INTRODUCTION

Helicobacter pylori (H. pylori) is one of the major etiological factors for peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. Also, the infection rate of H. pylori is over 50% both in eastern and western Asia. The Kyoto global consensus report defines H. pylori-associated gastritis as an infectious disease and recommends eradication therapy for all H. pylori-infected individuals. Several invasive and non-invasive diagnostic methods have been developed till date for the detection...
of *H. pylori* infection, with histology of gastric biopsy specimens being the gold standard. However, endoscopic biopsy causes physical discomfort and is prone to sampling error since *H. pylori* tends to be heterogeneously distributed in the stomach. Serology test is non-invasive and convenient although, it cannot distinguish between past and present infections. The *H. pylori* stool antigen test can detect active *H. pylori* infection, but is less appropriate for mass screening since delayed delivery of stool samples may lead to the degradation of *H. pylori* antigens.

The urea breath test (UBT) has been extensively used in clinical practice and mass screening since it can accurately detect active *H. pylori* infection [Table 1], and is more convenient to use than the diagnostic methods mentioned above. 13C-UBT, using 13C labeled urea, is based on the potent urease activity of *H. pylori* in the gastric mucosa due to which it hydrolyzes 13C labeled urea into NH3 and 13CO2, and hence, its infection can be diagnosed via breath measurements. The results of 13C-UBT are eventually presented as delta over baseline (DOB) value. However, false-negative results may occur if the patient has used antibiotics, bismuth, or proton pump inhibitors (PPIs) four weeks prior to the test. In addition, the reliability of 13C-UBT is undermined in patients with active upper gastrointestinal hemorrhage, atrophic gastritis, intestinal metaplasia (IM), or partial gastrectomy history. Moreover, individual variations in DOB values due to different body masses cannot be neglected. Therefore, instead of setting a strict cut-off point that is applicable in all circumstances, determination of a gray zone, in which the likelihood of both false-negative and false-positive results of 13C-UBT would be maximal, has been proposed to be more sensible. Thus, for individuals with a DOB value within the gray zone, a second test or a different diagnostic method would be recommended to re-evaluate the *H. pylori* status. Currently, there are relatively few studies on the 13C-UBT gray zone, and the exact range of the gray zone remains a controversial issue, although it mostly lies between 2‰ and 6‰. Moreover, while the sensitivity and specificity of 13C-UBT have been proven to be greater than 95‰, studies assessing the accuracy of 13C-UBT within the gray zone are not yet available.

This study aimed to evaluate the accuracy of 13C-UBT between 2‰ and 6‰, and to identify a more appropriate gray zone, if possible. Furthermore, the study explored the factors responsible for false-negative or false-positive results of 13C-UBT and provided some insights into the interpretation of 13C-UBT results in clinical practice.

**PATIENTS AND METHODS**

**Study design and participants**

This was a single-center observational study. All consecutive patients who received 13C-UBT at our center from June 2013 to January 2020 were screened based on their electronic medical records. Those who met the following inclusion criteria were included in the study: (1) having a DOB value between 2‰ and 6‰; (2) having undergone gastroscopy within six months of 13C-UBT; and (3) whose paraffin-embedded specimens were available for bacterial DNA extraction and quantitative real-time polymerase chain reaction (real-time PCR) to detect *H. pylori* infection. Patients were excluded from the study if they (1) received an eradication regimen or took antibiotics for more than three days between 13C-UBT and gastroscopy; (2) used PPIs, antibiotics, or bismuth four weeks prior to gastroscopy or 13C-UBT; (3) had a history of gastrectomy; and (4) had active upper gastrointestinal hemorrhage during gastroscopy. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of our center (No. 243-01; 2021/5/25). Written informed consent was obtained from all patients included in the study.

**Procedure of 13C-urea breath test**

Patients received 13C-UBT following a standardized protocol under the guidance of a clinician. Briefly, patients were instructed to fast for at least 4 hours before the collection of a basic breath sample. A capsule containing 75 mg 13C-urea (Headway Bio-Sci Co., Ltd, Shenzhen, China) was administered, and another breath sample was collected 30 minutes later. The collected breath samples were analyzed using an isotope-selective, non-dispersive infrared spectrometer (Headway Bio-Sci Co., Ltd, Shenzhen, China); 4‰ was used as the cut-off point, as validated in previous studies. DOB values <4‰ were considered negative, and those ≥4‰ were considered positive.

