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Asia-Pacific Survey on the Management of *Helicobacter pylori* Infection

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ABSTRACT

Background and Aim: Gastric cancer (GC)-related incidence and mortality rates remain high owing to *Helicobacter pylori* infection in Asia, and the importance of primary and secondary prevention of GC has been well recognized. We aimed to investigate the extent of overall agreement among clinicians in the Asia-Pacific region regarding the management of *H. pylori* infection.

Methods: The Upper Gastrointestinal (GI) Focus Group of the Asian Pacific Association of Gastroenterology-Emerging Leaders Committee developed an international survey, which was distributed to 98 clinicians in the Asia-Pacific region, compromising an online questionnaire focusing on the management of *H. pylori* infection.

Results: Participants responded from Japan (15, 15.3%), Hong Kong (15, 15.3%), Thailand (33, 33.7%), Vietnam (23, 23.5%), Malaysia (4, 4.1%), Singapore (3, 3.1%), and others (5, 5.1%). The most common first-line eradication regimen was clarithromycin (CAM) triple therapy, including proton pump inhibitor (PPI), amoxicillin (AMPC), and CAM (64.3%) for 14 days (70.4%). The most common second-line eradication regimen was levofloxacin (LVX) triple therapy, including PPI, AMPC, and LVX (22.4%) for 14 days (67.3%). Eradication therapy was deemed necessary for all asymptomatic adults and minors (aged ≤ 17 years) currently infected with *H. pylori* by 81.6% and 64.3% of respondents, respectively, with 82.7% considering upper GI endoscopy for GC screening useful in the secondary prevention of GC.

Conclusion: There appears to be a growing consensus among clinicians, acknowledging the necessity of eradication therapy. We anticipate that this study will establish a new benchmark in preventive medicine aimed at eradicating GC in the Asia-Pacific region.

1 | Introduction

The prevalence of *Helicobacter pylori* infection remains high in the Asia-Pacific region. In 2015, the pooled prevalence estimate of *H. pylori* for the general population was 51.7% in Japan, 55.8% in China, 43.6% in Thailand, 70.3% in Vietnam, 28.6% in Malaysia, and 40.8% in Singapore, based on a systematic review and meta-analysis [1]. According to GLOBOCAN 2020 data, gastric cancer (GC) ranks fifth in terms of incidence (5.6%) and fourth in terms of mortality (7.7%), and the age-standardized incidence of GC in East Asia is considerably higher than that in South Central Asia and Southeast Asia [2]. Large intercountry

variation is noted in GC incidence and *H. pylori* prevalence among Asian countries [3], which may be attributable to differences in environmental factors such as diet, ethnogenetic backgrounds, and the pathogenic factors of *H. pylori* [4].

The International Agency for Research on Cancer working group reported that *H. pylori* infection is a recognized cause of approximately 90% of all non-cardia GCs, and a 30%–40% reduction in the incidence of GC among patients following eradication therapy has been reported [5]. A recent systematic review and meta-analysis indicated that *H. pylori* eradication significantly reduced the risk of GC (odds ratio, 0.46; 95% confidence interval, 0.39–0.55) [6]. The importance of early detection and eradication therapy for *H. pylori* to prevent the development of GC is being recognized worldwide. For example, the Asia-Pacific consensus guidelines for *H. pylori* infection [7] and GC prevention [8] highlight that test and treat strategies are effective in communities with high GC incidence rates. However, joint ESPGHAN/NASPGHAN guidelines for managing *H. pylori* infection in children and adolescents do not currently recommend test and treat strategies owing to a lack of evidence [9]. Furthermore, antibiotic-resistant bacteria rapidly spreading in the Asia-Pacific region remain problematic, posing challenges to eradication efforts. Findings from a systematic review and meta-analysis indicated that the rate of resistance to clarithromycin (CAM) is higher than that to metronidazole (MNZ) (19% and 10%, respectively) in Japan, but the reverse is the case in Thailand and Vietnam [10].

In addition to primary prevention of GC, secondary prevention of GC following eradication therapy is necessary [11]. In a systematic review and meta-analysis, the pooled prevalence for chronic atrophic gastritis and intestinal metaplasia (IM) in Asia was 26.4% and 22.9%, respectively, suggesting that up to 26% of individuals harbored preneoplastic gastric lesions in Asia [12]. In studies conducted in Japan and South Korea, endoscopic screening has been shown to be effective in the early detection of GC and in reducing mortality rates [13–15]. However, its effectiveness has not been fully validated, and endoscopic screening for GC has not been implemented at the national level in other Asian countries.

In this study, we aimed to conduct an international survey to investigate the extent of overall agreement among clinicians in the Asia-Pacific region regarding the management of *H. pylori* infection.

2 | Methods

2.1 | Study Design

An international survey was developed by the Upper Gastrointestinal (GI) Focus Group of the Asian Pacific Association of Gastroenterology (APAGE)-Emerging Leaders Committee (ELC).

2.2 | Study Participants and Consent to Participate

An online questionnaire, consisting of 41 questions that focused on the management of *H. pylori* infection, was distributed to 98 clinicians who were members of APAGE-ELC or their colleagues. The study participants were provided with a hyperlink to the survey using e-mail or messaging applications, where they were informed of the study's purpose. Informed consent was obtained from each participant aged ≥ 18 years who agreed to participate in this study, with the assurance that declining to participate or withdrawal from the study would not result in any consequences. The clinicians could proceed to the questionnaire page only upon agreement to participate. The study ensured anonymity and confidentiality for all participants. Details of the questionnaire are described in Data S1.

Inclusion criteria compromised clinicians who were aged ≥ 18 years and agreed to participate. Exclusion criteria compromised those who did not meet the inclusion criteria, those who did not provide consent, or those who subsequently declined to participate.

2.3 | Objective

The primary objective of this study was to investigate the extent of overall agreement among clinicians in the Asia-Pacific region regarding the management of *H. pylori* infection.

2.4 | Ethics Approval

The study protocol was approved by the Ethical Committee of Osaka Metropolitan University Graduate School of Medicine on October 18, 2023 (approval number: 2023-084). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki for medical research involving human participants.

2.5 | Statistical Analysis

Data are expressed as the number of respondents and the percentage of responses from 98 clinicians. Between-group differences were compared using Pearson's chi-square or Fisher's exact tests. Statistical analyses were performed using IBM SPSS Statistics Version 26 software (IBM Corporation, Armonk, NY).

