





# Effect of vitamin D on *Helicobacter pylori* infection and eradication: An updated systematic review and meta-analysis

Ahmed N Albatineh <sup>1</sup>, Rozbeh Sohrabi <sup>2</sup>, Vajiheh Baghi <sup>3</sup>, Reza Ghanei Gheshlagh <sup>4\*</sup>

<sup>1</sup> Department of Community Medicine and Behavioural Sciences, Faculty of Medicine, Kuwait University, Kuwait

<sup>2</sup> Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran

<sup>3</sup> Besat Hospital, Kurdistan University of Medical Sciences, Sanandaj, Iran

<sup>4</sup> Social Determinants of Health Research, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran

\* **Corresponding author:** Reza Ghanei Gheshlagh, Social Determinants of Health Research, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran. **Email:** rezaghanei30@gmail.com

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## Abstract

**Background:** Various studies that have examined the association between *Helicobacter pylori* (*H pylori*) and vitamin D (25-hydroxyvitamin D [25(OH)D]) have reported different and sometimes controversial results.

**Objectives:** Therefore, this systematic review and meta-analysis was performed to investigate the relationship between vitamin D and *H pylori* infection and its eradication.

**Methods:** Observational studies published in English were searched in PubMed, Scopus, and ISI databases until 1 August 2021. The standardized mean difference (SMD) was used to evaluate the probability ratio of *H pylori* infection and its eradication in the group with low vitamin D levels and the control group. Pooled estimation was calculated by random effects model. Heterogeneity was assessed by Cochran's Q test and  $I^2$  index.

**Results:** Twelve studies were analyzed in this meta-analysis, and the results showed that the level of 25(OH)D in *H pylori*-positive patients was significantly lower than those without infection (SMD= -0.66 ng/mL, 95% CI: -0.99, -0.33,  $P<0.001$ ). Also, the level of 25(OH)D in *H pylori* successful eradication individuals was significantly higher than those with unsuccessful eradication (SMD=1.53 ng/mL, 95%CI: 1.34-1.71,  $P<0.001$ ).

**Conclusion:** There is a significant relationship between vitamin D levels and *H pylori* infection and its eradication. Therefore, it is necessary to pay attention to the vitamin D level in treating *H pylori* infection.

**Keywords:** *Helicobacter pylori*, Eradication, Vitamin D.

## Introduction

*Helicobacter pylori* (*H pylori*) infection is a known cause of chronic gastritis, which affects 50% of the world's population and is important in the pathogenesis of gastrointestinal diseases such as gastric ulcer, gastric adenocarcinoma, and gastric lymphoma.<sup>1</sup> About 76% to 95% of gastric cancers and more than 90% of duodenal cancers are associated with *H pylori* infection.<sup>2</sup> *H pylori* infection is transmitted through the fecal-oral route and can infect all age groups worldwide.<sup>3</sup> This infection is most

common in developing countries and populations with a low socioeconomic background.<sup>4,5</sup> Major variations in the prevalence of *H pylori* in different ethnic groups indicate possible genetic susceptibility of this infection.<sup>5-8</sup> *H pylori* is also not limited to gastrointestinal diseases. However, it is also associated with various systemic diseases such as coronary artery disease, Alzheimer's, and iron deficiency anemia.<sup>9-13</sup>

The National Institute of Health Consensus Development Conference (NIHCDC) states that patients

with *H pylori* infection should receive antimicrobial therapy because the risk of gastrointestinal ulcer recurrence and related complications is not reduced unless the infection is treated.<sup>14</sup> Although triple therapy with proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole has been used as the first line of treatment for *H pylori*, the American College of Gastroenterology reports that the rate of treatment in 2007 was 70% to 85%.<sup>15</sup>

One of the factors that may be associated with *H pylori* infection and even its treatment is the level of vitamin D.<sup>16</sup> It is estimated that about one billion people worldwide have moderate to severe vitamin D deficiency.<sup>17,18</sup> Vitamin D deficiency causes osteoporosis, muscle weakness and increased risk of fractures. It is also associated with an increased risk of infectious, autoimmune, malignant, and chronic diseases.<sup>19-25</sup> The results of the study by Kawaura et al. showed that vitamin D could significantly reduce the rate of *H pylori* infection.<sup>26</sup> Various studies in this field have reported different and controversial results.<sup>3, 27-37</sup>

## Objectives

Accordingly, the present systematic review and meta-analysis study was conducted to investigate the relationship between vitamin D and *H pylori* infection and its eradication.