**Endoscopic biopsy and histological evaluation**

As usual, two biopsy specimens, one from the gastric

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**Table 1: Test performance for common non-invasive *H. pylori* diagnostic tests**

| Test                  | Sensitivity     | Specificity     | Positive likelihood ratio | Negative likelihood ratio |
|-----------------------|-----------------|-----------------|---------------------------|---------------------------|
| Urea breath test      | 0.96 (95% CI, 0.95-0.97) | 0.93 (95% CI, 0.91-0.94) | 12.32 (95% CI, 8.38-18.10) | 0.05 (95% CI, 0.03-0.07) |
| Serology              | 0.88 (95% CI, 0.85-0.90) | 0.69 (95% CI, 0.62-0.75) | 2.5 (95% CI, 1.6-4.1) | 0.25 (95% CI, 0.19-0.33) |
| Stool antigen test    | 0.94 (95% CI, 0.93-0.95) | 0.97 (95% CI, 0.96-0.98) | 24 (95% CI, 15-41) | 0.07 (95% CI, 0.04-0.12) |

CI, confidence interval
antrum and the other from the gastric corpus, were obtained from patients undergoing endoscopic biopsy, according to our local guidelines.18,19 Thereafter, the specimens were paraffin-embedded and sliced, and Warthin–Starry (WS) staining was performed to detect H. pylori, and hematoxylin and eosin staining was performed to assess inflammation, atrophic gastritis, and IM according to the updated Sydney grading system.20

Real-time PCR for the detection of H. pylori in paraffin-embedded specimens

For real-time PCR detection of H. pylori infection, five 5-µm thick paraffin rolls were sliced from each gastric mucosal specimen, and DNA was extracted therefrom using a Bacteria Genomic DNA Kit (CoWin Biotech Co., Ltd, Jiangsu, China). The H. pylori–specific 23S rRNA gene was detected by real-time PCR using a Helicobacter pylori detection kit (CoWin Biotech Co., Ltd, Jiangsu, China). Positive and negative controls were used for each sample. Real-time PCR analysis was performed with an ABI 7500 instrument (Applied Biosystems, Foster City, CA, USA) using the following reaction conditions: an initial denaturation step at 95°C for 8 minutes, followed by 45 cycles of amplification at 95°C for 15 seconds and fluorescence collection at 60°C for 1 minute, and finally, cooling at 25°C for 1 minute. Details of the primers and probes used are presented in Table 2. The results were analyzed as follows: when the cycle threshold (Ct) value of 6-FAM (6-carboxyfluorescein) channel was >35, indicating that the initial concentration of DNA target was less than 1 genome per assay reaction, the test result was considered negative.21 When the Ct value was ≤35, the test result was considered positive.

Reference standard for the diagnosis of H. pylori infection

A patient was diagnosed with H. pylori infection when either WS staining or real-time PCR results was positive; diagnosis was negative when both results were negative.4

Statistical analysis

Statistical analyses were conducted using SPSS Statistics 20 software (IBM, Armonk, NY, USA). Continuous variables conforming to normal distribution were shown as mean ± standard deviation; otherwise, they were shown as medians (interquartile ranges). Categorical variables were shown as the number of cases (percentage). Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for the 13C-UBT, in the range of 2.0% to 6.0% with an interval of 0.1%, were calculated. Inter-group comparisons of categorical variables were performed using the Chi-squared test or Fisher’s exact test. Factors affecting the accuracy of 13C-UBT were analyzed using binary logistic regression. All P values were two-tailed, and a P value <0.05 was considered statistically significant.

RESULTS

Study population

A total of 53,987 patients received 13C-UBT at our center from June 2013 to January 2020; of them, 3,139 (5.81%) had a DOB value between 2‰ and 6‰. Among such patients, 208 (6.63%) fulfilled the inclusion and exclusion criteria [Figure 1]. Overall, 103 patients (49.52%) had DOB values ranging from 2‰ to <4‰ and 105 patients (50.48%) had DOB values ranging from 4‰ to ≤6‰. The mean patient age was 48.30 ± 17.12 years, and the median time between 13C-UBT and gastroscopy was 2 (IQR 3) months. Histologic evaluation revealed atrophic gastritis in 61 patients (29.33%) and IM in 71 patients (34.13%) [Table 3].

