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Effect of *Helicobacter Pylori* eradication on patients with ITP: a meta-analysis of studies conducted in the Middle East

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Background
Immune thrombocytopenia (ITP) is a bleeding disorder. *Helicobacter pylori* is a Gram-negative bacterium that is presumed to be associated with ITP and therapeutic response of patients. To evaluate the effect of *H. pylori* eradication on platelet count of ITP patients, we analyzed the studies conducted on the association between *H. pylori* infection and response to therapy in ITP patients in Western Asia focusing on the Middle East region.

Methods
A systematic search of databases (PubMed/Medline, ISI Web of Science, Cochrane Central) and Google Scholar search engine results was conducted up until January 2020. The keywords included in the search were *Helicobacter pylori* and/or *H. pylori*, ITP and/or immune thrombocytopenia.

Results
Seven studies comprising a total of 228 *H. pylori-infected* patients (193 with successful eradication) were included in this study. The association between *H. pylori* eradication and ITP was expressed as odds ratios (OR) and 95% confidence intervals (CI). The findings showed that patients who received eradication treatment for *H. pylori* infection had significantly higher OR (OR, 8.83; 95% CI, 2.03–38.35; P=0.004) than those in the non-eradicated group.

Conclusion
Our results indicate a significant therapeutic effect of *H. pylori* eradication on the platelet count of patients with chronic ITP. Given the inherent limitations of this study, including the small number of patients, further studies with more patients are recommended.

Key Words *Helicobacter pylori*, *H. Pylori*, ITP, Immune thrombocytopenia

INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by a decreased platelet count in peripheral blood and increased destruction of platelets and megakaryocytes in peripheral blood and bone marrow, respectively [1]. The incidence of ITP is estimated to be 100 cases per million years and increases with age [2]. Based on its duration, ITP can be categorized as newly diagnosed, persistent, or chronic infection [3]. Patients with platelet counts lower than 100×10^9/L may show different clinical findings, ranging from skin symptoms, such as petechiae, purpura, and ecchymosis, to life-threatening clinical complications, including intracranial bleeding [4, 5]. Children account for approximately 50% of ITP cases, and often recover spontaneously from the disease, while adults go through the chronic phase of the disorder [2]. Most ITP cases are primary infections, and only 20% percent of cases are secondary to underlying complications [6]. These complications include lymphoproliferative disorders (mainly chronic lymphoblastic leukemia), autoimmune disorders such as lupus

erythematosus (SLE), infection with different viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), hepatitis C virus (HCV), and infection with the bacterium *Helicobacter pylori* (*H. pylori*) [7]. Although the pathogenesis of ITP remains ambiguous, one can assume that due to impaired immunological tolerance following viral infection, immune cells recognize and attack platelet glycoproteins (GPs) (mainly GP IIb/IIIa and Ib/IX) as viral immunogens as a result of molecular mimicry, which ultimately results (including T lymphocytes) in the destruction of platelets [1, 6, 8, 9]. In parallel to the direct destruction of platelets by T lymphocytes, the immune system can produce autoantibodies against platelets. These auto-antibody-coated platelets are cleared by macrophages of the reticuloendothelial system (RES), which leads to increased destruction of platelets, and increased risk of bleeding [7]. Similar to other autoimmune disorders, ITP is subject to certain effective factors, including genetic factors such as mutations in human leukocyte antigens (HLAs) and polymorphisms of interferon-γ [10-12]. In addition to genetic factors, other factors, such as *H. pylori* infection, are presumed to be associated with the initiation of ITP and the response of patients to therapy. Different studies have reported an association between *H. pylori* infection eradication and improved platelet count in patients with ITP [13-16]. However, due to the difference in *H. pylori* infection prevalence rates in different countries and races, as well as the lack of sufficient evidence to determine the impact of *H. pylori* eradication on platelet count, such findings cannot be accepted with certainty. Therefore, to arrive at a definitive conclusion, previous studies conducted in different countries on various populations and races should be reconsidered and thoroughly reviewed. To this end, we analyzed the studies that have already been conducted on the association

Table 1. Summary of the characteristic of the included studies.

