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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of 7-Day Non-Bismuth Concomitant Quadruple Therapy for First-Line *Helicobacter pylori* Eradication in the Elderly

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Abstract

Background Aging may affect the efficacy of *Helicobacter pylori* eradication. The aim of our study was to assess the efficacy and safety of 7-day non-bismuth concomitant quadruple therapy as a first-line *H. pylori* infection eradication regimen in elderly individuals.

Methods We retrospectively analyzed a cohort with prospectively collected data from January 2013 to December 2019 at Chang Gung Memorial Hospital in Kaohsiung. There were 408 naive infected subjects aged 20 years or older who were treated with 7 days of concomitant therapy as a first-line *H. pylori* eradication regimen. We divided the patients into an elderly group (aged ≥ 65 years) and a control group (aged < 65 years). Two patients were lost during follow-up in the elderly group and 29 patients were lost in the control group, resulting in 56 in the ≥ 65-year age group and 321 in the control group. The patients were asked to perform urea breath tests 8 weeks later.

Results The eradication rates for the elderly and control groups were 93.1% (95% confidence interval (CI): 83.3–98.1) and 84.0% (95% CI 79.7–87.7) ($p = 0.070$), respectively, in the intention-to-treat analysis, and 96.4% (95% CI 87.6–99.6) and 91.6% (95% CI 88.0–94.4) ($p = 0.210$), respectively, in the per-protocol (PP) analysis. The adverse event rates were 8.9% in the elderly group and 12.8% in the control group ($p = 0.417$). The compliance was 100% in both groups. No significant difference was seen in antibiotic resistance in either group. Multivariate analysis revealed that metronidazole resistance (odds ratio (OR) 6.870, 95% CI 1.182–39.919, $p = 0.032$) and dual-therapy resistance (OR 7.188, 95% CI 1.326–38.952, $p = 0.022$) were independent factors for eradication failure.

Conclusions The efficacy of non-bismuth concomitant quadruple therapy in the elderly cohort was comparable with that in the non-elderly cohort for first-line *H. pylori* eradication with acceptable adverse effects.

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Key Points

In the per-protocol analysis, the efficacy of non-bismuth 7-day concomitant quadruple therapy was excellent in this Taiwanese elderly cohort for first-line *H. pylori* treatment.

The adverse event rates were similar between the elderly and control groups (8.9% vs. 12.8%, $p = 0.417$).

1 Introduction

Helicobacter pylori infection is correlated with a variety of potential complications, including atrophic gastritis, peptic ulcer disease, gastric adenocarcinoma, mucosal-associated lymphoid tissue lymphoma, iron deficiency anemia, and thrombotic thrombocytopenic purpura [1]. These complications contribute to a huge economic burden globally. An epidemiologic study reported a higher prevalence of *H. pylori* infection in elderly individuals, with a ratio of over 70% in patients with gastrointestinal diseases and a ratio of approximately 60% in asymptomatic patients [2]. Elderly patients with *H. pylori* infection suffer from more serious complications, resulting in higher hospitalization and mortality rates [3]. A long-term study has shown that eradication of *H. pylori* could prevent progression toward precancerous atrophic gastritis lesions, with a 77.2% reduction in patients from Matsu Island of Taiwan [4]. Nevertheless, older patients with a life expectancy of less than 5–10 years, especially those with moderate to severe gastric atrophy, may not benefit from the eradication of *H. pylori* to prevent gastric cancer [5]. Eradication of *H. pylori* still has benefits in the older population, who have a higher prevalence of the use of antiplatelet agents and nonsteroidal anti-inflammation drugs (NSAIDs). *H. pylori* testing and treatment are advisable for high-risk patients who are already long-term aspirin and NSAID users with the consequence of lower recurrent peptic ulcer bleeding [6, 7].

