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Levofloxacin-based therapy as an efficient alternative for eradicating *Helicobacter pylori* infection in Iran: a systematic review and meta-analysis

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ABSTRACT

Objectives: Despite excessive resistance of *Helicobacter pylori* to clarithromycin among the Iranian population, clarithromycin-based therapy is still prescribed in Iran. Recent studies have shown high rates of *H. pylori* eradication in patients treated with levofloxacin. The main purpose of this study was to compare the effect of levofloxacin with clarithromycin on the eradication of *H. pylori* infection in the Iranian population.

Methods: A comprehensive meta-analysis was done for relevant cohort studies and clinical trials to compare the therapeutic effects of levofloxacin and clarithromycin in the Iranian population. We pooled the data using odds ratio (OR) and corresponding 95% confidence interval (CI) to determine the clinical efficacy of levofloxacin versus clarithromycin to treat *H. pylori* infection. Heterogeneity and publication bias were also measured for the included studies.

Results: Thirteen studies were included in the quantitative synthesis. The eradication rate was significantly higher in patients receiving levofloxacin compared with clarithromycin (75.2% vs. 66.3%; OR = 1.76, 95% CI 1.40–2.20). Additionally, in the subgroup analyses it was confirmed that the cure rate was relatively higher in levofloxacin-treated cases. However, there was significant heterogeneity and publication bias, thus the results should be interpreted with caution.

Conclusion: We found that the success of levofloxacin treatment was significantly higher than clarithromycin. Therefore, it is suggested that clarithromycin-based triple therapy be replaced by levofloxacin-based triple therapy in countries with high resistance to clarithromycin such as Iran. Nevertheless, the findings of this study need to be approved with a larger investigation on the Iranian population.

1. Introduction

Helicobacter pylori is the main cause of gastrointestinal disorders, particularly peptic ulcer, chronic gastritis, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma [1]. The prevalence of infection with *H. pylori* in Iran varies from 36% in Kurdistan to 90% in Ardabil [2]. Depending on resistance to clarithromycin, combined treatment regimens have been introduced in three categories as follows: (i) first-line therapy, comprising a proton pump inhibitor (PPI) plus two antibiotics such as amoxicillin and clarithromycin (in areas with low clarithromycin resistance); (ii) bismuth quadruple therapy, comprising a PPI plus bismuth salt, tetracycline and metronidazole (in areas with high clarithromycin resistance); and (iii) non-bismuth quadruple therapy, comprising one PPI plus three antibiotics such as clarithromycin, amoxicillin, and metronidazole or tinidazole [3–5]. Nowadays, increasing antibiotic resistance as well as degradation of antibiotics in the stomach are considered two major obstacles in eradicating *H. pylori* infection [3]. Excessive antibiotic resistance, especially to clarithromycin, leads to a reduction in treatment success with triple therapy regimens to ≤80% [6,7]. The incidence of treatment failure in patients receiving quadruple ther-

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apy is estimated at 20–30%, and lack of complete eradication of this bacterium might lead to the development of gastric adenocarcinoma and metachronous recurrence [8,9]. Despite this, in recent studies the clinical efficacy of levofloxacin in the eradication of infection has led to the selection of this antibiotic as one of the drugs in second-line treatment [10]. If the first-line regimen is not effective, a second-line regimen (quadruple bismuth therapy or levofloxacin triple therapy) and, finally, quadruple bismuth-based levofloxacin therapy or rifabutin triple therapy are recommended [3,4]. In recent studies conducted in Iran, resistance to metronidazole, clarithromycin and amoxicillin has been estimated to be 64.9%, 25.3% and 20.7%, respectively [11,12]. However, triple therapy containing clarithromycin is one of the most popular treatment regimens recommended in Iran [2,12,13]. Recently, various studies have reported that levofloxacin-containing treatment regimens are better than clarithromycin-based triple therapy [14,15]. The main aim of this study was to compare the clinical effect of a levofloxacin-based treatment regimen with a clarithromycin-containing treatment regimen as standard triple therapy (STT) in eradicating *H. pylori* infection in the Iranian population.

2. Methods

2.1. Search strategy and selection criteria

In this meta-analysis, efforts were made to compare the effect of levofloxacin and clarithromycin regardless of triple, quadruple and sequential treatments in eradicating *H. pylori* infection in the Iranian population. The study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. Our search strategy was carried out according to four steps, including 'Identification', 'Screening', 'Eligibility' and 'Included'. In the 'Identification' step, all clinical trials comparing the therapeutic effects of levofloxacin and clarithromycin in the Iranian population infected with *H. pylori* were collected until November 2020. In this step, we used global databases such as PubMed, Scopus, Embase, Cochrane Library and Google Scholar as well as national databases such as IranMedex, SID and ISC. Considering MeSH terms such as '*Helicobacter pylori*', '*H. pylori*', 'gastric cancer', 'peptic ulcer', 'MALT lymphoma', 'eradication rate', 'levofloxacin', 'clarithromycin' and 'Iran', a literature search was carried out separately by two groups of authors (PA/MK1 and KGH/MK2) without considering limitations on the publication date. In the 'Screening' step, irrelevant articles, reviews and case reports were excluded. In the 'Eligibility' step, we excluded studies with insufficient (or unavailable) data as well as non-human samples. In the 'Included' step, we retrieved all eligible full-text articles for systematic review and meta-analysis (Fig. 1). Finally, to evaluate the clinical effects of levofloxacin and clarithromycin on the eradication of *H. pylori*, all included studies were divided into two groups, namely cases (patients receiving levofloxacin) and controls (patients receiving clarithromycin), and the results were compared in both groups.

2.1.1. Inclusion criteria

Inclusion criteria included: (i) original studies, case–control studies, clinical trials, cohort studies and cross-sectional studies, as well as meta-analysis on the clinical effects of the two antibiotics on bacterial eradication; (ii) studies limited to the Iranian population; (iii) articles published in English or Persian; (iv) studies with clear diagnostic methods (e.g. ELISA, PCR, rapid urease test, urea breath test, *H. pylori* stool antigen and conventional microbiology tests) and results; and (v) studies with standard methods for monitoring treatment.

2.1.2. Exclusion criteria

Exclusion criteria included: (i) duplicate studies as well as several articles from a single study; (ii) studies on non-Iranian populations; (iii) studies containing non-levofloxacin and non-clarithromycin regimens; (iv) studies on non-human samples; and (v) uncertain and inadequate studies.