3 | Results

3.1 | Background of Respondents in the Asia-Pacific Region

All 98 participants consented to participate in the study and completed the questionnaire. Of these, respondents were from Japan (15, 15.3%), Hong Kong (15, 15.3%), Thailand (33, 33.7%), Vietnam (23, 23.5%), Malaysia (4, 4.1%), Singapore (3, 3.1%), India (2, 2.0%), Bangladesh (1, 1.0%), Cambodia (1, 1.0%), and the Philippines (1, 1.0%) (Figure 1a). The respondents were gastroenterologists (74.5%), general practitioners (10.2%), physicians (internists) (9.2%), surgeons (5.1%), and radiologists (1.0%) (Figure 1b). The respondents were affiliated with university hospitals (39.8%), public hospitals (33.7%), private hospitals (13.3%), private clinics (7.1%), or medical check-up institutions (6.1%) (Figure 1c). The

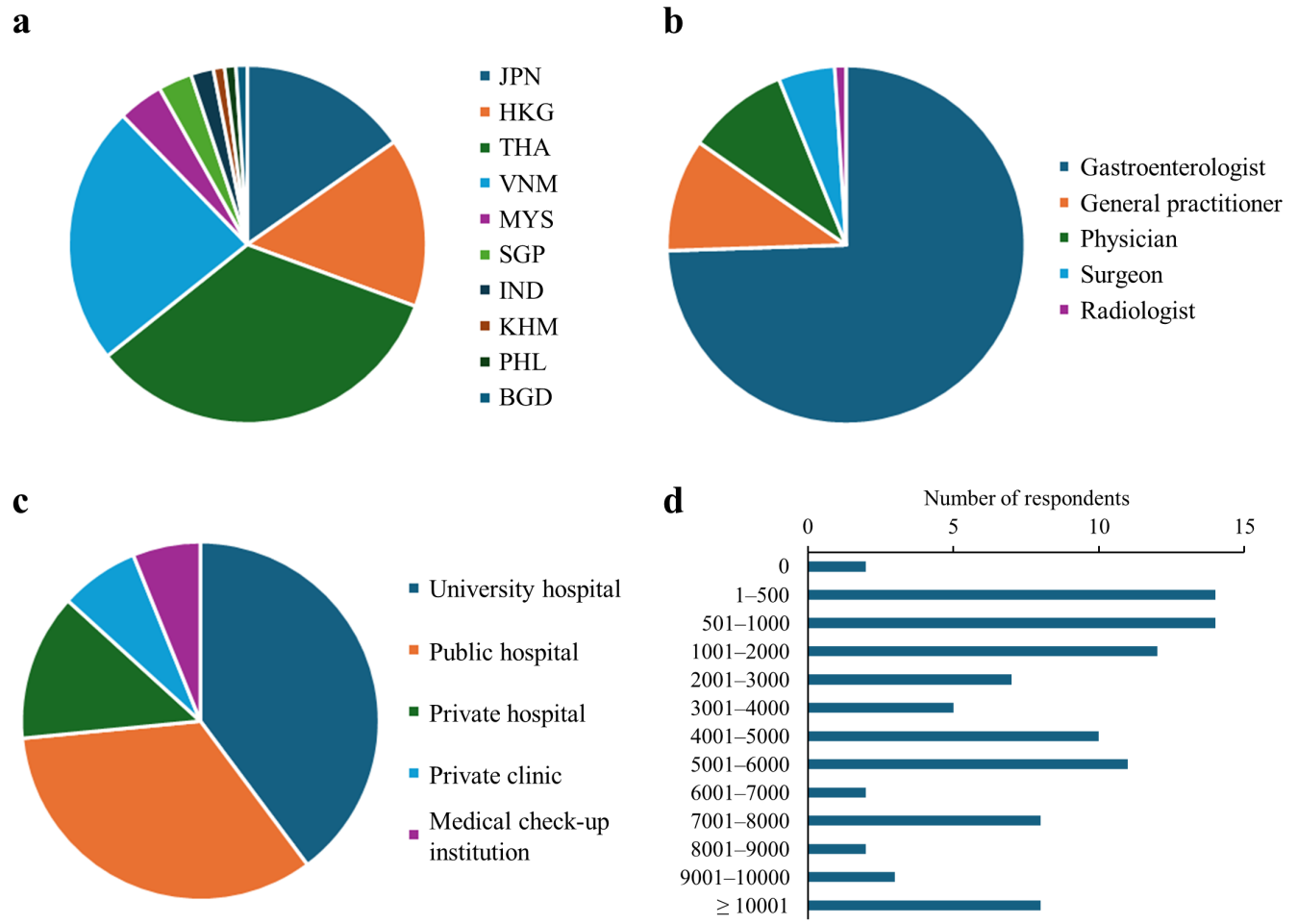

FIGURE 1 | Background of respondents in the Asia-Pacific region. (a) Country of residence, (b) specialty, (c) institution, (d) total number of upper gastrointestinal endoscopies performed in the last year. BGD, Bangladesh; HKG, Hong Kong; IND, India; JPN, Japan; KHM, Cambodia; MYS, Malaysia; PHL, Philippines; SGP, Singapore; THA, Thailand; VNM, Vietnam.

most common range for the total number of upper GI endoscopies performed annually was 1–500 (14.3%) and 501–1000 (14.3%) (Figure 1d). Prevalence data concerning the patients currently infected with *H. pylori* are presented in Data S2.

3.2 | Methods of *H. pylori* Diagnosis

One third of respondents (33.7%) typically performed a second test to diagnose *H. pylori* infection when the first test yielded negative results (Figure 2a). The urea breath test (UBT) was the most frequently used method for diagnosing *H. pylori* infection among 71 (72.4%) respondents (Figure 2b). Regarding assessing the clearance of *H. pylori* after eradication therapy, 28.6% of respondents usually performed a second test when the first test was negative (Figure 2c). The UBT was also the predominant choice for assessing clearance post-therapy among 90 (91.8%) respondents (Figure 2d). Furthermore, 35.7% of respondents reported experience in diagnosing non-*H. pylori* Helicobacter (NHPH) infection (Figure 2e). Among those familiar with diagnosing NHPH, histopathological examination was the most common diagnostic method for 17 (48.6%) respondents, followed by endoscopic findings for 13 (37.1%) respondents (Figure 2f).

3.3 | Regimens and Adverse Events of *H. pylori* Eradication Therapy

The most common drug combination for first-line eradication therapy was proton pump inhibitor (PPI), amoxicillin (AMPC), and CAM (64.3%) in total. The most common doses of AMPC and CAM were 2000 and 1000 mg (48.0%), and the most common duration was 14 days (70.4%). The most common drug combination for second-line eradication therapy was PPI, AMPC, and levofloxacin (LVX) (22.4%) in total. The most common doses of AMPC and LVX were 2000 and 500 mg (21.4%), and the most common duration was 14 days (67.3%). For third-line eradication therapy, the most commonly used regimen was PPI, bismuth, tetracycline, and MNZ (12.2%); PPI, bismuth, AMPC, and LVX (12.2%); or potassium-competitive acid blocker (PCAB), AMPC, and LVX (12.2%) in total. The most common treatment duration was 14 days (73.5%).