Diagnostic accuracy of 13C-UBT between 2‰ and 6‰

According to our pre-defined criteria for H. pylori status, 129 patients (62.02%) were diagnosed with H. pylori infection, and 79 (37.98%) were not infected. Real-time PCR results, WS staining results, and the corresponding DOB values of the patients included are shown in Table 4. Of the 91 patients with negative WS staining, 12 (13.19%) were real-time PCR positive; of the 117 patients with positive WS staining, 63 (53.85%) were real-time PCR negative [Table 4].

Table 2: Sequences of primers and probes for detection of 23S rRNA gene of H. pylori

| Target | Primer/Probe | Sequence (5’-3’) |
|--------|--------------|-----------------|
| 23S    | Primer-F     | GTGTCACTGGTGACACAGTTGTCTG |
| rRNA   | Primer-R     | GCTCAGACATCTACCTATCAAGC |
|        | Probe        | FAM-TCCGTGGGTAGCTACACACGATGATAA-BHQ |

6-FAM, 6-carboxyfluorescein

Figure 1: Flow chart of patient selection. 13C-UBT, 13C-urea breath test; DOB, delta over baseline; PCR, quantitative polymerase chain reaction; PPI, proton pump inhibitor
Among the 103 patients with $^{13}$C-UBT results from 2‰ to <4‰, 37 were diagnosed with *H. pylori* infection. Of the 105 patients with $^{13}$C-UBT results ranging from 4‰ to ≤ 6‰, 13 were not infected. The sensitivity, specificity, NPV, and PPV of $^{13}$C-UBT between 2‰ and 6‰ were 71.32%, 83.54%, 64.08%, and 87.62%, respectively.

The false-negative and false-positive rates of $^{13}$C-UBT between 2‰ and 6‰ were 35.92% and 12.38%, respectively. Specifically, the false-negative rates in the 2‰–3‰ and 3‰–4‰ ranges were 28.79% and 48.65%, and the false-positive rates in the 4‰–5‰ and 5‰–6‰ ranges were 19.57% and 6.78%, respectively. Furthermore, the false-negative rate in the 3‰–4‰ range was significantly higher than that in the 2‰–3‰ range ($P = 0.044$). In addition, false-positive rate in the 4‰–5‰ range significantly exceeded that in the 5‰–6‰ range ($P = 0.048$).

**A more appropriate gray zone for $^{13}$C-UBT**

Using different values between 2‰ and 6‰ as the cut-off point, we found that the NPV of $^{13}$C-UBT reached a maximum of 76.47% (13/17) when the cut-off point was changed to 2.15‰, and the PPV of $^{13}$C-UBT reached a maximum of 93.22% (55/59) when the cut-off point was changed to 4.95‰ 

Table 4: Real-time PCR results, WS staining results and the corresponding DOB values of the patients included

| DOB 2‰<4‰ | PCR (-) | PCR (+) | Total |
|-----------|--------|--------|-------|
| DOB 2‰<4‰ | 66 | 10 | 13 | 14 | 103 |
| DOB 4‰ - 6‰ | 13 | 2 | 50 | 40 | 105 |
| Total | 79 | 12 | 63 | 54 | 208 |

PCR, quantitative real-time polymerase chain reaction; WS, Warthin-Starry; DOB, delta over baseline

NPV of 76.47‰, which was still lower than 90‰, and was not significantly higher than the NPV from 2.15‰ to <4‰ (61.63‰, $P = 0.244$). Therefore, the lower limit of 2‰ of the original gray zone should remain the same. The results of $^{13}$C-UBT from 4.95‰ to ≤ 6‰ had a PPV of 93.22‰, which significantly exceeded the PPV from 4‰ to <4.95‰ (80.43‰, $P = 0.048$). Therefore, the upper limit of 6‰ could be reduced to 4.95‰. Overall, the new gray zone was set as 2‰–4.95‰. The sensitivity, specificity, NPV, and PPV of $^{13}$C-UBT between 2‰ and 4.95‰ were 50.00‰, 88.00‰, 64.08‰, and 80.43‰, respectively.