Reference (country)	N (F/M) Age mean±SD or median (range)	Detection of HP infection (follow up period)	Duration of ITP (type of ITP relapse)	Platelet count at enrollment	Platelet after treatment	Response in all infected patients	Eradicated patients (non-eradicated patients)
Iran [18]	129 (51.2/48.8) 29.2±7.0 (18–46)	79 patients were infected & only 71 completed eradication 1 yr	61 mo (6–210 mo) Chronic NR	58.32±17.74×10^9/L (range, 31–96×10^9/L)	Eradicated patients 137.77×10^9/L $P<0.001$	Response in 30 eradicated patients CR: 30	62 9
Iran [19]	30 (67/33) 12 (9–16)	5 patients were infected 1 yr	NR Chronic 1 out of 5 eradicated patients (20%)	20×10^9/L (10–30×10^9/L)	81×10^9/L (69–89×10^9/L) $P=0.043$	Response in 5 eradicated patients PR: 4 CR: 0 PR+CR: 4 patients	5 0
Iran [20]	52 (50/50 in 26 patients) 38 (17–71)	*H. pylori* eradication achieved in 89.5% (26/29) 6 mo	NR NR NR	57.9×10^9/L (22–96×10^9/L)	104×10^9/L (26–196×10^9/L) $P<0.001$	Response in 26 eradicated patients CR: 15 PR: 0 PR+CR: 15	26 3
Iran [21]	92 (53/47) 41 (19–71)	Only 47 patients remained after excluding other patients 6 mo	2.2 mo (1–4.5 mo) Chronic NR	34.6×10^9/L (21–48×10^9/L)	52.8×10^9/L (23–86×10^9/L) ($P<0.001$)	Response in 41 eradicated patients CR: 0 PR: 3 PR+CR: 3	41 6
Pakistan [22]	197 (54.5/45.5 in 22 patient) 43.18±12.5 yr	22 patients were infected NR	NR NR NR	53.36±24.5×10^9/L	80.86±51.0×10^9/L $P=0.003$	Response in 22 infected patients CR: 7 PR: 10 PR+CR: 17	7 15
Pakistan [23]	85 (62.3/37.6) Infected patients: 43.89±7.06 Uninfected patients: 44.75±7.91	34 patients were infected NR	NR Chronic NR	48.56±21.7×10^9/L	94.2±26.8×10^9/L $P=0.001$	Response in 34 eradicated patients CR: 19 PR: 10 PR+CR: 29	34 0
Turkey [24]	34 (35.3/64.7) 52.5 yr (range, 16–93)	20 patients were infected 13 mo	NR Chronic NR	39.7±19.2×10^9/L	164.2±63.2×10^9/L $P<0.05$	Response in 18 eradicated patients CR: 5/18 PR: 3/18 PR+CR: 8	18 2

Abbreviations: CR, complete response; ITP, immune thrombocytopenia; NR, not reported; PR, partial response.

between *H. pylori* infection and response to therapy in patients with ITP in the Middle East to evaluate the effect of *H. pylori* eradication on platelet count.

MATERIALS AND METHODS

To conduct this systematic review and meta-analysis, the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines were used [17].

Literature search

To find relevant papers published on the effect of *H. pylori* eradication on the platelet count of patients with ITP, we systematically searched three international indexing databases (PubMed/Medline, ISI Web of Science, Cochrane Central) and Google Scholar search engine up to January 2020. The keywords used in the search process included "helicobacter pylori" and/or "H. Pylori," "ITP" and/or "Immune thrombocytopenia." Two authors (S.M.S.P. and A.Y.A.) independently screened the article titles and abstracts for inclusion. The titles and abstracts of 126 articles were investigated thoroughly to determine the competency of the articles. Among the 30 full-text articles related to Asia, seven studies were compatible with our inclusion criteria and were reviewed for inclusion in the present study (Table 1). The inclusion criteria were as follows: i) definite diagnosis of ITP, ii) documented *H. pylori* infection with reliable tests such as stool antigen test or serologic test for antibody, iii) outcome of eradication (platelet count or response rate), and iv) Western Asia and Middle Eastern origin. The identification, screening, eligibility assessment, and final included studies are summarized in Fig. 1.

Statistical analysis

The association between *H. pylori* eradication and ITP, expressed as odds ratios (OR) and 95% confidence intervals (CI), was calculated using Comprehensive Meta-Analysis (CMA) software. If the OR was higher than 1, it was considered a better response for patients in the eradication group. The random-effects model was used for pooling the data, and the possibility of publication bias was evaluated using a funnel plot.