2.2. Data extraction and quality assessment of studies

The full-texts of eligible articles were assessed by all authors [17–29]. Information including first author, publication year, location of each study, number of patients, mean patient age, eradication regimen, follow-up time, eradication rate and side effects are summarised in Table 1. In the present study, the Newcastle–Ottawa scale (NOS) was used to assess the quality of eligible studies. Disputes were also reviewed and decided upon by a fourth author (MK2).

2.3. Data analysis

Data were pooled using Comprehensive Meta-Analysis (CMA) software v.2.2 (Biostat Inc., Englewood, NJ, USA). To compare the treatment regimens containing levofloxacin and clarithromycin in the eradication of *H. pylori* infection, we used the odds ratio (OR) with 95% confidence intervals (CI). The eradication rates in case and control groups as well as side effects were calculated and reported as event rate (with percentage). Heterogeneity between studies was also measured using the I^2 index and Cochran test. According to the DerSimonian–Laird method, a random-effects model was used when there was heterogeneity between studies (I^2 index $>25\%$ and Cochrane Q-test P-value > 0.05). In addition, based on the Mantel–Haenszel method, a fixed-effects model was used when lacking heterogeneity. We also provided subgroup analysis based on each individual's anti-*H. pylori* therapeutic regimen to reduce the source of potential heterogeneity. Publication bias was also assessed by funnel plot asymmetry, Egger's P-value and Begg's P-value [30].

3. Results

3.1. Description of selected studies

Of 429 articles identified following the preliminary search and in accordance with the criteria, 13 eligible articles were selected and registered in the current analysis. The search flowchart for selecting articles is provided in Fig. 1.

Selected studies were conducted in cities including Qazvin ($n = 1$), Tehran ($n = 2$), Shahrekord ($n = 2$), Khorramabad ($n = 1$), Ahvaz ($n = 1$), Sari ($n = 1$), Gorgan ($n = 1$), Ilam ($n = 1$), Bandar Abbas ($n = 1$), Birjand ($n = 1$) and Kashan ($n = 1$) during 2016–2020. In these studies, several common tests such as rapid urease test, urea breath test and *H. pylori* stool antigen were used to monitor the therapeutic response. Overall, in the total studies recorded, we found that 963 patients received levofloxacin (case group) and 949 patients received clarithromycin (control group). The NOS was used to assess the quality score based on three major modules, including: selection of study groups; comparability; and ascertainment of exposure and outcome (out of 9, the maximum possible NOS score for case–control studies). Of the 13 eligible studies, all studies included a quality score of $\geq$6, indicating that these studies were suitable for quantitative analysis (Table 1). The mean ages of patients in the case and control groups were estimated to be 41.7 years and 42.0 years, respectively. Owing to lack of access to raw data or incomplete information, we could not measure the distribution of cancer and peptic ulcer in the studied patients. Based on

Table 1
Characteristics of the included studies

First author	Publication year	City	No. of patients		Mean age (years)		Diagnostic method	Eradication regimen		Follow-up time (weeks)	Eradication rate (%)		Adverse effects (%)		NOS score
			Case	Control	Case	Control		Case	Control		Case	Control	Case	Control	
Safarnezhad [17]	2016	Qazvin	56	54	43.3	42.8	RUT, HpSA	Levofloxacin (500 mg daily), amoxicillin (1 g twice daily) and omeprazole (20 mg daily) for 2 weeks	Clarithromycin (500 mg twice daily), amoxicillin (1 g twice daily) and omeprazole (20 mg daily) for 2 weeks	2	75	51.7	5	3.6	
Alirezaei et al. [18]	2017	Tehran	44	44	45.5	36.2	HpSA	Levofloxacin, amoxicillin and omeprazole for 2 weeks	Clarithromycin, amoxicillin and omeprazole for 2 weeks	4	86.4	77.3	NA	NA	6
Hafizi et al. [19]	2017	Shahrekord	49	47	33.2	45.5	RUT, HpSA	Omeprazole, amoxicillin, levofloxacin and tinidazole for sequential therapy	Omeprazole, amoxicillin, and clarithromycin	4	67.3	66	1	1	7
Moradniani et al. [20]	2018	Khorramabad	97	96	40.2	42.1	UBT	Omeprazole 20 mg, amoxicillin 1 g and levofloxacin 500 mg twice daily for 7 days	Omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg twice daily for 7 days	6	87.6	76	13	8	9
Sebghatollahi et al. [21]	2018	Shahrekord	74	72	44.5	47.3	UBT	Pantoprazole 40 mg, bismuth subcitrate 240 mg, amoxicillin 1 g and tinidazole 500 mg for 7 days, followed by levofloxacin 500 mg for 14 days	Pantoprazole 40 mg, bismuth subcitrate 240 mg, amoxicillin 1 g and clarithromycin 500 mg for 7 days	2	70.8	81.1	20	21	8
Hajiani et al. [22]	2018	Ahvaz	78	78	NA	NA	UBT	Pantoprazole (40 mg twice daily), amoxicillin (1 g twice daily), levofloxacin (500 mg twice daily) and tinidazole (500 mg twice daily) for 10 days	Pantoprazole, clarithromycin, bismuth subcitrate and amoxicillin for 14 days	4	78.2	83.3	NA	NA	7
Fakheri et al. [23]	2019	Sari	70	70	NA	NA	UBT	Pantoprazole 40 mg twice daily, amoxicillin 1000 mg twice daily and levofloxacin 500 mg/day for 10 days	Pantoprazole 40 mg, amoxicillin 1 g and clarithromycin 500 mg, all twice daily for 10 days	8	58.8	75.7	2	5	8
Seyyedmajidi et al. [24]	2019	Gorgan	58	57	46.2	45.7	UBT	Omeprazole 40 mg/day, levofloxacin 1 g/day and amoxicillin 2 g/day	Omeprazole 40 mg/day, bismuth subcitrate 480 mg/day, furazolidone 400 mg/day and amoxicillin 2 g/day	2	86.7	78.3	51.7	11.7	7
Shahbazi and Shariatpanahi [25]	2019	Ilam	89	82	NA	NA	UBT	Esomeprazole 40 mg, tinidazole 1 g and levofloxacin 500 mg once daily for 14 days	Lansoprazole 30 mg, amoxicillin 1 g and clarithromycin 500 mg twice daily for 14 days	4	90.5	86	NA	NA	9
Mohammad-Alipour [26]	2019	Bandar Abbas	100	100	37.4	35.7	UBT	Pantoprazole 20 mg daily, levofloxacin 500 mg daily and amoxicillin 1000 mg twice daily for 14 days	Pantoprazole 20 mg daily, clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 14 day	4	64.4	18.2	84.9	72.7	9
Mokhtare et al. [27]	2020	Tehran	94	92	NA	NA	UBT	Levofloxacin 500 mg, tinidazole 500 mg, esomeprazole 40 mg and amoxicillin 1 g for 14 days	Clarithromycin 500 mg, tinidazole 500 mg, esomeprazole 40 mg and amoxicillin 1 g for 14 days	8	85.1	83.7	97.8	98.9	9
Abasnia et al. [28]	2021	Birjand	67	55	39.1	38.1	UBT	Levofloxacin, pantoprazole and amoxicillin for 14 days	Amoxicillin, pantoprazole, clarithromycin and bismuth citrate for 14 days	4	91.8	70.5	NA	NA	7
Arj et al. [29]	2020	Kashan	87	102	46.3	44.6	HpSA	Bismuth subcitrate, omeprazole, amoxicillin and levofloxacin for 2 weeks	Bismuth subcitrate, omeprazole, amoxicillin and clarithromycin for 2 weeks	4	89.7	69.6	19	72	9