Common adverse events experienced during eradication therapy were diarrhea/loose stool, dysgeusia, dizziness, and stomach ache. The incidence of diarrhea/loose stool in Thailand was significantly lower than in other countries in first-line, second-line, and third-line eradication therapy (18.2% vs. 56.9%, respectively; $p < 0.001$; 12.1% vs. 49.2%, respectively; $p < 0.001$; 3.0% vs.

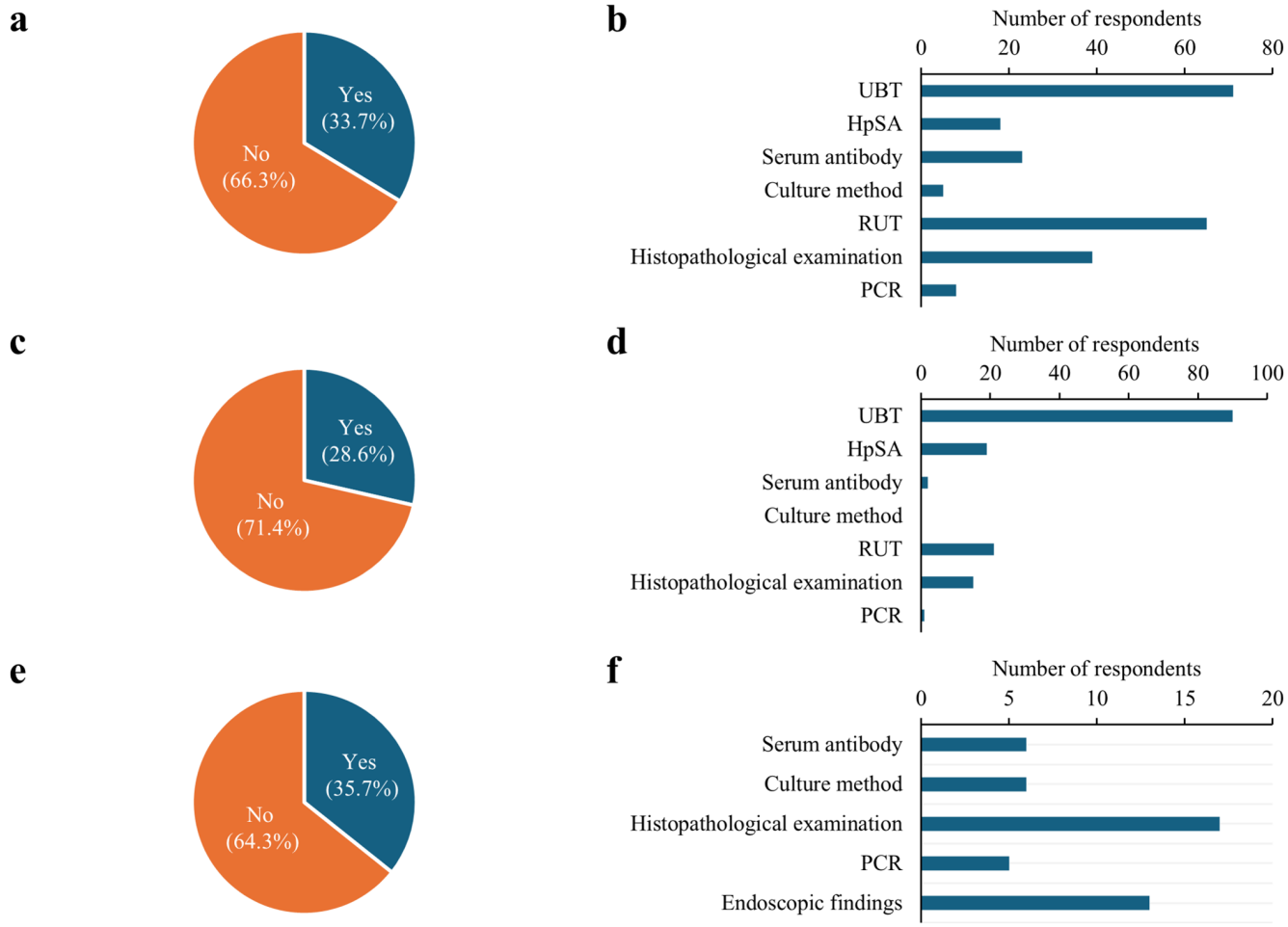

FIGURE 2 | Methods of *H. pylori* diagnosis in respondents' clinical practice. (a) A second test to diagnose *H. pylori* infection when the first test is negative, (b) tests commonly performed to diagnose *H. pylori* infection (select all that apply), (c) a second test to assess the clearance of *H. pylori* after eradication therapy when the first test is negative, (d) tests commonly used to assess the clearance of *H. pylori* after eradication therapy (select all that apply), (e) experience of diagnosing non-*H. pylori* Helicobacter (NHPH) infection, (f) tests to diagnose NHPH infection among respondents with experience in diagnosing NHPH infection (select all that apply). HpSA, *H. pylori* stool antigen test; PCR, polymerase chain reaction; RUT, rapid urease test; UBT, urea breath test.

49.2%, respectively; $p < 0.001$). No adverse events were significantly more reported in second-line and third-line eradication therapy than in first-line eradication therapy in total (23.5% vs. 14.3%, respectively; $p = 0.004$; 29.6% vs. 14.3%, respectively; $p = 0.001$) (Table 1).

3.4 | Timing of the Antibiotic Susceptibility Test and Measures to Prevent Adverse Events Through Eradication Therapy

Antibiotic susceptibility testing was deemed necessary prior to third-line eradication therapy in 60 (61.2%) respondents, prior to second-line eradication therapy in 14 (14.3%) respondents, and prior to first-line eradication therapy in 12 (12.2%) respondents (Figure 3a). In total, 57 (58.2%) respondents deemed allergy tests for allergic patients unnecessary prior to eradication therapy (Figure 3b). While 57 (58.2%) respondents considered that patients with chronic kidney disease (CKD) who were not undergoing dialysis should be treated with reduced doses of antibiotics for eradication therapy (Figure 3c), a similar proportion of respondents prescribed normal and reduced-dose antibiotics for patients with CKD who were receiving dialysis (Figure 3d). A minority of respondents (19.4%) routinely prescribed probiotics as part of eradication therapy (Table 2).

