

## Comparison of 10 day bismuth quadruple therapy with high-dose metronidazole or levofloxacin for second-line *Helicobacter pylori* therapy: a randomized controlled trial

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**Objectives:** This prospective study was designed to compare the efficacies of levofloxacin-containing and high-dose metronidazole-containing quadruple therapies after failure of standard triple therapies.

**Methods:** A total of 150 *Helicobacter pylori*-infected patients were enrolled in our study and randomly assigned to levofloxacin-containing quadruple therapy (EBTL group) (40 mg of esomeprazole twice daily, 300 mg of bismuth subcitrate four times daily, 500 mg of tetracycline four times daily and 500 mg of levofloxacin once daily for 10 days) ( $n=76$ ) or high-dose metronidazole-based quadruple therapy (EBTM group) (40 mg of esomeprazole twice daily, 300 mg of bismuth subcitrate four times daily, 500 mg of tetracycline four times daily and 500 mg of metronidazole four times daily for 10 days) ( $n=74$ ). Follow-up endoscopy or urea breath test was done 16 weeks later to assess the treatment response. Patients' responses, CYP2C19 genotypes and antibiotic resistances were also examined. All participants, caregivers and those assessing the outcomes were blinded to group assignment.

**Results:** Intention-to-treat analysis revealed that both groups showed similar eradication rates: EBTL, 78.9% (60/76) (95% CI 69.7%–88.1%) and EBTM, 79.7% (59/74) (95% CI 70.5%–88.7%) [risk ratio (RR) 0.97, 95% CI 0.44–2.14]. Per-protocol results were EBTL=87.0% (60/69) (95% CI 79.4%–94.9%) and EBTM=90.8% (59/65) (95% CI 83.8%–97.8%) (RR 0.68, 95% CI 0.23–2.0). We did not find significant differences in compliance (RR 0.5, 95% CI 0.54–2.3) and adverse events (RR 1.11, 95% CI 0.54–2.3) between the two groups. Logistic regression analysis showed that only compliance was an important predictor for eradication failure. CYP2C19 polymorphism did not influence the eradicating effect.

**Conclusions:** The 10 day bismuth quadruple therapies with high-dose metronidazole or levofloxacin were effective even in areas with high resistance. These two therapies were equally safe and tolerated. Besides this, the metronidazole-containing therapy was cheaper. So it is persuasive that high-dose metronidazole-containing quadruple therapy could be a good choice for second-line *H. pylori* eradication in areas with high resistance.

**Keywords:** *H. pylori*, rescue therapy, CYP2C19

## Introduction

The 7 day triple therapy of proton pump inhibitor (PPI), amoxicillin and clarithromycin has been the recommended first-line therapy for *Helicobacter pylori* infection.<sup>1</sup> However, the failure rate of triple anti-*H. pylori* therapies has increased up to 30% due to the rapid increasing prevalence of clarithromycin-resistant strains.<sup>2,3</sup> Therefore, the Maastricht IV Consensus has recommended that clarithromycin should not be used in areas with 15%–20% *H. pylori* clarithromycin-resistant strains.

Approaches to overcoming drug resistance include increasing the dosage and treatment duration of drugs, using multiple drugs or pre-treatment with agents to reduce the bacterial load (e.g. probiotics, PPIs or bismuth). The better strategy of second-line therapy has focused on quadruple therapy.

Recently, fluoroquinolones have been used in the treatment of *H. pylori* infection both as first-line<sup>4,5</sup> and second-line<sup>4,6</sup> therapy. However, the rapid increase in fluoroquinolone resistance has made this approach difficult in many areas.<sup>7–9</sup> On the other hand, previous studies have shown that a high dose (1500 mg/day) of metronidazole might overcome resistance.<sup>10,11</sup>

This study was designed to survey the efficacy of bismuth quadruple therapies containing levofloxacin or high-dose metronidazole in second-line *H. pylori* infection.