NOS, Newcastle–Ottawa Scale; RUT, rapid urease test; HpSA, *H. pylori* stool antigen; UBT, urea breath test; NA, not available.

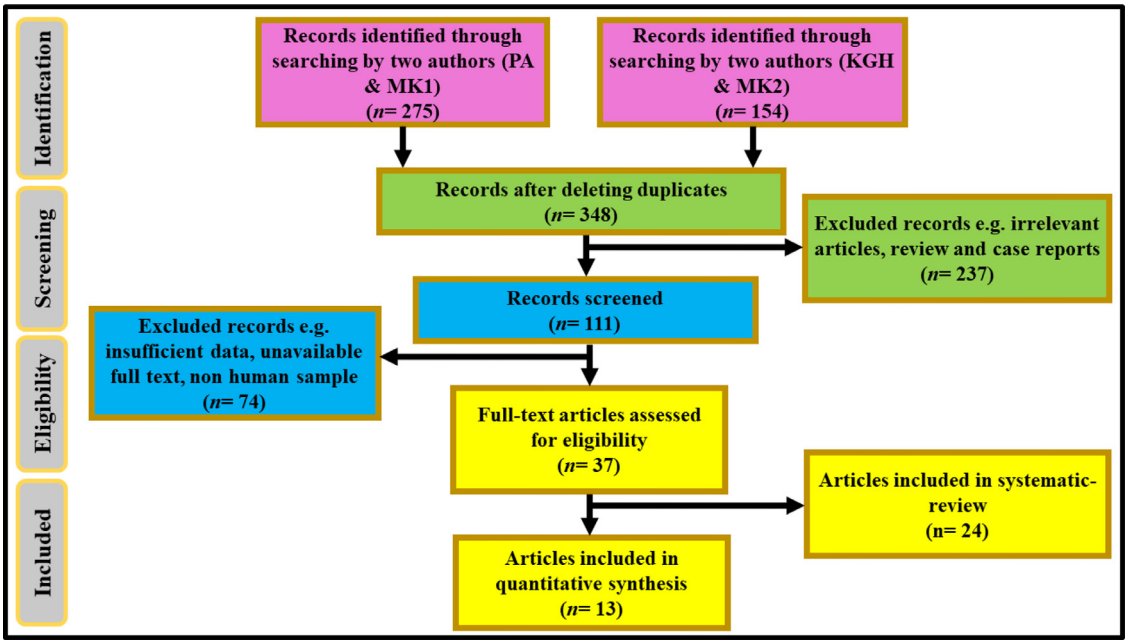

Fig. 1. Flowchart of literature search and study selection.

the information received, therapeutic regimens varied among the patients receiving levofloxacin or clarithromycin; a triple-therapy regimen was used in eight studies [17,18,20,23–26,28], while in the other studies the treatment was as follows: quadruple therapy in two studies [21,27] and sequential therapy in the case group and triple or quadruple therapy in the control group in three studies [19,22,29]. In the evaluation phase of the candidate studies, we removed several articles for reasons such as not using clarithromycin and levofloxacin, using non-levofloxacin fluoroquinolones, multiple articles from one study, and using levofloxacin in patients with previously failed clarithromycin-based treatment [31–42]. Based on the results of statistical analysis, eradication of *H. pylori* infection in the case and control groups was assessed to be 75.2% (95% CI 71.9–77.9%) and 66.3% (95% CI 62.9–69.6%), respectively. Eradication of *H. pylori* infection was significantly higher in the levofloxacin-based group (OR = 1.76, 95% CI 1.40–2.20; $P = 0.01$; $I^2 = 82.19$; Q-value = 0.01; Begg's P-value = 0.1; Egger's P-value = 0.4) than that in the clarithromycin-based group (Fig. 2). The results showed that the side effects of levofloxacin were slightly fewer than those of clarithromycin (OR = 0.89, 95% CI 0.64–1.23; $P = 0.5$; $I^2 = 87.68$; Q-value = 64.98; P-value = 0.01; Begg's P-value = 0.5; Egger's P-value = 0.3).