## Methods

In this systematic review and meta-analysis study, all published English-language articles examining the association between vitamin D levels and *H pylori* infection and its eradication were reviewed according to PRISMA guidelines.<sup>38</sup>

### Data sources and search strategy

ISI/WoS, Scopus, PubMed, and Embase databases were searched without a time limit until August 1, 2020 with the following keywords: *Helicobacter pylori*, *H pylori*, vitamin D, 25(OH)D, 25-hydroxyvitamin D, hydroxycholecalciferols, hypovitaminosis D, cholecalciferol, 25 hydroxycholecalciferols, calcitriol, 25-hydroxyvitamin D3. To access more articles, a list of references to selected articles were also reviewed.

### Selection criteria

In this systematic review and meta-analysis, observational studies published in English that were full-text and reported vitamin D levels in patients infected with *H pylori* and the control group or vitamin D levels in patients with successful and unsuccessful eradication were included in the study. Intervention articles, letters to the editor, and reviews were excluded from the analysis. The modified Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality of the articles. NOS evaluates the quality of an article through three criteria: 1) selection, 2) comparison, and 3) exposure.<sup>39</sup>

### Data analysis

This systematic review and meta-analysis study was performed to estimate the standardized mean difference (SMD) of vitamin D in *H pylori* infection individuals, *H pylori* eradication individuals, and control groups.  $I^2$  index and Cochrane Q test were used to evaluate the heterogeneity among the studies.<sup>40, 41</sup> To combine the studies and calculate the SMD, if the  $I^2$  index > 50% or the Cochrane Q test was significant ( $p$ -value < 0.1), the random effects model was used and otherwise the fixed effects model was used. A Forrest plot was used to display SMD for each study and its 95% confidence interval. Sensitivity analysis with the Leave-one-out method was used to evaluate each study's effect on the pooled SMD.<sup>42</sup> A bar graph was used to visually display the mean vitamin D and its standard deviation in the *H pylori*-positive and *H pylori*-negative groups. Due to the small number of studies, regression-based methods, Egger's regression test, and Begg's rank test were used to examine the publication bias and small study effect.<sup>43, 44</sup> Stata software version 12 was used to analyze the data.

### Statistical analysis

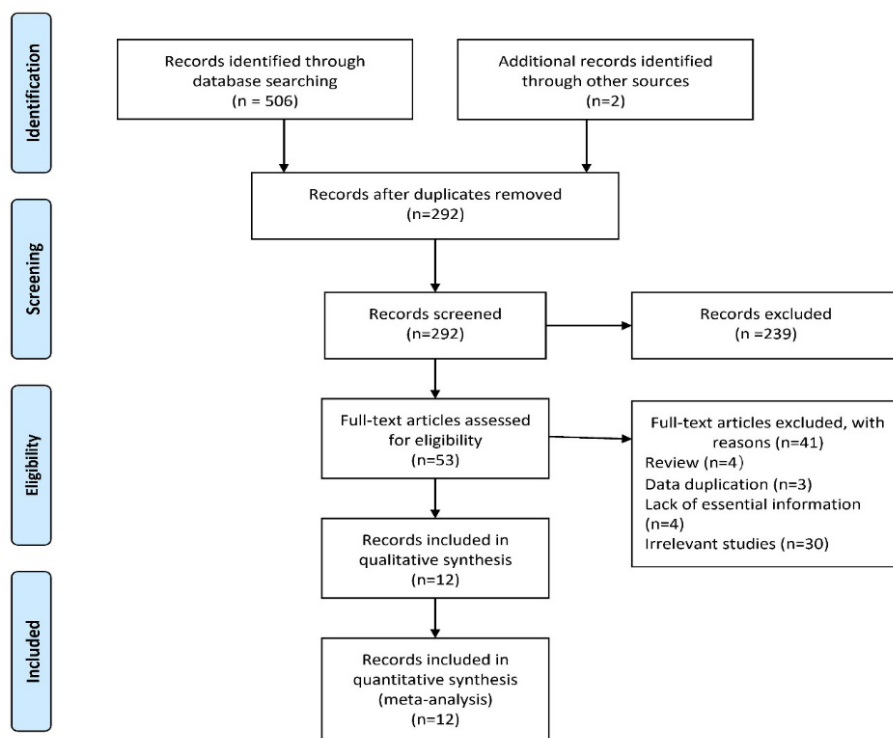
The continuous variables were expressed as the mean  $\pm$  SD, and the categorical variables were presented as a percentage and frequency. Because the data showed a non-normal distribution, the Mann-Whitney test was used to compare the parameters between patients and health groups. The relations between parameters were evaluated using the Pearson correlation coefficient. All statistical analyses were performed with SPSS (version 16.0, SPSS

Inc, Chicago, IL, USA). A “P-value” less than 0.05 was considered significant.