RESULTS

Among the articles reviewed, only seven studies concerning the association between *H. pylori* eradication and response to treatment in patients with ITP in the Middle East were included in this meta-analyze (Fig. 1) [18-24]. Table 1 summarizes the main characteristics and outcomes of the treatments used in the included studies. In all included studies, the authors used standard guidelines for the diagnosis of ITP, which are mainly based on ruling out other possible causes of thrombocytopenia (viral infections, lymphoproliferative disorders, and autoimmune disorders) and confirming a decreased platelet count (less than 100×10^9/L).

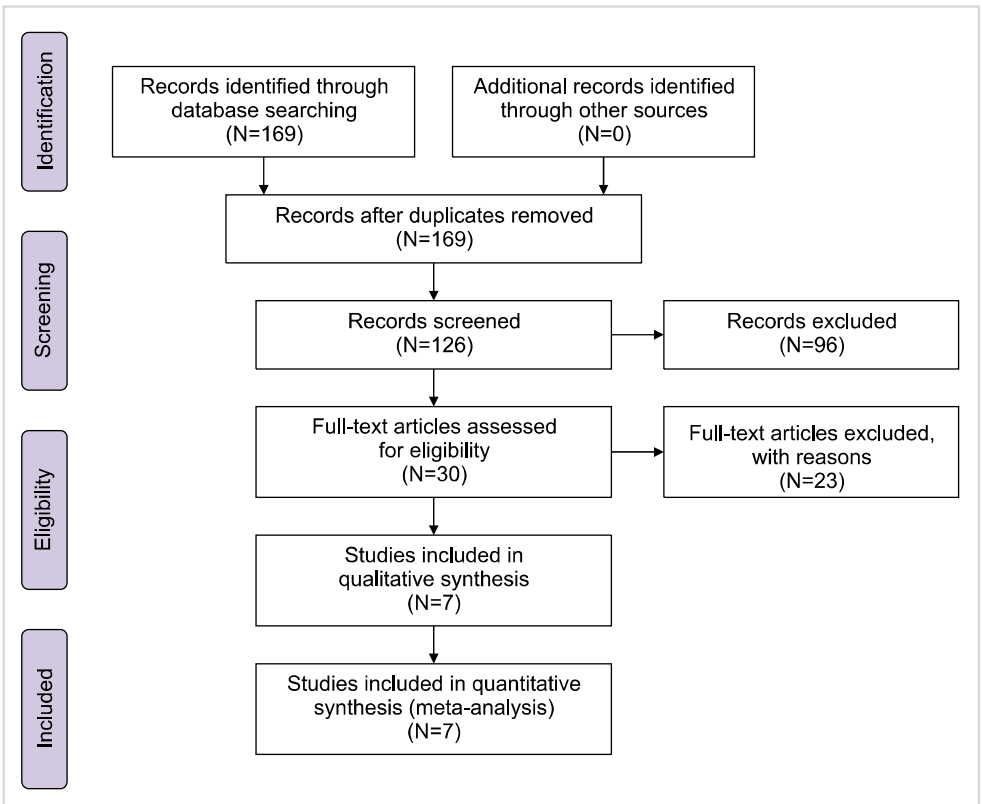

Fig. 1. Identification, screening, eligibility assessment, and final included studies.

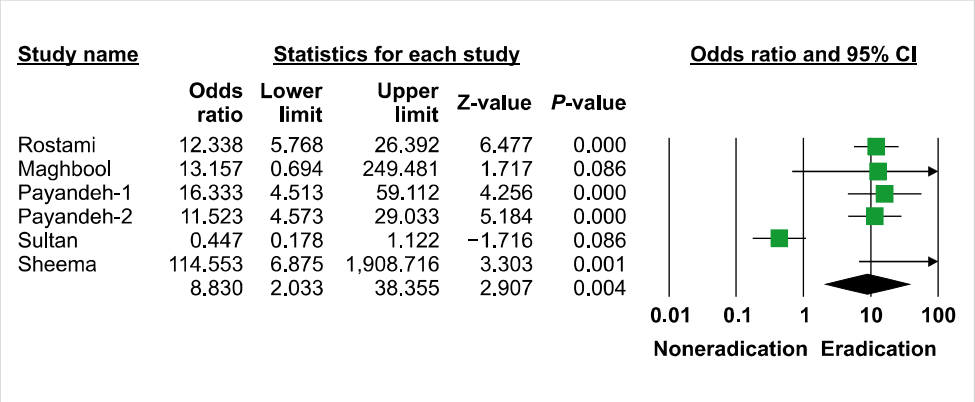

Fig. 2. Odds ratios of the patients with eradication of *H. Pylori*.

