subjects.[10] Thus, the non-invasive diagnostic test for detection of AG and HP is a promising tool for systematic screening of GC risk groups.[11 12] 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 atrophic gastritis, but as a screening test, endoscope is expensive for the majority, especially in low-income countries.[13] Several studies have showed that traditional endoscopy cannot reliably diagnose HP gastritis, atrophy or intestinal metaplasia.[14-16] Endoscopy is an invasive test, which causes much discomfort, thus reducing patient compliance.[17] For the screening of HP infection, the current non-invasive methods are urea breath tests, serology and stool antigen tests. Urea breath tests has high diagnostic accuracy while

serology and stool antigen tests were less accurate.[18 19] However the urea breath tests also have some limitations, for instance the ^{14}C-UBTs are radioactive, and people should know the potential risks, so ^{14}C-UBTs cannot be performed in children or pregnant women, and repeated tests should be avoided.[20] The major drawback to use of ^{13}C-UBTs is the cost of the equipment to measure $^{13}CO_2$ in expired breath.[21] Therefore, novel diagnostic methods are urgently needed to allow detection of early AG and HP infection. The novel non-invasive tool significantly improves patient's compliance. In addition, an accurate non-invasive test would be very helpful to improve our knowledge of the epidemiology of atrophic gastritis or HP infection in the general population. The global consensus report has agreed that serological tests (pepsinogen I and II and HP antibody) are useful for identifying individuals at increased risk for gastric cancer and for the diagnosis of chronic gastritis and gastric atrophy.[22] International guidelines and the Maastricht V/Florence Consensus Report also recommend that serological tests may be useful to the patients with HP infection.[4 13]

GastroPanel® test (GP) is the non-invasive diagnostic tool based on physiology of three biomarkers specific to stomach structure and function, complemented by ELISA (IgG) testing for pepsinogen I and II, Gastrin-17, and HP antibody.[23-25] Over the last decade, GP had been proposed as a non-invasive test for the diagnosis of atrophic gastritis and HP infection.[23 26] 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.[12 27] Two systematic reviews and Meta-analyses confirmed the accuracy of GP for diagnosing AG in 2016 and 2017.[25 28] 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-analysis 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.[29-32]

OBJECTIVES

This study aims to present a protocol for systematic review and meta-analysis to

estimate the diagnostic performance indices of GP for atrophic gastritis 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.[33]

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 biomarker panel GP test for diagnosing AG and HP infection.

Index test

The index test is mainly 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. Growing demand for non-invasive tests to screen the gastric cancer (GC) risk. GP was designed by Biohit Oyj and used for stomach health as the first serological test.[23-25] Over the last decade, GP has been proposed as a non-invasive test for the diagnosis of atrophic gastritis and HP infection.[23 26]

Reference standards

Compared with other Hp detection methods, histology is the gold standard. Gastroscopy and histology are the gold standard for diagnosis of atrophic gastritis.[13] Therefore we considered only gastroscopy and histology as the reference standard/ gold standard for diagnosis of atrophic gastritis and HP infection.

Target conditions or diseases

There are two types of atrophic gastritis (AG): a gastric body predominant type in

patients with infection of HP, and an autoimmune type, limited to the gastric body and fundus.[34] It is well known that the intestinal-type gastric adenocarcinoma develops in a stepwise manner with a sequence of events that evolves from atrophic gastritis 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.[35]

Type of studies

All applicable studies that evaluate the accuracy of GP in diagnosis of atrophic gastritis and HP infection for the appropriate patient population regardless 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 (alternatively Thesaurus or Subject Headings) for the best possible information retrieval. A search field converting 'Title', 'Abstract' and 'Keywords' will be use 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 medical subject headings 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 references lists from related reviews and studies that were included in our analysis. A complete search update of all databases will be performed before the references lists that conduct the final analysis and hand screening

in the included studies.

Selection of studies

The duplicated 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 flowchart.

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:

(1) First author;

(2) Year of publication;

(3) Study design (prospective or retrospective cohort studies, cross-sectional studies or randomized controlled trials);

(4) Population characteristics (age, gender, country, etc.);

(5) Geographic origin of the study;

(6) Inclusion and exclusion criteria for participants;

(7) Whether use of proton pump inhibitors (PPIs) over the last two weeks;

(8) Number of AG and HP infection;

(9) The threshold values used for each test of the panel;

(10) Description of the reference/golden 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 atrophic gastritis (atrophy at any grade of severity or moderate-severe atrophy);

(15) Constructed 2 × 2 tables that contained the precise numbers of true positive (TP), false negative (FN), false positive (FP) and truenegative (TN);

(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 lab 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 (QUADAS-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 categorized as “low”, “high”, or “unclear”. Discrepancies in the interpretation were 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 odds ratio (DOR) with 95% confidence intervals (95% CI) using a random effect bivariate model.

We will explore the heterogeneity between studies through visual examination of the

hierarchical receiving 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, β (beta), where β=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-analytic 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 homogenous and 25% to <50% are considered as having low heterogeneity. For values of 50% or more, significant heterogeneity is assumed. And heterogeneity will also be assumed at significance level of $P< 0.05$ and tested by chi-square.

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 atrophic gastritis and helicobacter pylori infection and adding them as covariates, if appropriate, to a bivariate regression model: country, geographic origin, sample size, time of publication (early, recent), setting, study design.

Besides, for diagnosis of atrophic gastritis, we will perform subgroup analyses and meta-regressions by GC incidence (high-, intermediate-, low-), grade and extent of AG, activity of mucosal inflammation. For diagnosis of HP infection, subgroup analyses and meta regressions will be performed by application of PPIs, nonsteroidal anti-inflammatory drugs and antibiotic 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 analyzed using precision funnel plots and the test statistics.

Patients 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 atrophic gastritis have been recognized as two major risk factors for gastric cancer.[7-9] To identify subjects with an underlying AG and HP infection plays a vital role in preventing and improving the prognosis for GC. The accurate non-invasive tool would be very helpful to identify these subjects, especially in the general population. GP test is the non-invasive diagnostic tool based on physiology of three biomarkers specific to stomach structure and function, complemented by ELISA (IgG) testing for Hp antibodies.[23-25] 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 atrophic gastritis and HP infection by GastroPanel ®. This study will synthesize the current literature on the diagnostic performance indices of GastroPanel ® for atrophic gastritis and helicobacter pylori infection. However, there will be many limitations for this study. Firstly, the majority of included studies will be cross-sectional study, which might cause bias. Secondly, there may be heterogeneity because this test combines four biomarkers which have different evaluation criteria. Thirdly, publication bias is still of concern because this study will be limited to the English- and Chinese-language publications.

ETHICS AND DISSEMINATION

Due to this study as 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 concepted 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.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

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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

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6, 7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7, 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8, 16
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9, 10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9, 10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10, 11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

NA, not applicable.