3.2. Subgroup analyses

We performed subgroup analyses to moderate possible heterogeneity. According to the results, eradication of infection in patients treated with levofloxacin-based triple therapy (levofloxacin 500 mg daily plus amoxicillin 1 g twice daily plus omeprazole 20 mg daily, for 2 weeks) was significantly increased compared with eradication of infection in patients treated with clarithromycin-based triple therapy (clarithromycin 500 mg twice daily plus amoxicillin 1 g twice daily plus omeprazole 20 mg daily, for 2 weeks) (OR = 1.98, 95% CI 1.4–2.7; $P = 0.01$; $I^2 = 86.46$; Q-value = 36.93, P-value = 0.02). However, in patients treated with quadruple therapy (pantoprazole 40 mg, bismuth subcitrate 240 mg, amoxicillin 1 g and tinidazole 500 mg, for 7 days) followed by levofloxacin 500 mg or clarithromycin 500 mg for 7 days, replacement of levofloxacin with clarithromycin had no significant effect (OR = 0.78, 95% CI 0.45–1.3; $P = 0.39$; $I^2 = 29.05$; Q-value = 1.41). Interestingly, infection eradication was significantly increased in patients who received levofloxacin-based triple therapy compared with clarithromycin-based quadruple group (OR = 5.62, 95% CI 2.80–11.27; $P = 0.01$; $I^2 = 0.00$; Q-value = 0.05). Finally, based on statistical analysis, eradication of infection in the levofloxacin-based sequential group was slightly increased compared with clarithromycin-based triple or clarithromycin-based quadruple groups (OR = 1.06, 95% CI 0.45–2.48; $P = 0.08$; $I^2 = 0.00$; Q-value = 0.00; and OR = 1.63, 95% CI 0.92–2.8; $P = 0.09$; $I^2 = 87.77$; Q-value = 8.18). Publication bias was assessed using Begg's P-value and Egger's P-value. We observed no significant publication bias in this study; however, the funnel plot showed slight publication bias in some cases (Fig. 3).

4. Discussion

Helicobacter pylori is a successful Gram-negative pathogen that has infected a large proportion of the population around the world [43]. Colonisation with this bacterium is present in all geographical areas and is affected by factors such as bacterial virulence, socioeconomic status and health [44,45]. Iran is a developing country in the Middle East where the rate of *H. pylori* infection is reported to be up to 90% [46]. According to the literature, like other parts of the world, antibiotic-resistant strains are increasing in Iran, and treatment failure can be associated with worse outcomes such as gastric cancer and metachronous recurrence [11,47,48]. First-line treatment including a PPI, clarithromycin and amoxicillin for 14 days is a common treatment regimen recommended in Iran [14]. As mentioned earlier, based on previous studies, resistance to clarithromycin is increasing in *H. pylori* strains isolated from Iran, which in turn may lead to treatment failure [11,47]. In the present study, for the first time we compared the clinical effects of levofloxacin-based therapy with clarithromycin-based therapy in the eradication of *H. pylori* infection in the Iranian population. According to the results of the statistical analysis, it was confirmed that eradication of this bacterium in patients receiving levofloxacin was significantly increased compared with patients treated with clarithromycin (OR = 1.76, 95% CI 1.40–2.20). Levofloxacin is one of the most common fluoroquinolones that acts as a broad-spectrum antibiotic effective both against Gram-positive and Gram-negative

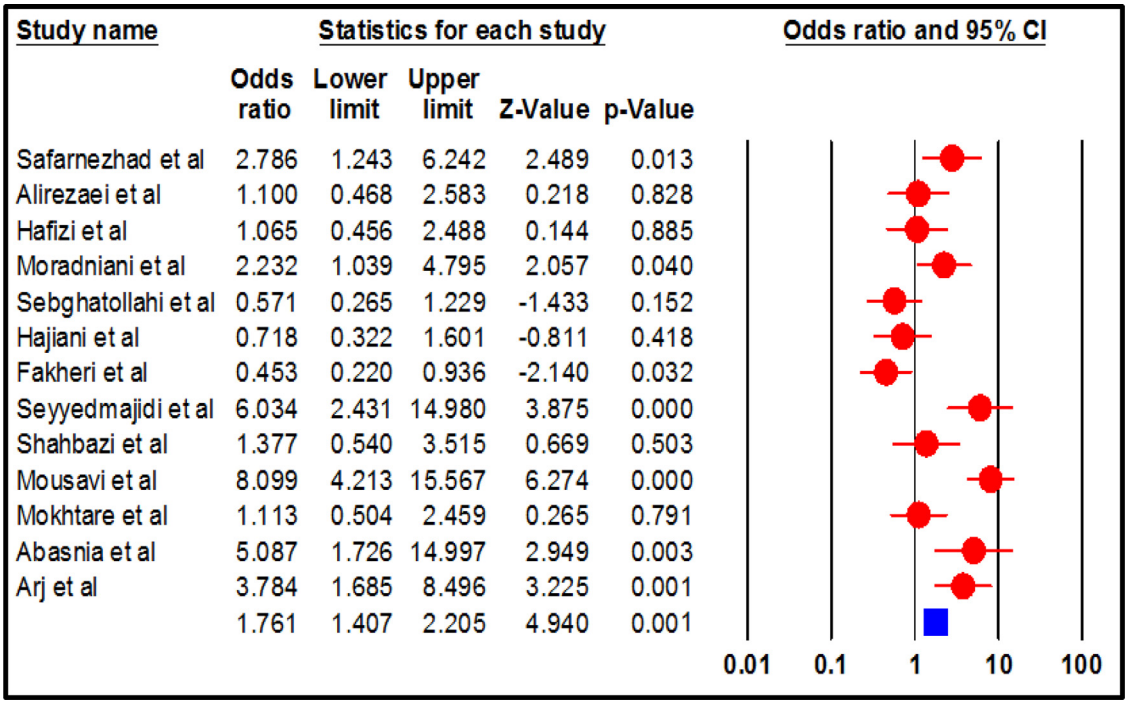

Fig. 2. Clinical efficacy of levofloxacin-based versus clarithromycin-based therapy against *Helicobacter pylori* infection based on 13 studies conducted in the Iranian population. CI, confidence interval.