## Results

In the initial search, 508 articles were found. After reviewing the titles and removing duplicates, 292 articles

remained. After reviewing the titles and abstracts, 280 unrelated articles were removed from the analysis and 12 final eligible studies were analyzed. The selected articles were of good quality. The process of searching and screening articles in detail is presented in Figure 1.



**Figure 1.** The process of searching and screening using PRISMA for access to qualified articles

In six studies, the effect of vitamin D on the eradication of *H. pylori* was investigated,<sup>29,32,34-37</sup> and in six other studies, the level of vitamin D in the group with *H. pylori* infection was compared with the control group.<sup>3,27,28,30,31,33</sup> The study of Ibrahim et al. was performed on two groups of women with (Ibrahim (a)) and without abortion (Ibrahim (b)), and the results were reported separately, so

each group was included in the analysis as an independent study.<sup>33</sup> Eight studies were conducted in Asia, two in Africa, and two in Europe. Of the six studies that reported *H. pylori* eradication, four selected 14-day triple therapy,<sup>29,34-36</sup> and 14-day quadruple therapy.<sup>32,37</sup> Considering that  $I^2 > 50\%$ , the random effects model was used to perform the meta-analysis (Tables 1 and 2).

**Table 1.** Studies that have examined the association between vitamin D and *H. pylori* infection

First author	Year	Country	Hp+ (n)	Vitamin D level in Hp+ (ng/mL)	Hp- (n)	Vitamin D level in Hp- (ng/mL)
Ibrahim <sup>33</sup>	2020	Iraq	52	6.91±4.17	48	11.35±7.28
			17	9.91±5.43	83	16.97±5.20
Assaad <sup>28</sup>	2019	Lebanon	225	18.04±7.16	235	30.74±15.66
Han <sup>31</sup>	2019	China	496	17.0±6.9	257	19.2±8.0
Surmeli <sup>3</sup>	2019	Turkey	43	9±8.37	211	13.60±11.26
Gerig <sup>30</sup>	2013	Switzerland	85	19.60±12.00	315	20.80±11.60
Antico <sup>27</sup>	2012	Italy	21	11.10±8.40	212	21.30±12.20

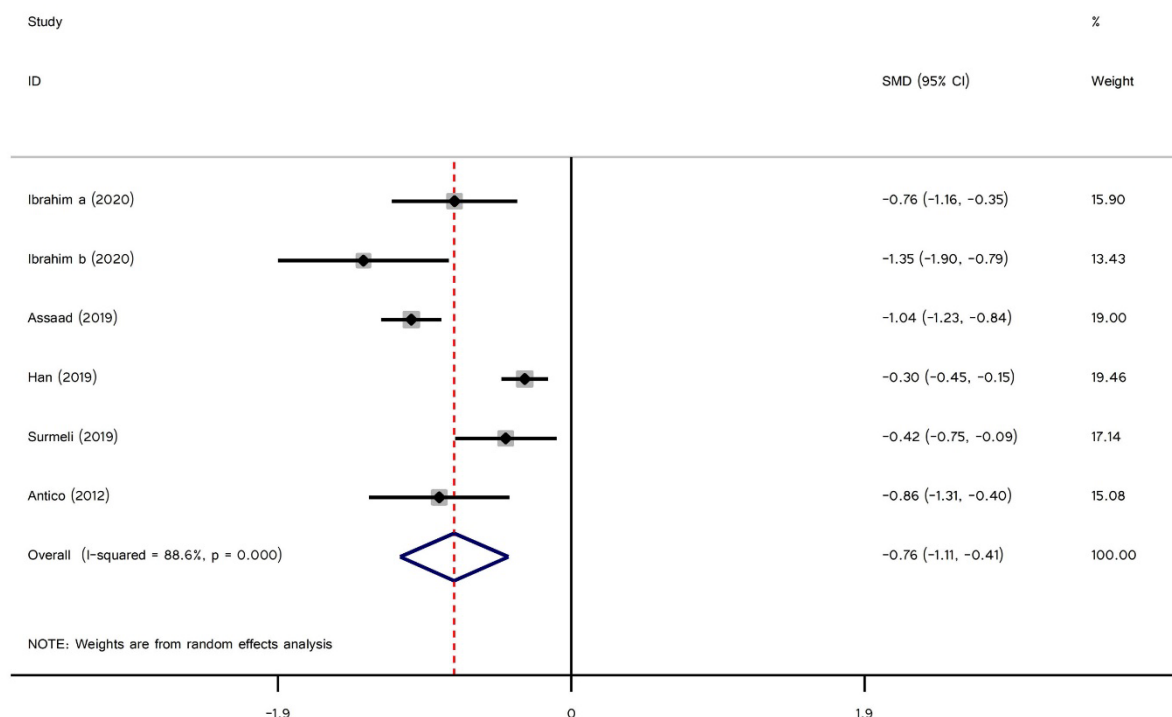
### Association between Helicobacter pylori infection and vitamin D