**Risk factors for false-negative or false-positive result of $^{13}$C-UBT**

In 129 patients diagnosed with *H. pylori* infection, multivariate analysis showed gastric antral IM (OR = 3.055, 95% CI: 1.003–9.309, $P = 0.049$) as an independent risk factor for false-negative results of $^{13}$C-UBT [Table 5].

![Figure 2: Negative predictive value (△) and positive predictive value (○) of 13C-UBT at various cut-off points. The negative predictive value reached the maximum of 76.47% at 2.15‰, and the positive predictive value reached the maximum of 93.22‰ at 4.95‰](image-url)
Among the 79 patients without *H. pylori* infection, neither atrophic gastritis nor IM was associated with false-positive results in $^{13}$C-UBT [Table 5].

**DISCUSSION**

The prevalence of dyspepsia in Saudi Arabia is the highest in the Gulf region.[24] Since the test-and-treat strategy with non-invasive test is cost-effective for the initial management of dyspepsia,[25] it is recommended in countries with a low gastric cancer rate.[1] Among all the non-invasive diagnostic tests, $^{13}$C-UBT is the best option owing to its excellent performances.[1] In a recent meta-analysis, the sensitivity and specificity of $^{13}$C-UBT were reported to be 97% and 96%, respectively.[20] Satisfactory accuracy of the test makes the definition of a gray zone seem redundant. However, most studies concerning $^{13}$C-UBT have been conducted with a sample size in hundreds.[15] As is well known, gray zone results only occur in a remarkably low percentage of patients (approximately 2%)[14] and thus, exert only little influence on the accuracy of $^{13}$C-UBT in such studies. China is the most populous country in the world, with approximately 55.8% of its people infected with *H. pylori*.[2] When screening for *H. pylori* with $^{13}$C-UBT, a considerable proportion of the results obviously fall in the gray zone; for example, in our study, 3,139 (5.81%) of 53,987 patients had a DOB value between 2‰ and 6‰. Therefore, introduction of a gray zone would enhance the performance of mass screening for *H. pylori*, over that with a single cut-off point, since the former would inform clinicians about the results that would require further confirmation compared to those that would not.

The gray zone of $^{13}$C-UBT was first proposed by Mion et al.,[15] over a range of 2.5‰–3.5‰. Till date, other gray zones, such as 2‰–5‰, 3.5‰–4‰, and 2.5‰–6‰ have also been proposed,[15,12,27] most being between 2‰ and 6‰. $^{13}$C-UBT results greater than 6‰ are basically true positives, and those less than 2‰ are largely true negatives.[18] Kwon et al.[18] found that although the sensitivity and specificity of $^{13}$C-UBT (cut-off point 4‰) were only 68.9% and 84.9%, respectively, in patients with a high prevalence of atrophic gastritis (28.7%), DOB values less than 2.5‰ had an NPV of 98.48% and those greater than 6‰ had a PPV of approximately 90%. Since inaccurate results of $^{13}$C-UBT are basically distributed from 2‰ to 6‰, a gray zone calculated with only these results would be more precise than that using a vast range of DOB values. Therefore, we precluded $^{13}$C-UBT results less than 2‰ or greater than 6‰ in this study, and found the appropriate gray zone at around 2‰–4.95‰. In our study, 1.10% (594/53987) of the $^{13}$C-UBT results were distributed between 4.95‰
We found the NPV of $^{13}$C-UBT to be only 64.08% between 2% and 4.95%, and the detection rate of IM to be as high as 34.13% (71/208). Further analysis showed the gastric antral IM to be an independent risk factor for false-negative $^{13}$C-UBT, which had also been shown in previous studies.[11,28,29] Gastric IM is a crucial step in gastric carcinogenesis, and usually develops 10 years after initiation of gastric atrophy.[12,30] In this study, 48.72% (19/39) of patients with antral IM were diagnosed with antral atrophic gastritis. Therefore, false-negative results of $^{13}$C-UBT were not only due to IM, but also due to atrophic gastritis, which had sabotaged the living environment of H. pylori for decades. First of all, H. pylori mainly colonizes the gastric antral mucosa. Atrophic gastritis and IM prevent the colonization of H. pylori,[29] and decrease its bacterial density. Lower the colonization density of H. pylori, lower are the $^{13}$C-UBT results.[31] Secondly, atrophic gastritis and IM reduce the number of G-cells in the gastric antrum and, therefore, downstage the secretion of gastrin into circulation.[32] As a result, the secretion of gastric acid is impaired, and the gastric pH level rises. High pH levels inhibit UreI protein, a H$^+$-gated urea channel regulating cytoplasmic urease, which is essential for the survival and colonization of H. pylori, and reduces the urea hydrolysis rate,[33] which eventually leads to false-negative results in $^{13}$C-UBT. According to the explanations above, gastric corpus IM could also be a risk factor for false-negative $^{13}$C-UBT. However, we failed to conclude the same, since only 11 patients were diagnosed with gastric corpus IM and none of them had false-negative $^{13}$C-UBT results. After all, gastric corpus atrophic gastritis and IM predominantly appear in autoimmune gastritis, whereas H. pylori-associated atrophic gastritis and IM usually develop in the antrum.[34]