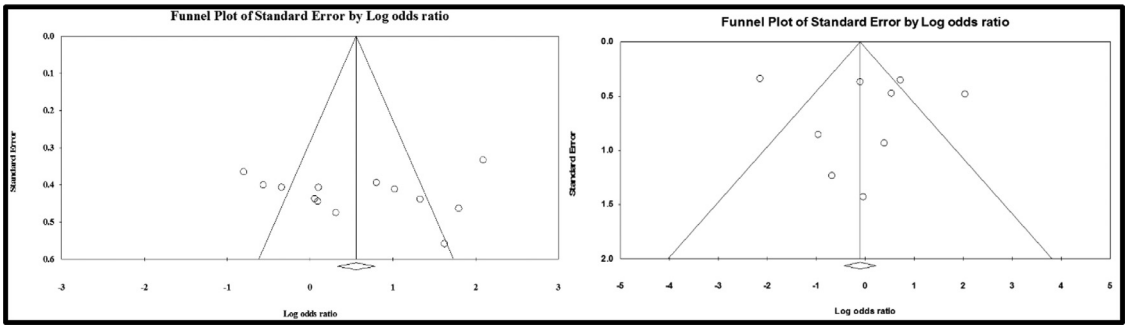

Fig. 3. Funnel plot asymmetry represents slight publication bias on the efficacy of levofloxacin versus clarithromycin in *Helicobacter pylori* eradication.

bacteria; it is recommended for the treatment of infections of the skin as well as the respiratory, gastrointestinal and urinary tracts [49]. Based on in vivo studies, growth of *H. pylori* strains resistant to clarithromycin and metronidazole is inhibited by levofloxacin [50]. Since the beginning of 2000, many studies have been conducted on the effect of levofloxacin as a first-line treatment in the eradication of *H. pylori* infection, which shows an eradication rate of approximately 75–96% [51]. In their meta-analysis, Xiao et al. showed that the effect of treatment with levofloxacin-based therapy depends on the antibiotic resistance burden of *H. pylori* strains [52]. Levofloxacin is considered to be the first line of treatment in areas where the rate of clarithromycin resistance is >20% [53]. In a comparative study by Hsu et al., they showed that tetracycline–levofloxacin quadruple therapy was more effective than amoxicillin–levofloxacin quadruple therapy against *H. pylori* infection in the areas with high levofloxacin resistance [54]. In addition, clarithromycin resistance is estimated to have been >20% in Iran during 2010–2020 [11]. We also showed that levofloxacin triple therapy is more effective in eradicating *H. pylori* infection than standard triple therapy (STT) (including a PPI, clarithromycin and amoxicillin), which might be due to increased resistance to clarithromycin in these bacteria (Fig. 4). However, in their meta-analysis, Peedikayil et al. showed that eradicating the infection with levofloxacin-based first-line treatment for 7 days was equivalent to standard first-line treatment [51]. It seems that changes in treatment guidelines in each country should be in accordance with the specific strains of that geographical area [55,56].

Comparison of the clinical efficacy of levofloxacin-based triple therapy with clarithromycin-containing quadruple therapy showed that the rate of infection eradication in patients receiving levofloxacin was significantly higher than that in patients receiving standard quadruple therapy (Fig. 5).

According to two previously conducted meta-analyses, in cases of *H. pylori* eradication failure, levofloxacin-based triple therapy (levofloxacin, amoxicillin and PPI for 10 days) is more effective than clarithromycin-based triple therapy or even bismuth-based quadruple therapy, which is in accordance with our results [15,57]. Given the high prevalence of *H. pylori* infection in China (up to 80% in Changle) as well as geographical similarities between Iran and China (Asian countries), it is predictable that the results from China are similar to those from Iran. Recently the rates of resistance to metronidazole, clarithromycin and levofloxacin in Chinese patients were 78.2%, 22.1% and 19.2%, respectively [58,59]. Although a recent systematic review and meta-analysis has been

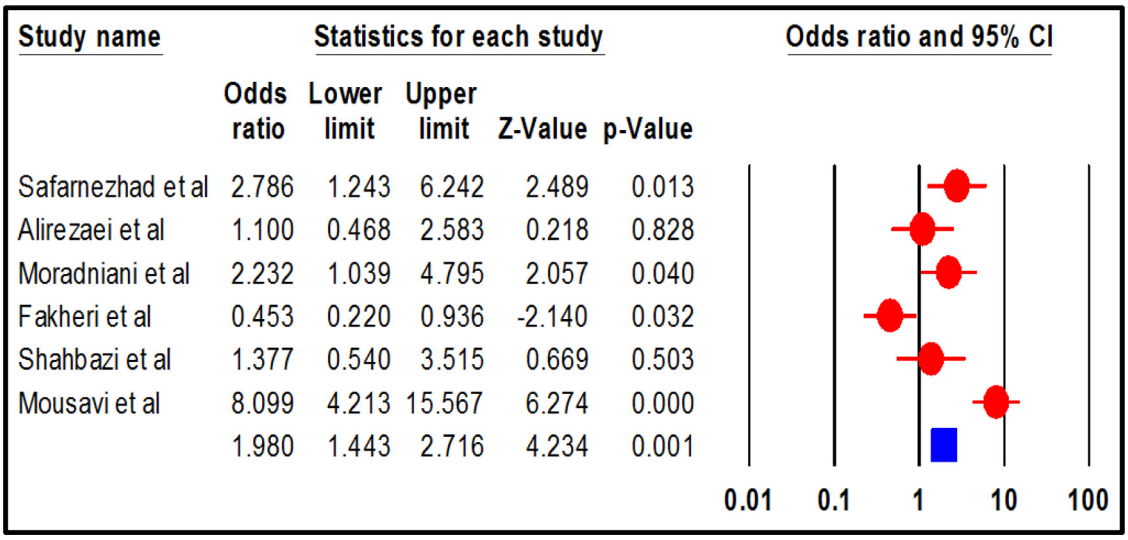

Fig. 4. Forest plot for efficacy of levofloxacin-based triple therapy versus clarithromycin-containing standard triple therapy for eradication of *Helicobacter pylori* infection. CI, confidence interval.

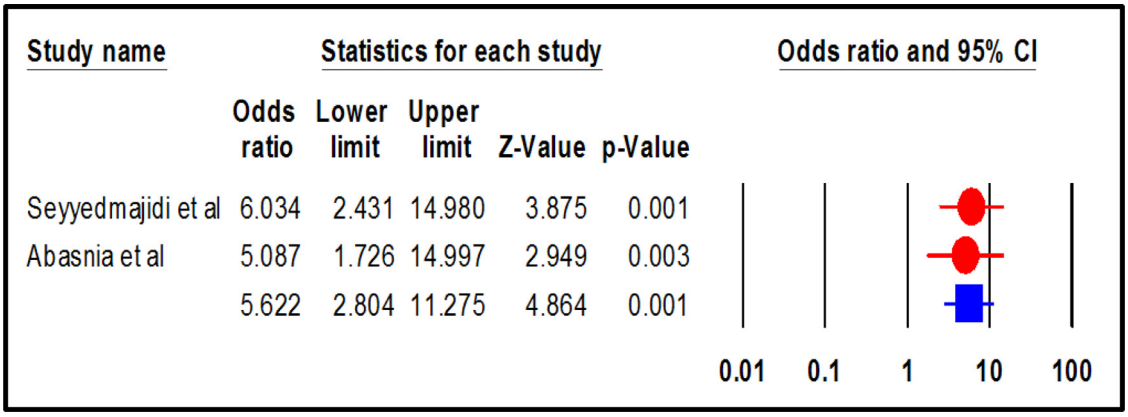

Fig. 5. Forest plot for efficacy of levofloxacin-based triple therapy versus standard quadruple therapy for eradication of *Helicobacter pylori* infection in previous treatment failure cases. CI, confidence interval.