3.5 | Clinicians' Opinions Concerning Primary and Secondary Prevention of GC

In total, 80 (81.6%) of respondents considered that all asymptomatic patients currently infected with *H. pylori* should receive eradication therapy for primary prevention of GC. However, the proportion of Vietnamese respondents holding this view was significantly lower than that in other countries (34.8% vs. 96.0%, respectively; $p < 0.001$). Significantly more respondents from Japan considered upper GI endoscopy necessary prior to eradication therapy for asymptomatic young patients currently infected with *H. pylori*, compared with those in other countries (80.0% vs. 31.3%, respectively; $p = 0.001$). Eradication therapy for patients after endoscopic treatment for early GC was considered necessary by 86 (87.8%) of respondents. Of the total respondents,

TABLE 1 | Regimens and adverse events of *H. pylori* eradication therapy in respondents' clinical practice according to country.

	Total	JPN	HKG	THA	VNM	MYS	SGP	Others[a]
Number of respondents	98	15 (15.3)	15 (15.3)	33 (33.7)	23 (23.5)	4 (4.1)	3 (3.1)	5 (5.1)
Drug combinations most commonly used for first-line *H. pylori* eradication therapy								
PPI + AMPC + CAM	63 (64.3)	2 (13.3)	14 (93.3)	26 (78.8)	12 (52.2)	4 (100.0)	2 (66.7)	3 (60.0)
(Most common dose) PPI + AMPC 2000 mg + CAM 1000 mg	47 (48.0)	0 (0.0)	13 (86.7)	21 (63.6)	7 (30.4)	2 (50.0)	2 (66.7)	2 (40.0)
PCAB + AMPC + CAM	20 (20.4)	13 (86.7)	1 (6.7)	3 (9.1)	2 (8.7)	0 (0.0)	1 (33.3)	0 (0.0)
(Most common dose) PCAB + AMPC 1500 mg + CAM 400 mg	8 (8.2)	7 (46.7)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
PPI + bismuth + TC + MNZ	7 (7.1)	0 (0.0)	0 (0.0)	1 (3.0)	6 (26.1)	0 (0.0)	0 (0.0)	0 (0.0)
Others[b]	8 (8.2)	0 (0.0)	0 (0.0)	3 (9.1)	3 (13.0)	0 (0.0)	0 (0.0)	2 (40.0)
Days for first-line *H. pylori* eradication therapy								
7 days	20 (20.4)	15 (100.0)	1 (6.7)	2 (6.1)	1 (4.3)	0 (0.0)	0 (0.0)	1 (20.0)
10 days	9 (9.2)	0 (0.0)	0 (0.0)	4 (12.1)	3 (13.0)	0 (0.0)	1 (33.3)	1 (20.0)
14 days	69 (70.4)	0 (0.0)	14 (93.3)	27 (81.8)	19 (82.6)	4 (100.0)	2 (66.7)	3 (60.0)
Drug combinations most commonly used for second-line *H. pylori* eradication therapy								
PPI + AMPC + LVX	22 (22.4)	0 (0.0)	7 (46.7)	9 (27.3)	3 (13.0)	1 (25.0)	0 (0.0)	2 (40.0)
(Most common dose) PPI + AMPC 2000 mg + LVX 500 mg	21 (21.4)	0 (0.0)	7 (46.7)	9 (27.3)	3 (13.0)	0 (0.0)	0 (0.0)	2 (40.0)
PPI + bismuth + AMPC + MNZ	21 (21.4)	0 (0.0)	4 (26.7)	9 (27.3)	6 (26.1)	0 (0.0)	1 (33.3)	1 (20.0)
(Most common dose) PPI + bismuth + AMPC 2000 mg + MNZ 500 mg	16 (16.3)	0 (0.0)	2 (13.3)	8 (24.2)	4 (17.4)	0 (0.0)	1 (33.3)	1 (20.0)
PCAB + AMPC + MNZ	15 (15.3)	13 (86.7)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (20.0)
(Most common dose) PCAB + AMPC 1500 mg + MNZ 500 mg	14 (14.3)	13 (86.7)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
PPI + bismuth + AMPC + LVX	12 (12.2)	0 (0.0)	1 (6.7)	5 (15.2)	6 (26.1)	0 (0.0)	0 (0.0)	0 (0.0)
PPI + bismuth + TC + MNZ	7 (7.1)	0 (0.0)	2 (13.3)	2 (6.1)	1 (4.3)	0 (0.0)	1 (33.3)	1 (20.0)
Others[c]	21 (21.4)	2 (13.3)	1 (6.7)	8 (24.2)	6 (26.1)	3 (75.0)	1 (33.3)	0 (0.0)
Days for second-line *H. pylori* eradication therapy								
7 days	17 (17.3)	15 (100.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (20.0)
10 days	15 (15.3)	0 (0.0)	1 (6.7)	9 (27.3)	5 (21.7)	0 (0.0)	0 (0.0)	0 (0.0)
14 days	66 (67.3)	0 (0.0)	14 (93.3)	24 (72.7)	17 (73.9)	4 (100.0)	3 (100.0)	4 (80.0)
Drug combinations most commonly used for third-line *H. pylori* eradication therapy								
PPI + bismuth + TC + MNZ	12 (12.2)	0 (0.0)	4 (26.7)	4 (12.1)	2 (8.7)	1 (25.0)	1 (33.3)	0 (0.0)
PPI + bismuth + AMPC + LVX	12 (12.2)	0 (0.0)	1 (6.7)	7 (21.2)	3 (13.0)	1 (25.0)	0 (0.0)	0 (0.0)
PCAB + AMPC + LVX	12 (12.2)	2 (13.3)	1 (6.7)	5 (15.2)	1 (4.3)	1 (25.0)	1 (33.3)	1 (20.0)

(Continues)

TABLE 1 | (Continued)