## Methods

### Participants

The treatment group was any patient visiting the gastroenterological clinics of Kaohsiung Medical University Hospital (KMUH) and Kaohsiung Veteran General Hospital (KVGH) between June 2009 and March 2011 with the complaint of dyspepsia. These *H. pylori*-infected patients received first-line eradication therapies with a standard triple regimen (40 mg of esomeprazole twice daily, 500 mg of clarithromycin twice daily and 1 g of amoxicillin twice daily). All of the patients underwent endoscopic examination with biopsy of the gastric mucosa or a [<sup>13</sup>C] urea breath test to establish *H. pylori* infection status after previous eradication. The eradication-failure patients were then enrolled for this study after signing informed consent. Exclusion criteria included (i) ingestion of antibiotics, bismuth or PPI within the prior 4 weeks; (ii) patients with allergic history to the medications used; (iii) patients with previous gastric surgery; (iv) the coexistence of serious concomitant illness; and (v) pregnant women.

### Questionnaire

The questionnaire contained questions regarding personal history of smoking. Compliance was defined as good (taken more than 80% of the total medication) or poor. Adverse events included abdominal pain, diarrhoea, constipation and dizziness, among others.

### Diagnosis of *H. pylori* infection

#### Pathological examination

Biopsy specimens were rubbed on the surface of a Columbia blood agar plate and then incubated at 35°C under microaerobic conditions for 4–5 days. This detailed procedure was reported in our previous study.<sup>12</sup> The specimens were interpreted and reported on by the same pathologist.

#### Rapid urease test

The results of CLO tests (Delta West Bentley, WA, Australia) were interpreted as positive if the colour of the gel turned pink or red 6 h after examination at room temperature.

#### [<sup>13</sup>C] urea breath test

The [<sup>13</sup>C] urea was manufactured by the Institute of Nuclear Energy Research, Taiwan. The detailed procedure was reported in our previous study.<sup>12</sup>

### Culture and antimicrobial resistance

One antral gastric biopsy specimen was obtained for isolation of *H. pylori*. The detailed procedure was reported in our previous study.<sup>12</sup> The strains were tested for resistance to tetracycline, metronidazole, amoxicillin and levofloxacin by using the Etest (bioMérieux Diagnostics, France). Strains with MICs >4 mg/L, >8 mg/L, >0.5 mg/L and >1 mg/L were considered to be resistant to tetracycline, metronidazole, amoxicillin and levofloxacin, respectively.

### Analysis of CYP2C19 genotypes

All enrolled patients' peripheral blood leucocytes were obtained before the eradication therapy was begun. DNA was extracted from the leucocytes with a commercially available kit (QIAGEN K.K., Tokyo, Japan) and stored until use. The detailed procedure was reported in our previous study.<sup>6</sup>

### Interventions

We included 150 cases (50 men and 100 women; mean age 53.7 ± 12.5 years, range 22–74 years). They were interviewed by a trained interviewer who used a standardized questionnaire to obtain demographic data and medical history. The participants were randomly assigned to two groups treated with bismuth quadruple therapies: the levofloxacin-containing group (EBTL group) (40 mg of esomeprazole twice daily, 300 mg of bismuth subcitrate four times daily, 500 mg of tetracycline four times daily and 500 mg levofloxacin once daily for 10 days) or the metronidazole-containing group (EBTM group) (40 mg of esomeprazole twice daily, 300 mg of bismuth subcitrate four times daily, 500 mg of tetracycline four times daily and 500 mg of metronidazole four times daily for 10 days). Patients were asked to return during the second week to assess drug compliance and adverse effects. Endoscopy with biopsy for the rapid urease test, histology and culture was repeated 16 weeks later to confirm *H. pylori* infection status. The urea breath test was used for patients who refused follow-up endoscopy. The technicians who performed the *H. pylori* tests (culture, rapid urease test and urea breath test) or filled in the questionnaires, as well as the pathologists, were blinded to the eradication regimens the patients received. This study was approved by the Institutional Review Board and Ethics Committee of Kaohsiung Medical University Hospital.

### Outcomes

The primary endpoint of our study was successful eradication of *H. pylori*. There were additional analyses about adverse events during therapies.

### Randomization

A computer-generated randomization list was drawn up by the statistician and given to our assistant responsible for randomization. In addition, we used a method of combined blocking and stratified randomization to

make sure of a close balance of the numbers and patients' characteristics in each group. We set separate randomization within each of two subsets of participants (age and sex). We also set a block of every 10 participants. The collaborating doctors found the patients suitable for enrolment into this study and allocated the next available number on entry into the trial, and then each patient collected the tablets directly from the hospital pharmacy. The code was revealed to the researchers once recruitment, data collection and laboratory analyses were complete. All study participants and doctors except the data monitoring committee were blinded to treatment assignment for the duration of this study. The data monitoring committee did not contact participants.