Moreover, we found WS staining to have a false-negative rate of 13.19% compared to real-time PCR. The latter is known to be more sensitive than histology, especially in patients with a relatively low bacterial load.[33] Among the 12 patients with false-negative WS staining, atrophic gastritis with or without IM was histologically diagnosed in 5 (41.67%) patients. Therefore, false-negative WS results may have been due to the reduced bacterial load caused by atrophic gastritis and IM.[29] Taken together, when using histology to detect H. pylori in such patients, multiple biopsies should be performed to improve sensitivity,[30] or PCR should be performed, if possible.

Although this was a single-center study, the patients in this study were screened from 53,987 out-patients over a period of 8 years. Their mean and median age were 48.3 and 47.0 years, and were confined to normal distribution ($P = 0.06$). We also found the detection rate of atrophic gastritis, with or without IM, to vary in the different age groups and tend to increase with older age (<20 years: 0.00% [0/6]; 20–39 years: 10.45% [7/67]; 40–59 years: 32.47% [25/77]; 60–79 years: 49.02% [25/51]; >79 years: 57.14% [4/7]), which was in line with previous studies conducted in the southwest part of China, Israel, and Latvia.[37–39] Therefore, the patients in this study represented a larger population, and the conclusions should be helpful in decision-making regarding other regions as well.

This study had several limitations. First, it was intrinsically limited by its retrospective design; for example, selection bias might exist. Among the 3,139 patients with DOB values between 2% and 6%, we only included 208 patients with concurrent endoscopic biopsy results, although there was no significant difference in age ($P = 0.269$), sex ($P = 0.250$), or DOB value distribution ($P = 0.555$) across the 208 patients included and 2,931 patients excluded. Second, unlike fresh specimens, paraffin embedding might have an adverse effect on the extraction of specimen DNA,[38] thereby affecting real-time PCR detection. Finally, the sample size was relatively small. Therefore, similar prospective studies should be conducted in future to avoid such limitations.