	Total	JPN	HKG	THA	VNM	MYS	SGP	Others[a]
(Most common dose) PCAB + AMPC 2000 mg + LVX 500 mg	9 (9.2)	2 (13.3)	1 (6.7)	4 (12.1)	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)
PPI + AMPC + LVX	11 (11.2)	0 (0.0)	1 (6.7)	3 (9.1)	5 (21.7)	1 (25.0)	0 (0.0)	1 (20.0)
(Most common dose) PPI + AMPC 2000 mg + LVX 500 mg	8 (8.2)	0 (0.0)	1 (6.7)	3 (9.1)	4 (17.4)	0 (0.0)	0 (0.0)	0 (0.0)
PCAB + AMPC + STFX	10 (10.2)	9 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
PCAB + bismuth + AMPC + LVX	5 (5.1)	0 (0.0)	0 (0.0)	4 (12.1)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
PPI + bismuth + MNZ + LVX	4 (4.1)	0 (0.0)	1 (6.7)	0 (0.0)	3 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)
PPI + bismuth + MNZ + MINO	4 (4.1)	0 (0.0)	3 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
PPI + AMPC + STFX	3 (3.1)	3 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PPI + bismuth + AMPC + STFX	3 (3.1)	0 (0.0)	0 (0.0)	2 (6.1)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Others[d]	22 (22.4)	1 (6.7)	4 (26.7)	8 (24.2)	7 (30.4)	0 (0.0)	1 (33.3)	1 (20.0)
Days for third-line *H. pylori* eradication therapy								
7 days	11 (11.2)	9 (60.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
10 days	12 (12.2)	0 (0.0)	0 (0.0)	7 (21.2)	4 (17.4)	0 (0.0)	0 (0.0)	1 (20.0)
14 days	72 (73.5)	6 (40.0)	13 (86.7)	26 (78.8)	16 (69.6)	4 (100.0)	3 (100.0)	4 (80.0)
Others[e]	3 (3.1)	0 (0.0)	2 (13.3)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events commonly experienced with first-line *H. pylori* eradication therapy (select all)								
Diarrhea/loose stool	43 (43.9)	8 (53.3)	12 (80.0)	6 (18.2)	9 (39.1)	4 (100.0)	2 (66.7)	2 (40.0)
Dysgeusia	31 (31.6)	3 (23.1)	2 (13.3)	19 (57.6)	4 (17.4)	1 (25.0)	1 (33.3)	1 (20.0)
Dizziness	21 (21.4)	0 (0.0)	2 (13.3)	9 (27.3)	9 (39.1)	0 (0.0)	1 (33.3)	0 (0.0)
Stomach ache	20 (20.4)	1 (6.7)	6 (40.0)	6 (18.2)	4 (17.4)	0 (0.0)	3 (100.0)	0 (0.0)
None	14 (14.3)	5 (33.3)	1 (6.7)	2 (6.1)	4 (17.4)	0 (0.0)	0 (0.0)	2 (40.0)
Rash	12 (12.2)	2 (13.3)	2 (13.3)	1 (3.0)	4 (17.4)	1 (25.0)	1 (33.3)	1 (20.0)
Others[f]	40 (40.8)	2 (13.3)	4 (26.7)	8 (24.2)	21 (91.3)	1 (25.0)	3 (100.0)	1 (20.0)
Adverse events commonly experienced with second-line *H. pylori* eradication therapy (select all)								
Diarrhea/loose stool	36 (36.7)	7 (46.7)	9 (60.0)	4 (12.1)	9 (39.1)	3 (75.0)	3 (100.0)	1 (20.0)
None	23 (23.5)	4 (26.7)	5 (33.3)	8 (24.2)	3 (13.0)	1 (25.0)	0 (0.0)	2 (40.0)
Dysgeusia	19 (19.4)	1 (6.7)	1 (6.7)	8 (24.2)	4 (17.4)	0 (0.0)	2 (66.7)	3 (60.0)
Dizziness	17 (17.3)	0 (0.0)	1 (6.7)	5 (15.2)	10 (43.5)	0 (0.0)	1 (33.3)	0 (0.0)
Stomach ache	16 (16.3)	0 (0.0)	6 (40.0)	5 (15.2)	3 (13.0)	0 (0.0)	2 (66.7)	0 (0.0)
Rash	10 (10.2)	3 (20.0)	0 (0.0)	1 (3.0)	4 (17.4)	0 (0.0)	1 (33.3)	1 (20.0)
Others[g]	35 (35.7)	7 (46.7)	4 (26.7)	9 (27.3)	13 (56.5)	0 (0.0)	2 (66.7)	0 (0.0)
Adverse events commonly experienced with third-line *H. pylori* eradication therapy (select all)								
Diarrhea/loose stool	33 (33.7)	9 (60.0)	8 (53.3)	1 (3.0)	9 (39.1)	3 (75.0)	2 (66.7)	1 (20.0)
None	29 (29.6)	3 (20.0)	3 (20.0)	12 (36.4)	6 (26.1)	1 (25.0)	1 (33.3)	3 (60.0)
Dysgeusia	22 (22.4)	1 (6.7)	5 (33.3)	8 (24.2)	5 (21.7)	0 (0.0)	2 (66.7)	1 (20.0)

(Continues)

TABLE 1 | (Continued)

	Total	JPN	HKG	THA	VNM	MYS	SGP	Others[a]
Stomach ache	17 (17.3)	0 (0.0)	6 (40.0)	7 (21.2)	1 (4.3)	1 (25.0)	1 (33.3)	1 (20.0)
Dizziness	15 (15.3)	1 (6.7)	3 (20.0)	4 (12.1)	6 (26.1)	0 (0.0)	1 (33.3)	0 (0.0)
Others[h]	56 (57.1)	8 (53.3)	8 (53.3)	10 (30.3)	21 (91.3)	0 (0.0)	7 (233.3)	2 (40.0)

Note: Number of respondents (%).
Abbreviations: AMPC, amoxicillin; CAM, clarithromycin; HKG, Hong Kong; *H. pylori*, *Helicobacter pylori*; JPN, Japan; LVX, levofloxacin; MINO, minocycline; MNZ, metronidazole; MYS, Malaysia; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor; SGP, Singapore; STFX, sitafloxacin; TC, tetracycline; THA, Thailand; VNM, Vietnam.
[a]India, Bangladesh, Cambodia, and Philippines.
[b]PPI + bismuth + TC + TNZ; PPI + AMPC + CAM + MNZ.
[c]PCAB + AMPC + LVX; PPI + AMPC + MNZ; PPI + AMPC.
[d]PPI + bismuth + AMPC (2000 mg) + MINO (200 mg); PCAB + AMPC (2000 mg) + MINO (200 mg); PCAB + MNZ (500 mg) + LVX (500 mg); PCAB + bismuth + AMPC (1500 mg) + STFX (200 mg).
[e]Based on culture result; referred to gastroenterologist.
[f]Nausea, stomatitis, constipation, vomiting, glossitis, liver dysfunction, renal dysfunction, flushed face, appetite loss.
[g]Flushed face, constipation, stomatitis, nausea, liver dysfunction, renal dysfunction, vomiting, glossitis, tired, black stool, insomnia.
[h]Constipation, stomatitis, nausea, glossitis, rash, liver dysfunction, renal dysfunction, vomiting, flushed face, fever, bloody stool, headache.