With aging, the change in lean body mass and body composition may increase the serum concentration of a drug and lengthen the half-life of a drug. Moreover, albumin levels may decrease with aging, which may cause elevated serum concentrations of free drug. The metabolism and elimination of drugs may also decrease with aging and some diseases. Multiple morbidities and polypharmacy are common in individuals who are elderly, and these patients may be at a higher risk of adverse drug reactions [8]. This could lead to decreased drug compliance and efficacy of medical therapy. In Taiwan, the prevalence of antibiotic resistance in *H. pylori* has been increasing over the years. However, few studies have assessed the issue of antibiotic resistance in elderly individuals. Non-bismuth concomitant therapy for 7 days was an alternative regimen in the Taiwan consensus [9]. It is convenient to be prescribed by clinicians and has been shown to work even when clarithromycin resistance was present [10, 11].

Therefore, the aim of our study was to compare the adverse effects and efficacy of 7-day non-bismuth concomitant quadruple therapy as a first-line *H. pylori* eradication regimen in patients aged ≥ 65 years and those aged < 65 years.

2 Materials and Methods

2.1 Ethics Statements

The data collection in this study was based on reviewing computerized medical charts. This study was approved by both the Institutional Review Board and Ethics Committee of Chang Gung Memorial Hospital, Taiwan, Permit number 202200941B0. None of our patients belonged to the minors/children age groups. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2 Questionnaire

A complete medical history and the patient's demographic data were obtained from each patient, and these data included age, sex, medical history, history of smoking, and alcohol consumption. Smoking was defined as the consumption of one pack or more cigarettes per week. Alcohol consumption was defined as drinking 1 glass or more per day. Adverse events were prospectively evaluated. The adverse events were assessed according to a 4-point scale system: none, mild (discomfort is annoying but is not interfering with daily life), moderate (discomfort is sufficient to interfere with daily life), and severe (discomfort is resulting in discontinuation of eradication therapy) [12]. Compliance was checked by counting unused medication at the completion of treatment. Poor compliance was defined as taking less than 80% of the total medication [13].

2.3 Patients

We conducted a retrospective study with prospectively collected data from January 2013 to December 2019 at Chang Gung Memorial Hospital in Kaohsiung. Patients with any positive results on a rapid urease test, histology, or culture confirmed the presence of *H. pylori.* The criteria for exclusion included the following: (1) previous surgery of the stomach, such as partial gastrectomy; (2) use of antibiotics within the preceding 4 weeks; (3) regular use of a proton pump inhibitor (PPI) or bismuth compounds (> 3 times per week) in the 28 days before enrollment; (4) presence of serious medical conditions, such as congestive heart failure, chronic kidney disease stage IV and V, and decompensated liver cirrhosis; (5) previously treated for *H. pylori* infection; (6) use of concomitant medication(s) known to interact with study medication, such as amiodarone, which could cause prolonged QTc after being given in combination with clarithromycin; (7) pregnancy or lactation; and (8) allergy to any medication in the study.