conducted by Iranian authors about the increasing antimicrobial resistance of this pathogen in Iran, the method used in the included studies is based on disk diffusion [60], whereas the gold-standard method for determining antimicrobial resistance of *H. pylori* is agar dilution [61]. However, sometimes the opposite results may occur; in their study, Chen et al. showed that there was no significant difference between levofloxacin triple therapy and second-line therapies [62]. Interestingly, in another meta-analysis, Iqbal et al. demonstrated that a regimen containing levofloxacin, doxycycline, nitazoxanide and PPI could eliminate *H. pylori* infection with an eradication rate of up to 92% [63]. Although nitazoxanide in combination with other antibiotics may be considered a better regimen than levofloxacin-based triple therapy, nitazoxanide as an antiprotozoal drug, mainly used for the treatment of diarrhoea caused by *Cryptosporidium parvum* or *Giardia lamblia*, does not have US Food and Drug Administration (FDA) approval for the treatment of *H. pylori*. Furthermore, an acidic pH (pH 5.0) reduces the antimicrobial activity of this drug [64,65]. It should be noted that the eradication rate of infection in patients receiving levofloxacin-based quadruple therapy depends on the minimum inhibitory concentration (MIC) of the antibiotic. A study by Drusano et al. showed that taking this drug once a day had no significant effect compared with standard triple or quadruple therapies; increasing the concentration of free drug molecules is associated with increasing the rate of eradication [66]. In a clinical trial conducted by Song et al. in China, the eradication rate of infection following cefuroxime–levofloxacin–PPI–bismuth quadruple therapy was reported to be 97.2% and 84.0% in levofloxacin-susceptible and levofloxacin-resistant cases, respectively [67]. In their study in the USA, Basu et al. reported that a four-drug regimen of levofloxacin, omeprazole, nitazoxanide and doxycycline could improve the eradication rate of infection up to 89.4% compared with 73.3% for STT ($P < 0.05$) [68]. Based on a study by Losurdo et al. in Italy, they found that the rate of secondary resistance was higher in patients receiving clarithromycin (64.8%) than in patients receiving levofloxacin (59.3%); however, they noted the progressive spread of levofloxacin-resistant strains [69]. In this regard, a comprehensive study was conducted by Caldas et al. in Spain on a large population of patients [70]. Their findings showed that the effectiveness of the 14-day bismuth–clarithromycin quadruple therapy (PPI–bismuth–clarithromycin–amoxicillin) was slightly lower than that of the 14-day levofloxacin triple therapy (PPI–levofloxacin–amoxicillin) (91% vs. 92%) [70]. Their study is acceptable in the European Registry on *Helicobacter pylori* Management (Hp-EuReg), an international registry that started in 2013. Interestingly, in a recent systematic review by Sukri et al., they estimated that levofloxacin resistance was higher than clarithromycin in Southeast Asian countries such as Cambodia, Indonesia, Laos, Malaysia, Singapore, Thailand and Viet-

Table 2
Published meta-analyses related to the effectiveness of levofloxacin against *Helicobacter pylori* worldwide