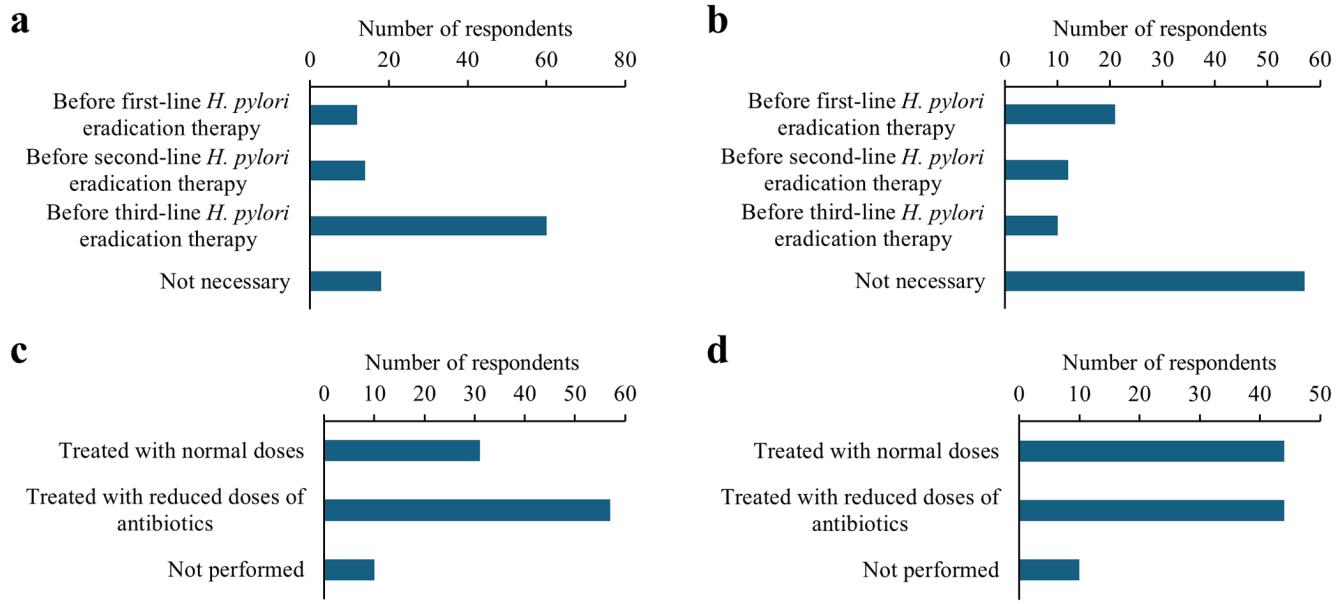

FIGURE 3 | Timing of the antibiotic susceptibility test and measures to prevent adverse events through eradication therapy in respondents' clinical practice. (a) When to perform an antibiotic susceptibility test before eradication therapy (select all that apply), (b) when to perform an allergy test (e.g., skin test, challenge test, or drug-induced lymphocyte stimulation test) prior to eradication therapy for allergic patients (select all that apply), (c) how to perform eradication therapy for patients with chronic kidney disease (CKD) who are not on dialysis, (d) how to perform eradication therapy for patients with CKD on dialysis. *H. pylori*, *Helicobacter pylori*.

81 (82.7%) considered GC screening through upper GI endoscopy useful for secondary prevention of GC (Table 2).

Of the total respondents, 54 (55.1%) considered that there should be no age limit for eradication therapy (Figure 4a), 49 (50.0%) considered there to be no need for follow-up for asymptomatic *H. pylori*-uninfected patients (Figure 4b), 52 (53.1%) considered there to be no need for follow-up upper GI endoscopies for patients with successful eradication therapy without IM (Figure 4c), 43 (43.9%) considered 12 months to be the most appropriate interval between upper GI endoscopies for patients with successful eradication therapy with IM (Figure 4d), 41 (41.8%) considered 12 months to be as the most appropriate interval between upper GI endoscopies for patients with successful eradication therapy after endoscopic treatment for early GC (Figure 4e), and 36 (36.7%) considered 6 months to be the most appropriate interval between upper GI endoscopies for patients currently infected with *H. pylori* after endoscopic treatment for GC (Figure 4f).

3.6 | Clinicians' Opinions Concerning Early GC Prevention in Minors

Screening tests to diagnose *H. pylori* infection in asymptomatic minors (aged ≤ 17 years) were deemed necessary by a significantly higher proportion of respondents in Japan than in other countries (80.0% vs. 21.7%, respectively; $p < 0.001$). The UBT was the most commonly performed screening test to diagnose *H. pylori* infection in asymptomatic minors, chosen by 65.3% of respondents. In total, 82 (83.7%) respondents considered upper GI endoscopy prior to eradication therapy unnecessary

TABLE 2 | Clinicians' opinions concerning primary and secondary prevention of GC according to country.

	Total	JPN	HKG	THA	VNM	MYS	SGP	Others[a]
Number of respondents	98	15 (15.3)	15 (15.3)	33 (33.7)	23 (23.5)	4 (4.1)	3 (3.1)	5 (5.1)
Routinely use probiotics for *H. pylori* eradication therapy in your practice								
Yes	19 (19.4)	5 (33.3)	0 (0.0)	0 (0.0)	12 (52.2)	0 (0.0)	0 (0.0)	2 (40.0)
No	79 (80.6)	10 (66.7)	15 (100.0)	33 (100.0)	11 (47.8)	4 (100.0)	3 (100.0)	3 (60.0)
All asymptomatic currently *H. pylori*-infected patients should receive *H. pylori* eradication therapy for primary prevention of GC								
Yes	80 (81.6)	13 (86.7)	15 (100.0)	32 (97.0)	8 (34.8)	4 (100.0)	3 (100.0)	5 (100.0)
No	18 (18.4)	2 (13.3)	0 (0.0)	1 (3.0)	15 (65.2)	0 (0.0)	0 (0.0)	0 (0.0)
Upper GI endoscopy prior to *H. pylori* eradication therapy is necessary for asymptomatic young patients currently infected with *H. pylori* (18–44 years)								
Yes	38 (38.8)	12 (80.0)	3 (20.0)	5 (15.2)	16 (69.6)	0 (0.0)	0 (0.0)	2 (40.0)
No	60 (61.2)	3 (20.0)	12 (80.0)	28 (84.8)	7 (30.4)	4 (100.0)	3 (100.0)	3 (60.0)
H. pylori eradication therapy is necessary for patients after endoscopic treatment for early GC is necessary								
Yes	86 (87.8)	14 (93.3)	14 (93.3)	26 (78.8)	21 (91.3)	3 (75.0)	3 (100.0)	5 (100.0)
No	12 (12.2)	1 (6.7)	1 (6.7)	7 (21.2)	2 (8.7)	1 (25.0)	0 (0.0)	0 (0.0)
Gastric cancer screening by upper GI endoscopy is useful for secondary prevention (early detection) of GC								
Yes	81 (82.7)	15 (100.0)	13 (86.7)	23 (69.7)	22 (95.7)	3 (75.0)	2 (66.7)	3 (60.0)
No	17 (17.3)	0 (0.0)	2 (13.3)	10 (30.3)	1 (4.3)	1 (25.0)	1 (33.3)	2 (40.0)
Screening tests to diagnose *H. pylori* infection is necessary for asymptomatic minors (aged ≤ 17 years)								
Yes	30 (30.6)	12 (80.0)	4 (26.7)	8 (24.2)	4 (17.4)	0 (0.0)	0 (0.0)	2 (40.0)
No	68 (69.4)	3 (20.0)	11 (73.3)	25 (75.8)	19 (82.6)	4 (100.0)	3 (100.0)	3 (60.0)
Upper GI endoscopy prior to *H. pylori* eradication therapy is necessary for asymptomatic minors currently infected with *H. pylori* (aged ≤ 17 years) is necessary								
Yes	16 (16.3)	2 (13.3)	2 (13.3)	4 (12.1)	5 (21.7)	0 (0.0)	1 (33.3)	2 (40.0)
No	82 (83.7)	13 (86.7)	13 (86.7)	29 (87.9)	18 (78.3)	4 (100.0)	2 (66.7)	3 (60.0)
H. pylori eradication therapy should be performed for asymptomatic minors currently infected with *H. pylori* (aged ≤ 17 years)								
Yes	63 (64.3)	11 (73.3)	11 (73.3)	26 (78.8)	6 (26.1)	3 (75.0)	1 (33.3)	5 (100.0)
No	35 (35.7)	4 (26.7)	4 (26.7)	7 (21.2)	17 (73.9)	1 (25.0)	2 (66.7)	0 (0.0)