Statistical analysis

Design

Assuming that the eradication rate of the levofloxacin-containing group was 75%, and the high-dose metronidazole-containing group achieved a 90% eradication rate, a 15% increase, our statistical power in this study is 81% under the sample size of about 75 subjects in each group and the two-sided *P* value is 0.05 if 95% of patients completed the follow-up.

Data analyses

The distribution of gender and the initial endoscopic diagnosis between subjects in the EBTM and EBTL groups were compared by  $\chi^2$  statistics. The same method was applied to compare the efficacy and the frequency of side effects of the two regimens. The analysed efficacy outcome was cure of *H. pylori* infection. The difference in ages in the two groups was examined using Student's *t*-test. To determine the predictors affecting the treatment response, clinical and bacterial parameters were analysed by logistic regression analysis. A two-sided *P* value <0.05 was considered statistically significant. The data were analysed using the SAS statistical package; all *P* values were two-sided.

Eradication rates were evaluated by intention-to-treat (ITT) and per-protocol (PP) analyses. ITT analysis included all randomly assigned patients. Patients whose infection status was unknown following treatment were considered treatment failures for the purposes of ITT analysis. The PP analysis excluded patients with unknown *H. pylori* status following therapy and those with major protocol violations.

Results

Characteristics of the study groups

A total of 812 *H. pylori*-infected patients received first-line eradication therapies with standard triple regimens. *H. pylori* eradication was achieved in 643 (79.2%) subjects. A total of 150 eradication failure patients were enrolled in our study and randomly assigned to the EBTL group (*n*=76) or EBTM group (*n*=74). The clinical characteristics of patients at entry are summarized in Table 1. Among the subjects, two patients retracted their permission after randomization to the EBTL group. The subjects were all included in the ITT analysis for *H. pylori* eradication. Besides this, five with poor compliance and nine lost to follow-up were excluded from PP analysis. Figure 1 summarizes patient distribution.

**Table 1.** Demographic distribution of the subjects receiving different eradication regimens

Characteristics	EBTL	EBTM	RR (95% CI)
Number	76	74	
Gender (male/female)	25/51	25/49	0.961 (0.487–1.895)
Age (years), mean $\pm$ SD	55.4 $\pm$ 12.4	52.8 $\pm$ 11.3	0.981 (0.955–1.009)
Smoking	8	10	1.332 (0.493–3.596)
Endoscopic findings	63	58	1.074 (0.799–1.443)
gastritis	27	26	
GU	13	11	
DU	20	16	
GU+DU	1	2	
polyp	2	1	
other	0	2	
Endoscopy follow-up (number)	50	46	0.854 (0.438–1.665)

DU, duodenal ulcer; GU, gastric ulcer.