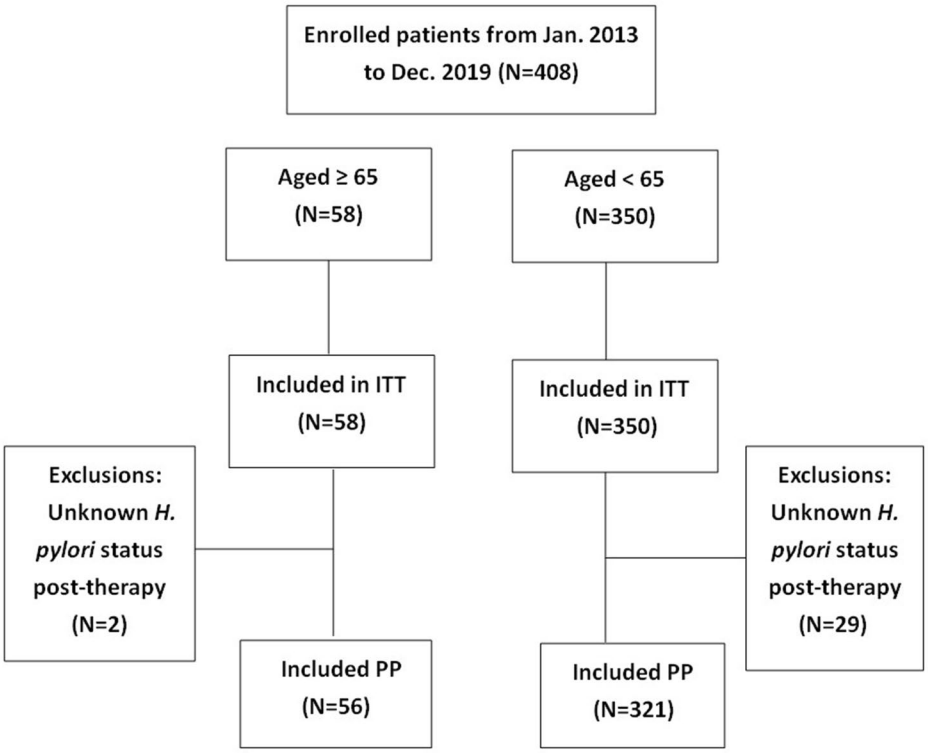


Fig. 1 Patient disposition. *ITT* intention-to-treat, *PP* per-protocol

There were 408 naive infected subjects aged 20 years or older who were treated with 7 days of concomitant therapy as a first-line *H. pylori* eradication regimen. We divided the patients into the elderly group (aged ≥ 65 years) and the control group (aged < 65 years). Two patients were lost during follow-up in the elderly group and 29 were lost in the control group, resulting in 56 in the ≥ 65-year age group and 321 in the control group (Fig. 1).

All patients were treated with 7-day non-bismuth quadruple therapy. The patients were treated with esomeprazole, 40 mg twice daily; amoxicillin, 1 g twice daily; metronidazole, 500 mg twice daily; clarithromycin, 500 mg twice daily for 7 days (EACM group, n = 183); lansoprazole-based regimen, 30 mg twice daily (LACM group, $n = 98$); dexlansoprazole MR-based regimen, 60 mg once daily (DACM group, n = 96).

2.4 Definition

Drug compliance was assessed by follow-up on the eighth day of treatment by reviewing any remaining medications. If patients failed to finish at least 80% of the medications, they were defined as having poor compliance [14]. Successful eradication of *H. pylori* was defined by a negative urea breath test performed at follow-up between 4 and 8 weeks after treatment. We also conducted additional analyses on the incidence of adverse events, including abdominal pain, constipation, diarrhea, dizziness, headache, nausea, vomiting, or skin rash during treatment.

2.5 Diagnosis of *H. pylori* Infection

2.5.1 Rapid Urease Test

The rapid urease test was performed according to our previous studies [15, 16]. Biopsy specimens taken from the antrum and corpus were placed immediately in 1 mL of a 10% solution of urea in deionized water (pH 6.8), and two drops of 1% phenol red solution were added. After this, the specimen was incubated at 37 °C for up to 2 h. If the yellowish color around the area of the specimen changed to a pink color in the following 2 h, this was considered a positive test.

2.5.2 Urea Breath Test (UBT)

^{13}C-urea breath test (UBT) was performed after a 4-h fast using the Proto Pylori kit (Princeton International Industries, Taiwan) containing 75 mg of ^{13}C-urea and additives (Mannitol powder 4,900 mg, and citric acid 25 mg). All samples were tested in duplicate and analyzed by an automated breath ^{13}C analyzer (IRIS® Infrared Red Isotope Analyzer, Germany). The results were obtained on *"delta over baseline* (DOB)*"*, which indicates the change in the $^{13}CO_2/^{12}CO_2$ ratio from the metabolic activity induced by administering the labeled urea. DOB values above 4.8%

were considered positive on the UBT. This UBT for *H. pylori* has an excellent sensitivity of 98% (95% confidence interval (CI) 96–99) and an excellent specificity of 95% (95% CI 92–97) after clinical data analysis.