Note: Number of respondents (%).
Abbreviations: GC, gastric cancer; GI, gastrointestinal; HKG, Hong Kong; *H. pylori*, *Helicobacter pylori*; JPN, Japan; MYS, Malaysia; SGP, Singapore; THA, Thailand; VNM, Vietnam.
[a]India, Bangladesh, Cambodia, and Philippines.

for asymptomatic minors currently infected with *H. pylori*. The proportion of respondents advocating eradication therapy for all asymptomatic minors currently infected with *H. pylori* was significantly lower in Vietnam than in other countries (26.1% vs. 76.0%, respectively; $p < 0.001$) (Table 2).

4 | Discussion

This survey for clinicians in Asian countries has highlighted the current situation and challenges in the management of *H. pylori*. As a non-invasive test with high sensitivity and specificity, the UBT was the most commonly used method for the diagnosis of *H. pylori* [16]. The *H. pylori* stool antigen test (HpSA) is also a non-invasive test with equivalent accuracy [17], but it is not as widely used as the UBT. When the first test result is borderline or inconsistent with endoscopic findings, a second test should be considered not to overlook patients infected with *H. pylori*. The rate of experience in diagnosing NHPH infection was 35.7%, which was higher than expected. Histopathological examination is the only method used to diagnose NHPH in general facilities. However, endoscopic findings characteristic of NHPH-induced gastritis, such as a white marbled appearance extending from the antrum to the

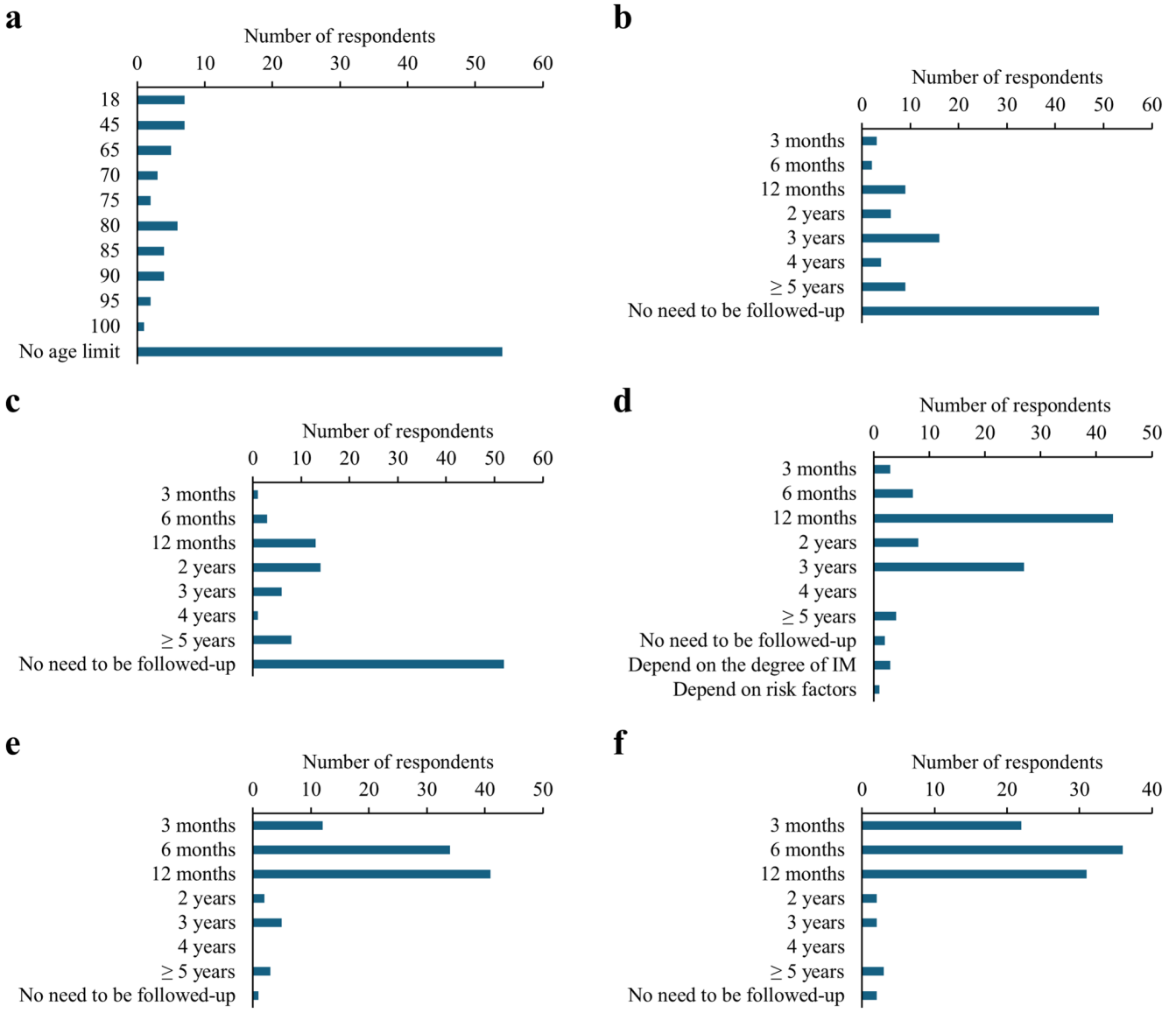

FIGURE 4 | Age limit for eradication therapy and the appropriate interval between upper gastrointestinal (GI) endoscopies. (a) Up to what age *H. pylori* eradication therapy should be performed, (b) appropriate interval between upper GI endoscopies for asymptomatic *H. pylori*-uninfected patients, (c) appropriate interval between upper GI endoscopies for patients with successful eradication therapy without intestinal metaplasia (IM), (d) appropriate interval between upper GI endoscopies for patients with successful eradication therapy with IM, (e) appropriate interval between upper GI endoscopies for patients with successful eradication therapy after endoscopic treatment for early gastric cancer (GC), (f) appropriate interval between upper GI endoscopies for currently *H. pylori*-infected patients after endoscopic treatment for early GC. IM, intestinal metaplasia.