Table 2. Random-effects model for pooling data.

Model	N of studies	Effect size and 95% interval			Test of null (2-tail)			Heterogeneity			Tau-squared			
		Point estimate	Lower limit	Upper limit	z-value	*P*	q-value	df (Q)	*P*	I-squared	Tau squared	Standard error	Variance	Tau
Fixed	6	6.013	3.833	9.435	7.806	0.000	42.809	5	0.000	88.320	2.674	2.290	5.244	1.635
Random	6	8.830	2.033	38.355	2.907	0.004								

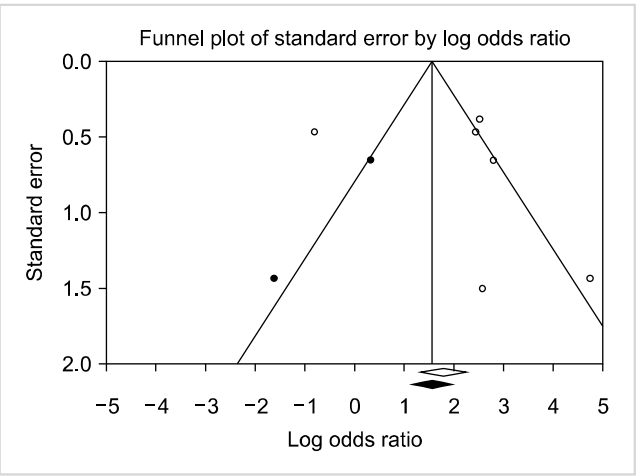

Fig. 3. Evaluation of publication bias by funnel plot.

However, most of these previous studies failed to report the duration of ITP in the patients examined. Moreover, all of the included studies, except two, reported that the participants were diagnosed with chronic ITP. For the two exceptions, after reviewing the description of patients (such as their mean age), we concluded that it was highly probable that they also studied chronic patients. The findings showed that among the seven included articles, three studies confirmed *H. pylori* infection using the Urea Breath Test (UBT) [20, 21, 24], three other studies [19, 22, 23] used the stool antigen enzyme immunoassay test, and one study [18] did not report the method used for *H. pylori* infection documentation. In the 228 patients included in these seven studies, the prevalence of *H. pylori* infection ranged from 16.6% [19] to 61.2% [18]. Moreover, all studies used standard triple therapy consisting of amoxicillin, clarithromycin, and a proton pump inhibitor (omeprazole in all studies) for 14 days to eradicate *H. pylori* infection. Three studies determined a complete response as a platelet count $>100\times10^9$/L [18, 20, 22], while four studies considered platelet counts $>150\times10^9$/L as a complete response in their patients [19, 21, 23, 24]. Furthermore, the highest rate of eradicated patients with increased platelet count was 85.3% [23], while the lowest rate was 7.3% [21]. The results also revealed that after eradication of *H. pylori*, ITP patients showed significantly increased platelet counts ($P<0.05$) in all studies (Table 1). Additionally, patients who received eradication treatment for *H. pylori* infection showed significantly higher OR (8.83; 95% CI, 2.03–38.35; $P=0.004$) than those who did not (Fig. 2). Overall, as the findings showed, there was significant heterogeneity among studies ($I^2=88.3\%$, $P=0.00$) (Table 2). In addition, as shown in Fig. 3, there is some evidence of publication bias due to the asymmetrical form of the funnel plot.