2.5.3 Histologic Diagnosis

Giemsa staining was described by Gray et al. [17]. The 2- to 3-mm tissue samples were stored in 10% formalin and then fixed in paraffin. The paraffin sections of the tissue blocks were transferred to an adhesive-coated slide system. The sample slide was deparaffinized and hydrated in distilled water. The slide was incubated in fresh-made *H. pylori* solution for 30 min. The *H. pylori* solution was made by Giemsa stain solution (Sigma−Aldrich®) in distilled water (1:20) with 12.5% methanol. After rinsing in distilled water for a while, the slide was dehydrated with 95% alcohol instead of air dried. Finally, the slide was mounted and sealed with a coverslip to prevent drying, and the stain was evaluated under a microscope.

2.6 Culture and Antimicrobial Resistance

All stock cultures were maintained at −80 °C in Brucella broth (Difco Laboratories, Detroit, MI, USA) supplemented with 20% glycerol (Sigma Chemical, St. Louis, MO, USA). The passage number of the strains used in this study was five times; on average the the *H. pylori* strains were grown at 37 °C on brain heart infusion (Difco) plates containing 7% horse blood (Cocalico Biological, Reamstown, PA, USA) in a 12% CO_2 incubator under 100% relative humidity. The minimum inhibitory concentration (MIC) was determined using the agar dilution test [16, 18]. Susceptibility was tested using the E-test (AB Biodisck, Solna, Sweden). EUCAST breakpoint-defined resistance was defined as follows: MIC value ≥ 0.125 for amoxicillin, ≥ 0.5 for clarithromycin, ≥ 1 for levofloxacin, ≥ 1 for tetracycline, and ≥ 8 mg/L for metronidazole [19].

2.7 Statistical Analysis

The eradication rates, adverse events, patient compliance, and antibiotic resistance between the two groups were compared using the X^2 test with or without Yates correction for stability and Fisher's exact test when appropriate. Information on the eradication rates in both the intention-to-treat (ITT) and per-protocol (PP) analyses was assessed, and patients with unknown outcomes were counted as treatment failures. A p value < 0.05 was considered statistically significant. Finally, factors influencing treatment response with a p value < 0.1 were analyzed by logistic regression analysis. All analyses were performed using the Statistical Package for Social Sciences (IBM SPSS®, version 22.0 for Windows).

3 Results

3.1 Demographic Data

Table 1 shows the demographic data and endoscopic appearance of the two patient groups. The mean ages of the elderly and control groups were 69.9 ± 3.8 and 49.7 ± 10.7, $p <$ 0.001, respectively. The elderly patients' lifestyles were associated with less smoking (3.6% vs. 13.1%, $p = 0.041$) and alcohol drinking (8.9% vs. 20.6%, $p = 0.040$) than the control group. In addition, there was no significant difference between the two groups in terms of sex, history of peptic ulcer, or current endoscopic findings.

Table 1 Demographic data and endoscopic appearance of the two patient groups

Characteristics	Age ≥ 65 years *N* = 56, %	Age < 65 years *N* = 321, %	*p*-value
Age (years) (mean ± SD)	69.9 ± 3.8	49.7 ± 10.7	< 0.001
Gender (female/male)	25/31 (44.6/55.4)	169/152 (52.6/47.4)	0.269
Smoking	2 (3.6)	42 (13.1)	0.041
Alcohol consumption	5 (8.9)	66 (20.6)	0.040
Previous history of peptic ulcer	5 (8.9)	20 (6.2)	0.454
Endoscopic Findings			
Gastritis	20 (35.7)	159 (49.5)	
Gastric ulcer	18 (32.1)	76 (23.7)	0.134
Duodenal ulcer	11 (19.6)	65 (20.2)	
Gastric and duodenal ulcer	7 (12.5)	21 (6.5)	