Eradication of *H. pylori*

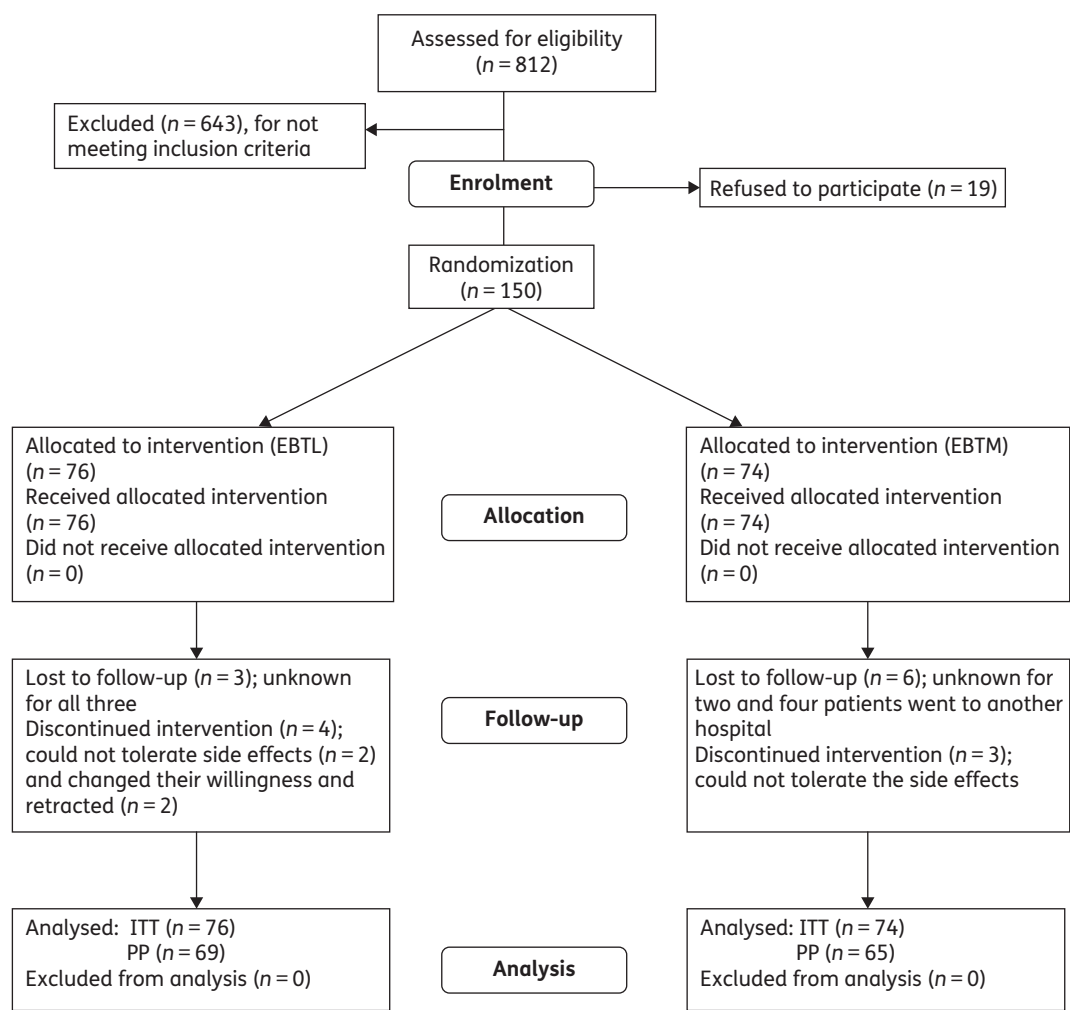
Table 2 lists the eradication rates of the EBTM and EBTL groups. ITT analysis revealed that both groups showed similar eradication rates: EBTL 78.9% (60/76) (95% CI 69.7%–88.1%) and EBTM 79.7% (59/74) (95% CI 70.5%–88.7%) [risk ratio (RR) 0.97, 95% CI 0.44–2.14]. PP results were EBTL 87.0% (60/69) (95% CI 79.4%–94.9%) and EBTM 90.8% (59/65) (95% CI 83.8%–97.8%) (RR 0.68, 95% CI 0.23–2.0). We did not find significant differences in compliance (RR 0.5, 95% CI 0.54–2.3) and adverse events (RR 1.11, 95% CI 0.54–2.3) between the two groups.

Factors influencing efficacy of anti-*H. pylori* therapy

Table 3 lists the clinical and bacterial factors that might predict the efficacy of eradication therapy. The eradication rates were significantly related to drug compliance (RR 12.4, 95% CI 1.821–84.447). Besides this, the CYP2C19 genotype and antibiotic resistances were not a significant risk factor in this study.

Antibiotic resistance

*H. pylori* strains were isolated from 46 of all enrolled patients who underwent bacterial culture in initial endoscopy. No strain developed resistance to tetracycline. Metronidazole-, amoxicillin-, clarithromycin- and levofloxacin-resistant strains were found in 58.7% (27/46) (95% CI 44.5%–72.9%), 4.3% (2/46) (95% CI 0%–10.2%), 45.7% (21/46) (95% CI 31.3%–60%) and 28.3% (13/46) (95% CI 15.2%–41.3%) of patients, respectively. Eight patients (four patients in the EBTL group and four in the EBTM group) did not have any resistance. Two of them had eradication failure—the genotypes were homozygous extensive metabolizer (1) and heterozygous extensive metabolizer (1).



**Figure 1.** Flow diagram of 10 day bismuth quadruple therapy with either high-dose metronidazole or levofloxacin for second-line *H. pylori* therapy. The diagram includes detailed information on the excluded participants.