First author	Year	Population	Study design	Concluding remarks
Gisbert et al. [15]	2006	Worldwide	Levofloxacin-based rescue regimens after *H. pylori* treatment failure	Eradication rate of levofloxacin-based regimens was 80%. Side effects of this regimen are low; this antibiotic is better tolerated than recommended quadruple therapy
Saad et al. [57]	2006	Worldwide	Levofloxacin-based triple therapy vs. bismuth-based quadruple therapy as rescue treatment for *H. pylori* infection	Levofloxacin-based triple therapy was more effective than quadruple therapy (RR = 1.41, 95% CI 1.25–1.59) with a lower incidence of side effects (RR = 0.51, 95% CI 0.34–0.75) and side effects prompting discontinuation of therapy (RR = 0.30, 95% CI 0.10–0.89)
Zhang et al. [73]	2008	Worldwide	Efficacy of PPI and levofloxacin-based first-line anti-*H. pylori* therapy	Levofloxacin-containing regimen was more effective than standard triple therapy (OR = 1.56, 95% CI 1.25–1.94) and there was no significant difference in compliance with the standard therapy regimen
Li et al. [74]	2010	Worldwide	Efficacy and safety of clarithromycin and second-generation fluoroquinolone-based triple therapy vs. bismuth-based quadruple therapy for the treatment of persistent *H. pylori* infection	Superior eradiation rate for 10-day levofloxacin-containing regimen over 7-day bismuth-based quadruple therapy (OR = 4.79, 95% CI 2.95–7.79; $P < 0.00001$). Levofloxacin-containing regimen was better tolerated than bismuth-based quadruple therapy with lower side effects (OR = 0.41, 95% CI 0.27–0.61; $P < 0.0001$). Levofloxacin is a safe antibiotic owing to its low rate of adverse events (OR = 0.13, 95% CI 0.06–0.33; $P < 0.0001$)
Di Caro et al. [75]	2012	Worldwide	Levofloxacin/amoxicillin-based schemes vs. quadruple therapy for *H. pylori* eradication in second-line	Eradication rate of levofloxacin/amoxicillin regimen was 76.5% (95% CI 64.4–97.6%). 10 days of this regimen was significantly more effective than quadruple therapy (OR = 5.05, 95% CI 2.74–9.31; $P < 0.001$; $I^2 = 75\%$)
Xiao et al. [52]	2014	Worldwide	Clinical benefit of levofloxacin-based triple therapy an alternative for first-line eradication of *H. pylori*	Regardless of treatment duration: the eradication rate with levofloxacin regimen was slightly higher than the clarithromycin regimen (80.2% vs. 77.4%; RR = 1.03, 95% CI 0.94–1.13). Efficacy of 7-day standard triple regimen was statistically superior to 7-day levofloxacin-based scheme in Asian group (RR = 0.91, 95% CI 0.86–0.97). Nevertheless, levofloxacin regimen was predominant in European countries (RR = 1.15, 95% CI 1.06–1.23) regardless of treatment duration
Peedikayil et al. [51]	2014	Worldwide	Levofloxacin-based first-line therapy vs. standard first-line therapy for *H. pylori* eradication	Eradication rate in patients receiving levofloxacin was 79.05% vs. 81.4% in the standard group (RR = 0.97, 95% CI 0.93–1.02). *H. pylori* eradication with 7 days of levofloxacin-containing regimen was safe and equal compared with 7 days of standard triple therapy
Lee et al. [76]	2015	Korean	Efficacy of first- and second-line therapies in Korea	Sequential therapy was superior to standard triple therapy for first-line. In cases with treatment failure, levofloxacin triple and bismuth-containing quadruple therapies were recruited as rescue regimens
Li et al. [77]	2015	Worldwide	Effectiveness of treatment for eradicating *H. pylori* infection with the lowest common adverse events	10 days or 14 days of levofloxacin-based triple treatment was optimum for the eradication of *H. pylori*
Xin et al. [78]	2016	Worldwide	Network meta-analysis on the efficacy of moxifloxacin or levofloxacin as second-line treatment	Analysis suggested that the new-generation PPIs and use of moxifloxacin or levofloxacin were associated with greater effectiveness
Chen et al. [62]	2016	Worldwide	Efficacy of levofloxacin triple therapy as first- or second-line treatments for *H. pylori* infection	Eradication rate of infection was 77.3% and 80.7% in first-line and second-line therapies, respectively. When levofloxacin resistance is >5–10%, the efficacy of the treatment regimen is <80% and it is therefore not recommended.
Kuo et al. [79]	2017	Asia-Pacific region	Primary antibiotic resistance of *H. pylori* in the Asia-Pacific region	Primary *H. pylori* resistance was reported at 17% (95% CI 15–18%) for clarithromycin, 44% (95% CI 39–48%) for metronidazole, 18% (95% CI 15–22%) for levofloxacin, 3% (95% CI 2–5%) for amoxicillin and 4% (95% CI 2–5%) for tetracycline
Zhang et al. [80]	2017	Worldwide	Evaluating the efficacy of both levofloxacin-based triple and bismuth-based quadruple therapies in the treatment of *H. pylori* infection as rescue regimens	Eradication rate of levofloxacin-based triple therapy regimen was higher compared with bismuth-based quadruple therapy (77.0% vs. 68.7%; OR = 1.52, 95% CI 0.96–2.42). Levofloxacin-based triple therapy had higher eradication rate in addition to fewer side effects
Lopo et al. [81]	2018	Portugal	Evaluation of *H. pylori* antibiotic resistance rate	Clarithromycin 42% (95% CI 30–54%), metronidazole 25% (95% CI 15–38%), ciprofloxacin 9% (95% CI 3–18%), levofloxacin 18% (95% CI 2–42%), tetracycline 0.2% (95% CI 0–1%) and amoxicillin 0.1% (95% CI 0–0.2%)
Savoldi et al. [53]	2018	Worldwide	Prevalence of antibiotic resistance in *H. pylori* in WHO regions	Primary and secondary resistance rates to clarithromycin, metronidazole and levofloxacin were ≥15% in all WHO regions. However, primary clarithromycin resistance in the Americas (10%; 95% CI 4–16%) and Southeast Asia region (10%; 95% CI 5–16%), and primary levofloxacin resistance in the European region (11%; 95% CI 9–13%) were <15%
Andreev et al. [82]	2020	Russian	Antibiotic resistance rate to clarithromycin, metronidazole, levofloxacin, amoxicillin and tetracycline	*H. pylori* resistance rate was 10.39% for clarithromycin, 33.95% for metronidazole, 20.0% for levofloxacin, 1.35% for amoxicillin and 0.98% for tetracycline
Khademi et al. [11]	2020	Iranian	Antibiotic resistance rate to metronidazole, clarithromycin, amoxicillin, tetracycline, levofloxacin, rifampicin and furazolidone	Metronidazole 64.9%, clarithromycin 25.3%, amoxicillin 20.7%, tetracycline 16.1%, levofloxacin 21.9%, rifampicin 22.8%, and furazolidone 27.2%
Zou et al. [58]	2020	Worldwide	Evaluating the current effects of antibiotic resistance on *H. pylori* eradication efficacy	Pooled RR of eradication rate in patients with *H. pylori* isolates susceptible vs. resistant to levofloxacin was measured at 0.794 (95% CI 0.669–0.941)
Sholeh et al. [60]	2020	Iranian	Antibiotic resistance rate to clarithromycin, metronidazole, ciprofloxacin, levofloxacin, erythromycin, furazolidone, tetracycline and amoxicillin	Clarithromycin 21% (95% CI 16–26%), metronidazole 62% (95% CI 57–67%), clarithromycin in combination with metronidazole 16% (95% CI 10–23%), ciprofloxacin 24% (95% CI 15–33%), levofloxacin 18% (95% CI 9–30%), erythromycin 29% (95% CI 12–50%), furazolidone 13% (95% CI 4–27%), tetracycline 8% (95% CI 5–13%), and amoxicillin 15% (95% CI 9–22%)

RR, risk ratio; CI, confidence interval; PPI, proton pump inhibitor; OR, odds ratio; WHO, World Health Organization.