In conclusion, although the accuracy of $^{13}$C-UBT between 2% and 6% was poor, the PPV was ideal between 4.95% and 6%; therefore, the gray zone of $^{13}$C-UBT could be changed to 2%–4.95%. For patients with $^{13}$C-UBT results in the new gray zone, a second $^{13}$C-UBT would be recommended in case of young patients, whereas histologic evaluation would be recommended, along with PCR, if possible, for older adults. The possibility of false-negative results would increase in patients with gastric antral IM.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Malfertheiner P, Megraud F, O’Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30.
2. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global Prevalence of Helicobacter pylori Infection: Systematic review and meta-analysis. Gastroenterology 2017;153:420-9.
3. Sugano K, Taek J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut 2015;64:1353-67.
4. Keller J, Hammer HF, Afolsabi PR, Benninga M, Borrelli O, Dominguez-Munoz E, et al. European guideline on indications, performance and clinical impact of 13C-breath tests in adult and pediatric patients: An EAGEN, ESNM, and ESPGHAN consensus, supported by EPC. United European Gastroenterol J 2021;9:598-625.
5. Morris A, Ali MR, Brown P, Lane M, Patton K. Campylobacter pylori infection in biopsy specimens of gastric antrum: Laboratory diagnosis and estimation of sampling error. J Clin Pathol 1989;42:727-32.
6. Lee JH, Kim N, Chung JI, Kang KP, Lee SH, Park YS, et al. Long-term follow up of Helicobacter pylori IgG serology after eradication and reinforcement of H. pylori in south Korea. Helicobacter 2008;13:288-94.
7. Liou JM, Malfertheiner P, Lee YC, Chen PC, Ou JT, Tsai MH, et al. Screening and eradication of Helicobacter pylori for gastric cancer prevention: The Taipei global consensus. Gut 2020;69:203-12.
8. Leung WK, Hung LC, Kwok CK, Leong RW, Ng DK, Sung JJ. Follow up of serial urea breath test results in patients after consumption of antibiotics for non-gastric infections. World J Gastroenterol 2002;8:703-6.
9. Mafa N, Van Laer W, Bossuyt A, Urbain D. The early effect of proton pump inhibitor therapy on the accuracy of the 13C urea breath test. Dig Liver Dis 2005;37:28-32.
10. Vörhend N, Soós A, Anne Engh M, Tinaus B, Szakács Z, Pécsi D, et al. Accuracy of the helicobacter pylori diagnostic tests in patients with peptic ulcer bleeding: A systematic review and network meta-analysis. Therap Adv Gastroenterol 2020;13:175628482065324.
11. Capurso G, Carnacchio A, Lahner E, P anzuto F, Baccini F, Delle Fave G, et al. Corpus-predominant gastritis as a risk factor for false-negative 13C-urea breath test results. Aliment Pharmacol Ther 2006;24:1453-60.
12. Kwon YH, Kim N, Lee YJ, Choi YJ, Yoon K, Hwang JJ, et al. The diagnostic validity of citric acid-free, high dose (13) C-urea breath test after helicobacter pylori eradication in Korea. Helicobacter 2015;20:159-68.
13. Kwon YH, Kim N, Lee YJ, Choi YJ, Yoon K, Yoon H, et al. The diagnostic validity of the (13) C-urea breath test in the gastrectomized patients: Single tertiary center retrospective cohort study. J Cancer Prev 2014;19:309-17.
14. Mion F, Rosner G, Rousseau M, Minaire Y. 13C-urea breath test for Helicobacter pylori: Cut-off point determination by cluster analysis. Clin Sci (Lond) 1997;93:3-6.
15. Gisbert JP, Pajares JM. Review article: 13C-urea breath test in the diagnosis of Helicobacter pylori infection -- A critical review. Aliment Pharmacol Ther 2004;20:1001-17.
16. Best LM, Takeoingi Y, Siddique S, Selladurai A, Gandhi A, Low B, et al. Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev 2018;3:CD012800.
17. Ferwana M, Abdulmajeed I, Alajhiahmed A, Madani W, Firwana B, Hasan R, et al. Accuracy of urea breath test in Helicobacter pylori infection: Meta-analysis. World J Gastroenterol 2015;21:1305-14.
18. Gisbert JP, Aibrara V. Accuracy of Helicobacter pylori diagnostic tests in patients with bleeding peptic ulcer: A systematic review and meta-analysis. Am J Gastroenterol 2006;101:848-63.
19. Gisbert JP, de la Morena F, Aibrara V. Accuracy of monoclonal stool antigen test for the diagnosis of H. pylori infection: A systematic review and meta-analysis. Am J Gastroenterol 2006;101:1921-30.