angulus [18], cracked mucosa [19], and nodularity [20], are useful for diagnosing NHPH. Diagnostic methods, including polymerase chain reaction (PCR), culture in an acidic medium, and enzyme-linked immunosorbent assay specific to *Helicobacter suis*, have been developed to facilitate its diagnosis [21, 22].

The Maastricht VI/Florence consensus report recommends performing routine antibiotic susceptibility tests, even prior to first-line eradication therapy [23]. However, this study revealed that a susceptibility test prior to first-line *H. pylori* eradication therapy has not been fully adopted by clinicians and is most commonly performed before third-line eradication therapy. Recently, a molecular diagnosis kit for detecting CAM resistance using PCR from intragastric fluid has been made available [24], making antibiotic susceptibility tests easier to be performed. If individual susceptibility tests are not available, bismuth quadruple therapy (BQT) or CAM triple therapy is recommended as first-line eradication therapy in areas of low resistance to CAM [23]. In this study, the CAM triple therapy was observed to be the most commonly used first-line eradication therapy in most Asian countries. In contrast, a combination of PCAB, AMPC, and CAM was mainly used in Japan. The eradication rates have been improved by using PCAB in CAM triple therapy in Japan [25], where the rate of resistance to CAM is high but bismuth cannot be used. If CAM resistance is identified in advance, combination therapy with PCAB and AMPC is an effective treatment option [26], as AMPC has low resistance rates in the Asia-Pacific region [27]. When CAM triple therapy fails, BQT or LVX quadruple or triple therapy is recommended as second-line eradication therapy [23].

In this study, LVX triple therapy was most commonly used for second-line therapy, and BQT, LVX quadruple therapy, or LVX triple therapy using PCAB was the most commonly identified therapy for third-line eradication therapy.

Adverse events were observed significantly more in first-line therapy than in second-line and third-line eradication therapy, suggesting that CAM was most likely responsible for adverse events. The low incidence of diarrhea/loose stool in Thailand may be attributed to differences in the resistance of intestinal microbiota to antibiotic-induced diarrhea. Diarrhea/loose stool and stomach ache can be prevented through combining probiotics with eradication drugs [28 –30], and > 50% of respondents routinely used probiotics in Vietnam.

Of the respondents, > 50% of respondents considered allergy testing unnecessary prior to eradication therapy for allergic patients, suggesting that allergy testing is not mandatory and is performed based on the allergy history of each patient. Almost 50% of respondents considered using normal doses of antibiotics for patients with CKD undergoing dialysis. As AMPC is excreted through the kidney, the peak serum level increases threefold, and the AMPC half-life is prolonged in patients undergoing regular dialysis [31]. Eradication therapy with reduced doses of AMPC to half to one-third of the dose may be appropriate.

Eradication therapy has been mainly performed for peptic ulcers and *H. pylori*-related diseases in Southeast and South Asian countries; however, 81.6% of respondents considered that all asymptomatic patients infected with *H. pylori* should receive eradication therapy. Only 34.8% of respondents from Vietnam considered eradication therapy necessary for all asymptomatic patients infected with *H. pylori*, which is attributed to the low incidence of GC. The test and treat strategy is more appropriate to implement this strategy in specific areas and among ethnic groups with a high risk of GC [7]. Regarding eradication therapy for older adult patients, its effectiveness in preventing GC varies depending on the conditions of the gastric mucosa [32], but it has been reported to effectively prevent peptic ulcers for a short period after eradication therapy [33]. More than 60% of respondents considered that upper GI endoscopy before eradication therapy for asymptomatic young patients currently infected with *H. pylori* was not always necessary. While it is mandatory under the health insurance system in Japan, a country with a high GC incidence rate, other countries have different healthcare policies and medical resource limitations. Most respondents (87.8%) considered eradication therapy necessary for patients after endoscopic treatment for GC, despite the potential challenge of detecting metachronous recurrence [34]. Furthermore, 82.7% endorsed upper GI endoscopy for GC screening, highlighting its utility in secondary prevention. It is anticipated that national-level promotion of GC screening through endoscopy will expand beyond Japan and South Korea in the Asia-Pacific region.

Most respondents considered 12 months to be the most appropriate follow-up interval between upper GI endoscopies for patients after eradication therapy, including those with IM and those who had undergone endoscopic treatment for GC. In contrast, the preferred interval was 6 months for patients currently infected with *H. pylori* who had undergone endoscopic treatment for GC. The presence of IM has been reported to be a risk factor for the development of GC following eradication therapy [35, 36]; therefore, regular surveillance is necessary for patients with IM even after eradication therapy.

The UBT offers high diagnostic accuracy even in minors, but collecting samples from children can be challenging. Therefore, urinary antibody tests or HpSA tests are recommended for screening because of their low cost and ease of sample collection. While 69.4% of respondents disagreed in terms of screening tests for *H. pylori* infection in asymptomatic minors, 64.3% of respondents supported eradication therapy for asymptomatic minors currently infected with *H. pylori*. Test and treat strategies for minors have not reached sufficient consensus. However, eradication therapy not only reduces the risk of developing GC but also prevents the transmission of *H. pylori* infection to the next generation, and no serious adverse events have been reported among minors who have undergone eradication therapy to date [37–39].

This study has some limitations. The values in this study were compiled based on the declarations of clinicians from their clinical practice. Not all countries in the Asia-Pacific region were included, and the sample sizes for different countries were heterogeneous; therefore, bias was inevitable. However, this study reflects the real-world opinions of clinicians in the Asia-Pacific region regarding *H. pylori* infection, and these limitations do not alter our key messages.

In conclusion, a consensus is currently being reached among clinicians in relation to *H. pylori* management as the benefits of eradication therapy are increasingly recognized. It is anticipated that this study may serve as a new benchmark in preventive medicine and the prevalence of *H. pylori* will continue to decrease with the efforts of clinicians aiming to eradicate GC in the Asia-Pacific region.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.