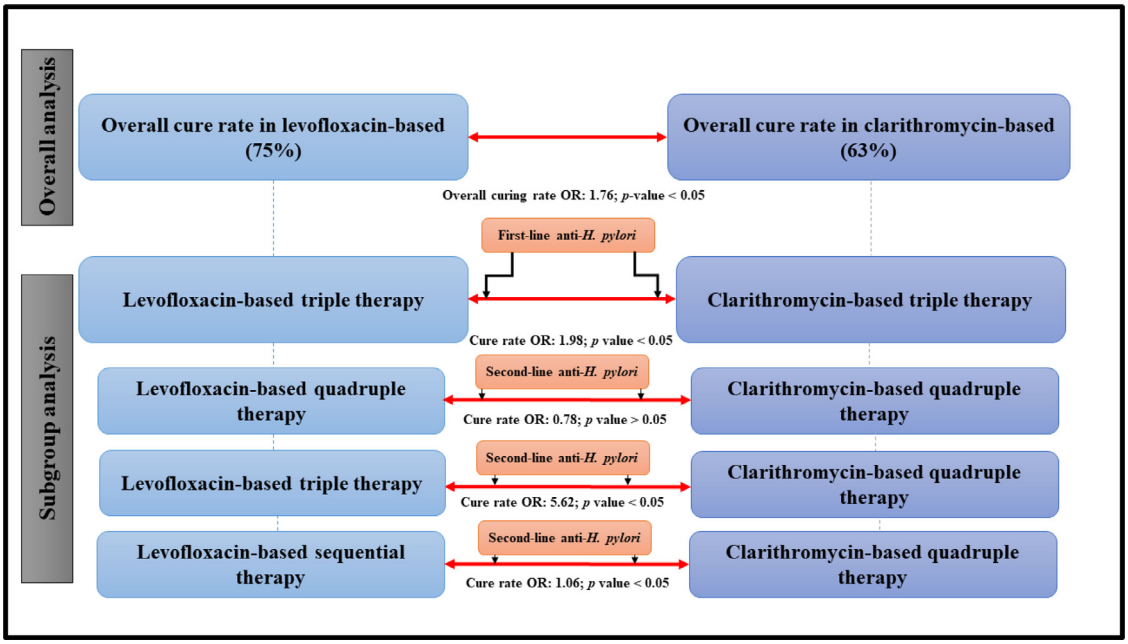

Fig. 6. Overall analysis and subgroup analysis of levofloxacin versus clarithromycin, OR, odds ratio.

nam [71]. Moreover, in a recent clinical trial conducted by Alsaadi et al. in Iraq, it was revealed that the rate of eradication success with clarithromycin-based therapy (74%) was significantly lower than with levofloxacin-based therapy (83%) and the side effects of first-line therapy were more than second-line therapy [72]. To compare the effects of levofloxacin with clarithromycin, we have listed 19 meta-analyses conducted around the world in Table 2.

At present, increasing antibiotic resistance is considered as one of the most important challenges of *H. pylori* treatment. Three international organisations that issue therapeutic guidelines based on monitoring antibiotic resistance include the European *Helicobacter* and Microbiota Study Group (Maastricht V/Florence Consensus Report), the Canadian Association of Gastroenterology/Canadian *Helicobacter* Study Group (Toronto Consensus) and the American College of Gastroenterology (ACG). According to recent statements, therapeutic regimens such as bismuth and non-bismuth quadruple therapies should replace clarithromycin-based therapy [83]. However, inaccessibility to bismuth in some regions of Asia and Africa on the one hand, and high resistance to metronidazole and clarithromycin in Asian countries such as Iran on the other hand, have led to the fact that levofloxacin triple therapy is recommended by the ACG as first-line treatment against *H. pylori* [83–85]. In addition, due to the low resistance of bacteria to this antibiotic, the levofloxacin triple-therapy regimen is accepted by all three organisations [83–86]. According to the literature, although bismuth and levofloxacin were recommended as the first-line of treatment by 2010, new trends in antimicrobial resistance were confusing in different geographical regions; for example, in Colombia initial resistance to levofloxacin increased from 11.8% in 2009 to 27.3% in 2014 [87,88]. In Asian countries where clarithromycin triple therapy is not used as first-line treatment, bismuth-based quadruple therapy, levofloxacin-based triple therapy or rifabutin-based triple therapy all are recommended as first-line treatments for infection with *H. pylori*, however in these areas some variations such as smoking, CYP2C19 polymorphism and levofloxacin resistance patterns differ [89,90]. For example, levofloxacin resistance in India and Bangladesh has been reported at 72.5% and 66.1%, respectively, while the rate of levofloxacin resistance in Iran (21.9%) is similar to Vietnam (27.9%) [11,91–93]. Therefore, depending on lifestyle and geographical features, the pattern of antibiotic resistance is specific to each country. Our results confirmed the efficacy of levofloxacin-containing regimens as a first-line treatment strategy, which in turn was similar to many other studies. We have also shown that levofloxacin triple therapy is the most reliable rescue regimen that is also accepted by international guidelines [83–87]. The Maastricht IV Consensus suggests that STT should be abandoned in areas where the clarithromycin resistance rate is >15%. Thus, various Asian countries with a high burden of clarithromycin resistance, i.e. China and South Korea, reject clinical usage of clarithromycin-based STT [94–97]. However, *H. pylori*-related therapeutic guidelines, despite high resistance to clarithromycin, have not been revised. In the present study, we accepted the clinical efficacy and safety of a levofloxacin-containing treatment regimen compared with a clarithromycin-based therapy as first-line as well as rescue regimen for treatment failure cases (Fig. 6).

In the present review, we suggest that levofloxacin-based anti-*H. pylori* treatment could be considered a suitable alternative to clarithromycin, particularly in Iran, a country with high clarithromycin resistance. Nevertheless, our study has several limitations, including the small number of included studies, small sample size, significant heterogeneity in the included studies, and the presence of publication bias. To confirm the current results, we need to monitor the drug susceptibility patterns of *H. pylori* strains from the Iranian population as well as perform further studies with larger sample sizes.

5. Conclusion

In general, we showed that the eradication rate of infection is higher in patients receiving levofloxacin than in those receiving clarithromycin. On the other hand, it was shown that treatment failure in the levofloxacin-based triple therapy group was significantly lower than cases treated with clarithromycin-containing quadruple therapy. Thus, levofloxacin may be a good alternative to clarithromycin in regions with high clarithromycin resistance such as Iran. Moreover, we compared additional research in other parts of the world with our results. According to international guidelines, levofloxacin-containing regimens can be recognised as the best alternative to clarithromycin-containing regimens, especially in cases of treatment failure. However, the sample size included

in this study was low and, owing to the heterogeneity and publication bias in our meta-analysis, the results should be interpreted with caution. Further investigation with a larger sample population is needed to study the efficacy of levofloxacin-based anti-*H. pylori* regimens in the Iranian population.

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Ethical approval

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