SD standard deviation

3.2 Outcome

The major outcomes of the two groups are displayed in Table 2. The eradication rates for the elderly and control groups were 93.1% (95% CI 83.3–98.1) and 84% (95% CI 79.7–87.7) ($p = 0.070$) in the ITT analysis and 96.4% (95% CI 87.6–99.6) and 91.6% (95% CI 88.0–94.4) ($p = 0.210$) in the PP analysis. The adverse event rates were 8.9% in the elderly group and 12.8% in the control group ($p = 0.417$). Compliance was 100% in both groups. With regard to complications, the elderly group had comparable adverse effects to the control group in terms of abdominal pain (1.8% vs. 3.7%, $p = 0.460$), diarrhea (3.6% vs. 6.5%, $p = 0.391$), dizziness (0% vs. 1.6%, $p = 0.347$), headache (1.8% vs. 1.9%, $p = 0.966$), and nausea/vomiting (3.6% vs. 4.4%, $p = 0.787$) (Table 3).

3.3 Antibiotic Resistance

Culture and susceptibility data were available for 117 patients. Table 4 shows the details of antibiotic resistance between the two groups. The antibiotic resistance rates showed a higher trend in the non-elderly group than in the elderly group, but without a significant change. There was no difference between clarithromycin (9.5% vs. 18.8%, $p = 0.309$), levofloxacin (57.1% vs. 76.0%, $p = 0.078$), metronidazole (28.6% vs. 31.3%, $p = 0.810$), or dual resistance to clarithromycin and metronidazole (4.8% vs. 7.3%, $p = 0.677$) in the elderly and control groups, respectively. Zero resistance to amoxicillin and tetracycline was observed in both groups.

3.4 Clinical Factors Influencing the Efficacy of *H. pylori* Eradication

In univariate analysis of the clinical factors influencing the efficacy of *H. pylori* eradication, clarithromycin resistance ($p < 0.016$), metronidazole resistance ($p < 0.001$), and dual resistance to clarithromycin and metronidazole ($p < 0.001$) were factors in the control group (Table 5). Multivariate analysis revealed that metronidazole resistance (odds ratio (OR) 6.870, 95% CI 1.182–39.919, $p = 0.032$) and dual resistance (OR 7.188, 95% CI 1.326–38.952, $p = 0.022$) were independent factors for eradication failure (Table 6).

Table 2 The major outcomes in the two patient groups

	Age ≥ 65 years % (*n*)	Age < 65 years % (*n*)	*p*-value
Eradication rate (ITT)	93.1 (54/58)	84.0 (294/350)	0.070
Eradication rate (PP)	96.4 (54/56)	91.6 (294/321)	0.210
Adverse events	8.9 (5/56)	12.8 (41/321)	0.417
Compliance	100 (119/119)	100 (258/258)	–

ITT intention-to-treat, *PP* per-protocol

Table 3 Adverse events in the two patient groups

Adverse event	Age ≥ 65 years *N* = 56, %	Age < 65 years *N* = 321, %	*p*-value
Abdominal pain	1 (1.8)	12 (3.7)	0.460
Constipation	0	0	–
Diarrhea	2 (3.6)	21 (6.5)	0.391
Dizziness	0	5 (1.6)	0.347
Headache	1 (1.8)	6 (1.9)	0.966
Nausea/vomiting	2 (3.6)	14 (4.4)	0.787
Skin rash	0	0	–

Table 4 Antibiotic resistance in the two patient groups

	Age ≥ 65 years *N* = 21, %	Age < 65 years *N* = 96, %	*p*-value
Clarithromycin	2 (9.5)	18 (18.8)	0.309
Metronidazole	6 (28.6)	30 (31.3)	0.810
Levofloxacin	12 (57.1)	73 (76.0)	0.078
Amoxicillin	0	0	–
Tetracycline	0	0	–
Dual resistance to clarithromycin and metronidazole	1 (4.8)	7 (7.3)	0.677