**Table 2.** Outcomes of EBTL and EBTM quadruple therapies

	EBTL (95% CI)	EBTM (95% CI)	RR (95% CI)
Eradication rate			
ITT <sup>a</sup>	78.9% (60/76) (69.7%–88.1%)	79.7% (59/74) (70.5%–88.7%)	0.97 (0.44–2.14)
PP	87.0% (60/69) (79.4%–94.9%)	90.8% (59/65) (83.8%–97.8%)	0.68 (0.23–2.0)
compliance	94.5% (69/73) (89.3%–99.7%)	97.2% (69/71) (93.4%–100%)	0.5 (0.54–2.3)
side effects	27.4% (20/73) (17.2%–37.6%)	29.6% (21/71) (19%–40.2%)	1.11 (0.54–2.3)

<sup>a</sup>In this analysis, patients with unknown outcomes are counted as treatment failures.

### Genotypes of CYP2C19

A total of 81 patients underwent CYP2C19 genotype analysis: (i) 38 patients were homozygous extensive metabolizers (46.9%); (ii) 32 patients were heterozygous extensive metabolizers (39.5%); and (iii) 11 patients were poor metabolizers (13.6%). We did not find a significantly different cure rate among the three genotypes.

### Adverse events and complications

The incidence of adverse events in two groups was similar [EBTL 27.4% versus EBTM 29.6% (RR 1.11, 95% CI 0.54–2.3)]. Headache was the most common adverse event in all patients. The most common adverse event was dizziness in the EBTL group, while abdominal pain, headache and nausea were most common in the EBTM group (Table 4). We found the patients

**Table 3.** Logistic regression model analysis of the clinical factors influencing the efficacy of *H. pylori* eradication therapy

Parameters	Number of patients	Eradication rate	RR (95% CI)
CYP2C19 genotype (homozygous extensive metabolizer)	33	84.8% (28/33)	1.214 (0.319–4.623)
Resistance to metronidazole	26	84.6% (22/26)	0.727 (0.139–3.803)
Resistance to levofloxacin	12	91.7% (11/12)	0.348 (0.037–3.26)
Age (years)			1.812 (0.598–5.498)
<60	96	90.6% (87/96)	
≥60	38	84.2% (32/38)	
Sex			0.516 (0.174–1.528)
male	44	84.9% (37/44)	
female	90	91.1% (82/90)	
Smoker			2.364 (0.577–9.677)
–	115	90.4% (104/115)	
+	15	80% (12/15)	
Compliance			12.4 (1.821–84.447)
good	128	96.7% (124/128)	
poor	7	71.4% (5/7)	
Side effects			0.158 (0.02–1.252)
+	39	97.4% (38/39)	
–	91	85.7% (78/91)	

**Table 4.** Adverse events<sup>a</sup> of EBTL and EBTM quadruple therapies

	EBTL (n=76)	EBTM (n=74)	RR (95% CI)
Abdominal pain	4	8	2.19 (0.629–7.629)
Diarrhoea	4	1	0.246 (0.027–2.261)
Constipation	1	1	1.029 (0.063–16.767)
Headache	7	8	1.197 (0.41–3.496)
Anorexia	1	2	2.087 (0.185–23.542)
Nausea	4	8	2.19 (0.629–7.629)
Vomiting	1	2	2.087 (0.185–23.54)
Skin rash	2	0	0
Dizziness	9	4	0.425 (0.125–1.448)
Bad taste	3	4	1.393 (0.3–6.459)
Fatigue	5	4	0.812 (0.209–3.155)
Other	4	3	0.761 (0.164–3.528)

<sup>a</sup>The numbers of patients who suffered from mild, moderate and severe adverse events.

taking drugs completely might have more side effects, but the eradication rates were better.

Discussion

In our study we did not find obviously different success rates between these two regimens (PP: EBTL 87.0% versus EBTM 90.8%, *P*=0.48). There were also no obvious differences in compliance and side effects between the two groups. The efficacies of the two quadruple therapies used in our study were similar, as in previous reports,<sup>13–15</sup> and could be regarded as effective regimens.<sup>16</sup> The results revealed that bismuth quadruple therapies with levofloxacin or high-dose metronidazole were effective in areas with high resistance.