20. Fang JY, Du YQ, Liu WZ, Ren JL, Li YQ, Chen XY, et al. Chinese consensus on chronic gastritis (2017, Shanghai). J Dig Dis 2018;19:182-203.
21. Fang JY, Liu WZ, Li ZS, Du YQ, Ren JL, Li YQ, et al. Chinese consensus on chronic gastritis (2012, Shanghai). Chin J Gastroenterol 2013;18:24-36. (in Chinese).
22. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney system. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996;20:1161-81.
23. Guthrie JL, Seah C, Brown S, Tang P, Jamieson F, Dews SJ. Use of Bordetella pertussis BP3385 to establish a cutoff value for an 18481-targeted real-time PCR assay. J Clin Microbiol 2008;46:3798-9.
24. Alwaisi A, Alghadeer S, Bablihaiz A, Wajid S, Alrabiah Z, Alhossan A, et al. Prevalence and severity of dyspepsia in Saudi Arabia: A survey-based study. Saudi Pharm J 2020;28:1062-7.
25. Ford AC, Qume M, Moayyedi P, Arents NL, Lassen AT, Logan RF, et al. Helicobacter pylori “test and treat” or endoscopy for managing dyspepsia: An individual patient data meta-analysis. Gastroenterology 2005;128:1838-44.
26. Abdul Rahim MA, Johani FH, Shah SA, Hassan MR, Abdul Manaf MR. 13C-urea breath test accuracy for helicobacter pylori infection in the asian population: A meta-analysis. Ann Glob Health 2019;85:110.
27. Chen TS, Chang FY, Chen PC, Huang TW, Ou JT, Tsai MH, et al. Simplified 13C-urea breath test with a new infrared spectrometer for diagnosis of Helicobacter pylori infection. J Gastroenterol Hepatol 2003;18:1237-43.
28. Kokkola A, Rautelin H, Puolakkainen P, Sipponen P, Färkkilä M, Haapianen R, et al. Diagnosis of Helicobacter pylori pylori infection in patients with atrophic gastritis: Comparison of histology, 13C-urea breath test, and serology. Scand J Gastroenterol 2000;35:138-41.
29. Lahner E, Vaarna D, Figura N, Pilozi A, Severi C, et al. Role of noninvasive tests (C-urea breath test and stool antigen test) as additional tools in diagnosis of Helicobacter pylori infection in patients with atrophic body gastritis. Helicobacter 2004;9:436-42.
30. Correa P. A human model of gastric carcinogenesis. Cancer Res 1988;48:3540-6.
31. Epple HJ, Kirstein FW, Bojarski C, Fege J, Fromm M, Riecken EQ, et al. 13C-urea breath test in Helicobacter pylori pylori diagnosis and eradication. Correlation to histology, origin of ‘false’ results, and influence of food intake. Scand J Gastroenterol 1997;32:308-14.
32. Leja M, Kupcinskas I, Funka K, Sudrabala A, Jonaitis I, Ivanaukas A, et al. Value of gastrin-17 in detecting antral atrophy. Adv Med Sci 2011;56:145-50.
33. Weeks DL, Eskandari S, Scott DR, Sachs G. A H+–gated urea channel: The link between Helicobacter pylori urease and gastric colonization. Science 2000;287:482-5.
34. Shah SC, Pazioel MB, Kuipers EJ, Li D. AGA clinical practice update on the diagnosis and management of atrophic gastritis: Expert review. Gastroenterology 2021;161:1325-32.e7.
35. Gastli N, Allain M, Lamarque D, Abitbol V, Billoët A, Collobert G, et al. Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev 2018;3:CD012800.
biopsy enhances the detection of \textit{Helicobacter pylori} infection in a background of gastritis with atrophy. BMC Gastroenterol 2012;12:182.

37. Wang R, Chen XZ. Prevalence of atrophic gastritis in southwest China and predictive strength of serum gastrin-17: A cross-sectional study (SIGES). Sci Rep 2020;10:4523.

38. Muhsen K, Sinnreich R, Merom D, Beer-Davidson G, Nassar H, Cohen D, \textit{et al.} Prevalence and determinants of serological evidence of atrophic gastritis among Arab and Jewish residents of Jerusalem: A cross-sectional study. BMJ Open 2019;9:e024689.

39. Leja M, Cine F, Rudazine D, Vilkoite I, Huttunen T, Daugule I, \textit{et al.} Prevalence of \textit{Helicobacter pylori} infection and atrophic gastritis in Latvia. Eur J Gastroenterol Hepatol 2012;24:1410-7.

40. Watanabe M, Hashida S, Yamamoto H, Matsubara T, Ohtsuka T, Suzawa K, \textit{et al.} Estimation of age-related DNA degradation from formalin-fixed and paraffin-embedded tissue according to the extraction methods. Exp Ther Med 2017;14:2683-8.