DISCUSSION

As a Gram-negative bacterium, *H. pylori* is responsible for most cases of peptic ulcers and gastric cancer worldwide. It is also associated with mucosa-associated lymphoid tissue (MALT) lymphoma, although the transmission pattern of this pathogen is not completely understood [25, 26]. Overall, it is widely known that *H. pylori* is transmitted through oral-oral, fecal-oral, and gastro-oral routes [27]. As a highly prevalent infection, *H. pylori* is commonly acquired in early

stages of life and grows in digestive tract and stays in the host's body for the rest of its life [28, 29]. The most common manifestation of *H. pylori* is gastritis, although its clinical manifestations vary from case to case [26, 29, 30]. Interestingly, the prevalence of *H. pylori* infection also varies from country to country, indicating the probable role of genetics and race in the prevalence of infection. For instance, Hooi *et al.* [31] estimated the prevalence of *H. pylori* infection to be 81%, 59%, and 77.2% in Pakistan, Iran, and Turkey, respectively, while they estimated the prevalence for Egypt and Denmark to be 40.9% and 22.1%, respectively. The significant difference in the reported prevalence of *H. pylori* infection might be due to factors such as access to clean water, population density, and the level of social health in the country. Gasbarrini *et al.* [32] reported an association between *H. pylori* and ITP for the first time in 1998; since then, different studies have several proposed possible mechanisms for this association. Using different mechanisms, it is believed that *H. pylori* escapes from innate immune mediators and attaches to gastric epithelial cells. After attachment, one of the important virulence factors of *H. pylori*, cytotoxin-associated gene A (CagA), induces inflammation through NF-κB signaling and interleukin (IL)-8 stimulation [33, 34]. In addition, CagA activates SHP-2 phosphatase and ERK (a mediator of the MPK signaling pathway), which results in the perturbation of gastric epithelial cell signaling [33]. CagA is an immunogenic protein that stimulates the production of antibodies. Because of the molecular mimicry between CagA and GP IIb/IIIa on platelets, it is possible that antibodies against CagA cause increased destruction of antibody-coated platelets by the reticuloendothelial system in patients with chronic ITP [35, 36]. Another aspect of this association is mediated by the vacuolating cytotoxin A gene (VacA), which is another important virulence factor of *H. pylori*. VacA perturbs IL-2 signaling, inhibits proliferation of helper T cells, and mediates adherence to platelets [33]. In addition, *H. pylori* can use the von Willebrand factor (VWF) to increase adherence to platelets [37], resulting in the activation and consumption of platelets, which is another possible cause of thrombocytopenia in *H. pylori-induced* ITP. Several meta-analyses and random clinical trials have already reported a positive outcome of *H. pylori* eradication on the platelet count of patients with ITP. For instance, the systemic reviews and meta-analyses of seventeen studies involving 788 ITP patients showed statistically significant increases in platelet counts in successfully eradicated patients compared to controls, and untreated and non-eradicated patients [weighted mean difference (WMD), 40.77×10^9/L (95% CI, 20.92–60.63), 52.16×10^9/L (95% CI, 34.26–70.05), and 46.35×10^9/L (95% CI, 27.79–64.91), respectively] [38]. Furthermore, a review of 25 studies involving 1,555 patients reported an overall response rate of 35.2% (95% CI, 28.0–42.4) [39]. Similarly, by reviewing six studies with 241 patients in the eradication group, Kim *et al.* [36] reported a significantly higher overall platelet response rate than the control group (OR, 1.93; 95% CI, 1.01–3.71; P=0.05).

In summary, despite the overall acceptance of the positive role of *H. pylori* eradication on platelet count in patients with ITP, important questions remain unanswered. For instance, the pathophysiology of *H. pylori-induced* chronic ITP, the mechanisms of response to infection, and the reason for the difference in infection prevalence in different populations remain unknown.

This study has several limitations, including the following: i) The number of studies and patients involved was small; ii) the included studies only examined chronic ITP in adults, and therefore, the results cannot be generalized to patients with acute ITP, especially children; iii) the studies showed heterogeneity in the method used for *H. pylori* infection; iv) the thresholds for complete response (CR) and partial response (PR) varied among the included studies; and v) some data were missing (such as the duration of ITP). In conclusion, the results indicated a significant therapeutic effect of *H. pylori* eradication on the platelet count in patients with chronic ITP. It is recommended that other studies be conducted to further explore the effect of *H. pylori* eradication on children with ITP, and the difference between *H. pylori* eradication in both acute and chronic forms of the infection.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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