Resistance to antibiotics (especially clarithromycin) has been shown to increase in patients who failed standard therapies. A susceptibility test could provide important information to avoid drug resistance. But whether or not susceptibility testing prior to second-line treatment is useful remains controversial.<sup>17,18</sup> Amoxicillin and tetracycline resistance are usually rare in most regions, and our results revealed similar findings.<sup>19,20</sup> The efficacy of tetracycline would be improved by combining it with a PPI.<sup>21,22</sup> The possible useful methods to achieve higher success rates in rescue therapies include increasing the dose, prolonging the duration, using multiple drugs or pre-treatment with agents to reduce the bacterial load, which would make survival of the minor populations less likely. Our previous study also found that the efficacy of eradication in concomitant therapy is not influenced by dual resistance in Taiwan.<sup>23</sup>

According to the Maastricht IV suggestions, standard second-line therapy should contain metronidazole. The efficacy of traditional metronidazole-containing quadruple therapy varied markedly, from 37% to 91%.<sup>24–27</sup> These heterogeneous results may be related to the variation of metronidazole resistance. Previous studies revealed that quadruple therapy was shown to be effective after 4 days in metronidazole-sensitive strains where resistant strains needed at least the full 7 day treatment.<sup>28,29</sup> It has been suggested that longer metronidazole usage may overcome the negative influence of metronidazole resistance.<sup>30–32</sup> Therefore, we used high-dose metronidazole (2000 mg/day), a longer period (10 days) and multiple drugs (quadruple) in this study.

Physicians have used levofloxacin instead of metronidazole in recent years. In fact, the resistance rate of quinolones is increasing.<sup>6</sup> Resistance to fluoroquinolones is not responsive to changes in dose or duration. So physicians should be careful in using levofloxacin for empirical treatment.<sup>33</sup> Our result was exciting because it revealed that bismuth quadruple therapies with levofloxacin are effective in areas with high resistance.

The dosage of PPI might influence the efficacy of bismuth-containing therapy; the PPI causes higher concentrations of bismuth in the mucosa.<sup>34</sup> Accordingly, the impact of CYP2C19 polymorphism might influence our outcomes. Esomeprazole has minimal first-pass metabolism, undergoes less hydroxylation via CYP2C19 and has been shown to have a greater gastric acid suppression effect than omeprazole.<sup>35,36</sup> So we used a high dose (40 mg twice daily) of esomeprazole to overcome the effect of CYP2C19 polymorphism. In this study, the influence of CYP2C19 genotypes was not statistically obvious, so our data supported that higher PPI dose and longer

treatment period would diminish the impact of CYP2C19 genotypes.<sup>37–39</sup> This finding has not been focused on in previous studies.

The major limitations of our therapies include a complex dosing regimen and a relatively high incidence of adverse events. Some studies might use doxycycline instead of tetracycline because doxycycline might improve the compliance due to its lower frequency.<sup>40</sup> In our study, the incidences of side effects were high in both groups and headache was the most common adverse effect. However, these side effects were mild and acceptable. Patient compliance was good in both groups. Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in those  $\geq 60$  years of age, in transplant recipients and with the use of concomitant steroid treatment. Another risk of fluoroquinolones is QT prolongation.<sup>41</sup> Clinicians can minimize this risk by avoiding prescriptions of multiple medications associated with QT-interval prolongation. Fortunately no case suffered from the above events in the EBTL group. Another possible limitation might be the duration of therapy. We gave only 10 days of therapy; some studies treated their patients with a 14 day regimen. Although a longer duration might result in a higher success rate, Rimbara *et al.* stated that both durations were acceptable.<sup>42</sup>

In summary, we found that 10 day bismuth quadruple therapies with levofloxacin or high-dose metronidazole were effective in areas with high resistance. These two therapies were equally safe and tolerated, and the metronidazole-containing therapy was cheaper. Thus it is persuasive that high-dose metronidazole-containing quadruple therapy could be a good choice for second-line *H. pylori* eradication in areas with high resistance.

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## Transparency declarations

None to declare.

## Author contributions

C.-H. K. designed the study, prepared the methods and analysed the results. H.-M. H., S. S. W. W., P.-I. H. and D.-C. W. helped to conduct the literature review, obtain informed consent and personal data collection. F.-C. K., C.-J. L., S.-K. C., Y.-H. C. and M.-C. H. offered the idea of this study and helped in the literature review. H.-H. T. designed and

supervised the study and directed its implementation, including quality assurance and control.

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