4 Discussion

In a Korean nationwide multicenter retrospective study, it was reported that concomitant therapy has been the best regimen for first-line *H. pylori* eradication for the last 10 years in Korea [20]. In our study, the overall eradication rate was 92.3% (348/377) in the PP analysis, which is similar to the report from Korea [20]. Kobayashi et al. reported a comparable eradication rate between elderly and non-elderly groups in conventional triple therapy [21]. Our study showed that the efficacy of 7-day non-bismuth concomitant quadruple therapy was similar in elderly and non-elderly groups for first-line *H. pylori* eradication in the PP analysis (96.4% vs. 91.6%, $p = 0.210$). There was a trend for a higher eradication rate in the elderly group than in the non-elderly group in the ITT analysis (93.1% vs. 84.0%, $p = 0.070$). More patients dropped out of the treatment protocol in the non-elderly group, and this could be because elderly individuals seem to be more likely to obey the doctor's orders.

In a Bulgarian study [22], there were no significant differences in the resistance rates (metronidazole, clarithromycin, tetracycline, and levofloxacin) between subjects aged > 65

Table 5 Univariate analysis of the clinical factors influencing the efficacy of *H. pylori* eradication for each therapy

Principal parameter	Age ≥ 65 years			Age < 65 years		
	Case no.	Eradication rate (%)	*p*-value	Case no.	Eradication rate (%)	*p*-value
Sex						
Female	24/25	96.0	0.877	152/169	89.9	0.262
Male	30/31	96.8		142/152	93.4	
Smoking						
(−)	52/54	96.3	0.782	255/279	91.4	0.751
(+)	2/2	100.0		39/42	92.9	
Alcohol						
(−)	49/51	96.1	0.652	232/255	91.0	0.440
(+)	5/5	100.0		62/66	93.9	
Previous history of peptic ulcer						
(−)	50/51	98.0	0.172	274/301	91.0	0.162
(+)	4/5	80.0		20/20	100.0	
Eradication regimens						
EACM	23/23	100.0	0.059	147/160	91.9	0.983
LACM	18/18	100.0		73/80	91.3	
DACM	13/15	86.7		74/81	91.4	
Culture ($n = 117$)	($n = 21$)			($n = 96$)		
Amoxicillin						
Sensitive	21/21	100.0	–	85/96	88.5	-
Resistant	0	–		0	–	
Clarithromycin						
Sensitive	19/19	100.0	–	72/78	92.3	0.016
Resistant	2/2	100.0		12/18	72.2	
Metronidazole						
Sensitive	15/15	100.0	–	64/66	97.0	< 0.001
Resistant	6/6	100.0		21/30	70.0	
Dual resistance to clarithromycin and metronidazole						
(−)	20/20	100.0	–	83/89	93.3	< 0.001
(+)	1/1	100.0		2/7	28.6	

EACM esomeprazole 40 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg bid for 7 days; *LACM* lansoprazole 30 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg bid for 7 days; *DACM* dexilanprazole 60 mg qd, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg bid for 7 days; *qd* once per day; *bid* twice per day

Table 6 Multivariate analysis of the clinical factors influencing the efficacy of *H. pylori* eradication

Clinical factor	Coefficient	Standard error	Odds ratio (95% CI)	*p*-value
Metronidazole resistance	1.927	0.898	6.870 (1.182–39.919)	0.032
Dual resistance to clarithromycin and metronidazole	1.972	0.862	7.188 (1.326–38.952)	0.022

years and younger adults in 2011–2016. In China, a multicenter cohort study reported that people aged > 40 years were particularly associated with a higher risk of developing dual drug resistance to levofloxacin and metronidazole [23]. However, this study did not show a difference in drug resistance between the elderly and non-elderly groups, which was comparable with previous data ($n = 1369$) from three hospitals in southern Taiwan (shown in the Online Supplementary Material) [24]. In our study, the first-line eradication rate of non-bismuth concomitant quadruple therapy

for the non-elderly group decreased to 28.6% where there was dual resistance. It is therefore rational that metronidazole resistance and dual resistance to clarithromycin and metronidazole were independent factors of treatment failure in this study. Our previous study showed that high-dose metronidazole (1500–2000 mg in divided doses per day) may overcome metronidazole resistance [25–27]. However, a recent meta-analysis reported that concomitant therapy may also overcome the declining *H. pylori* eradication rate caused by metronidazole resistance [28]. As concomitant therapy, we prescribed only metronidazole 1000 mg per day to the patient, which might be insufficient to kill the bacteria when resistant strains exist. A higher dose of metronidazole is obviously needed in this situation. Therefore, looking for better substitutions is mandatory. A recent network meta-analysis indicated that high-dose dual therapy for 14 days appeared to be an alternative first-line therapy for *H. pylori* eradication among the Asian population with comparable efficacy and compliance, but caused fewer adverse events [29, 30]. In our study, diarrhea was the most common side effect, while adverse events were generally rare in both groups. The efficacy of the concomitant regimen was acceptable because it was greater than 90%. It may also have suggested that a shorter treatment duration (7 days) can reduce adverse effects and reach satisfactory results for elderly individuals.

A case-control study assessed the effect of a clarithromycin-based triple therapy among elderly patients and concluded that being elderly did not affect the efficacy or safety of this regimen for *H. pylori* eradication [31]. Zullo et al. found that a sequential regimen achieved higher eradication rates than standard triple therapy, and there were also minor adverse effects (< 12%) in the elderly individuals [32]. A retrospective investigation of 1271 cases of *H. pylori* infection in the elderly indicated that the rate of adverse effects with both first- and second-line treatments using triple therapy was < 10%, suggesting that clinicians need not withhold treatment strictly based on old age [21]. However, we still paid more attention to drug-drug interactions with clarithromycin co-treatment [33].

UBT is considered the gold standard and the first choice of a noninvasive method for checking *H. pylori* infection status, with wide availability and high accuracy [34]. However, the mean UBT values were found to significantly increase with age [35], and the threshold value should be adjusted in each setting. In this study, the product-description optimization cutoff values for the UBT with aging are not available. The possible mechanisms of higher threshold values in elderly people could be impairment of gastric emptying or lower endogenous CO_2 production compared to younger people [36]. Severe gastric mucosal atrophy and intestinal metaplasia are also influencing factors for false positivity on the UBT [37].

There are some limitations to this study. First, it is a retrospective study that may have some missing data, including details on the current medication of each patient, and the effect of drug-drug interactions cannot be predicted precisely, especially in elderly patients with more underlying comorbidities. A rapid urease test may be insufficient to diagnose *H. pylori* infections since more elderly patients have atrophic gastritis, which results in false-negative reactions. Patients with atrophic gastritis may have fewer *H. pylori* bacteria. A combination of other tests, such as the UBT, *H. pylori* antigen stool test, or biopsy, can also be utilized to confirm the status of *H. pylori* [38].

In conclusion, the efficacy of non-bismuth concomitant quadruple therapy in the elderly cohort was comparable to that in the non-elderly cohort for first-line *H. pylori* eradication with acceptable adverse effects. Metronidazole resistance alone and dual resistance to metronidazole and clarithromycin were independent factors for eradication failure.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-022-00990-7.

Declarations

Conflicts of interest T-LM, W-CT, S-SL, C-CY, C-ML, S-KC declare that they have no commercial association, such as consultancies, stock ownership or other equity interests or patent-licensing arrangements.

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Author contributions S-K Chuah and C-M Liang participated in the design of the study, coordinated the study, and performed the statistical analysis. T-L Ma wrote the manuscript. S-S Loke, C-C Yao, and W-C Tai contributed with administrative, technical, and/or material support. All authors have read and approved the manuscript.

Data availability statement The data that support the findings of this study are available from the corresponding author on request. The data are not publicly available due to privacy or ethical restrictions.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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