In six studies, the vitamin D levels in H pylori-positive and H pylori-negative individuals were reported. Due to the heterogeneity among the studies ( $I^2=89.8\%$ ,  $Q=58.79$ ,  $p\text{-value}<0.0001$ ), a random effects model was used to estimate the difference between the mean of vitamin D in the two groups. The random effects model showed that the mean of vitamin D in the patients with H pylori infection was 0.66 ng/mL (95% CI: -0.99 to -0.33) less than the

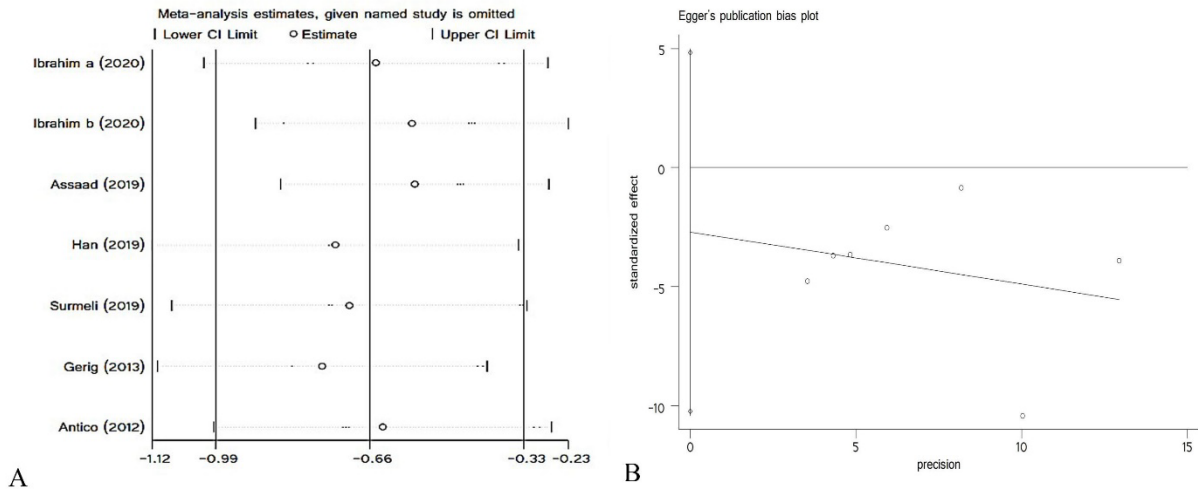
control group. The results of sensitivity analysis also showed that by omitting the Gergi study and using random effects estimates, the mean of vitamin D in the H pylori positive group was 0.76 ng/mL less than the control group ( $I^2=88.6\%$ ,  $Q = 43.96$ ,  $p\text{-value}<0.0001$ ) (Figure 2). It is worth noting that with the omission of this study, the heterogeneity among the studies did not change (Figure 3A). The publication bias of the studies using Egger’s ( $p=0.399$ ) and Begg’s ( $p=0.100$ ) test was not significant (Figure 3B).

**Table 2.** Studies that have examined the association between vitamin D and H pylori eradication.

First author	Year	Country	Hp+ successful eradication (n)	Vitamin D (ng/mL)	Hp- eradication unsuccessful (n)	Vitamin D (ng/mL)
Magsi <sup>35</sup>	2021	Pakistan	88	31.01±7.8	36	18.9±5.6
Shatla <sup>36</sup>	2021	Egypt	108	28.12±8.10	42	13.54±6.37
Huang <sup>32</sup>	2019	China	124	19.87±6.35	36	15.09±7.72
El Shahawy <sup>29</sup>	2018	Egypt	105	24.71±7.10	45	14.70±4.50
Yildirim <sup>37</sup>	2017	Turkey	170	19.00±8.10	50	9.10±4.70
Korkmaz <sup>34</sup>	2015	Turkey	29	25.50±10.00	43	14.70±8.50



**Figure 2.** A) SMD of vitamin D level in H pylori positive patients was 0.76 ng/mL less than that in H pylori negative patients.



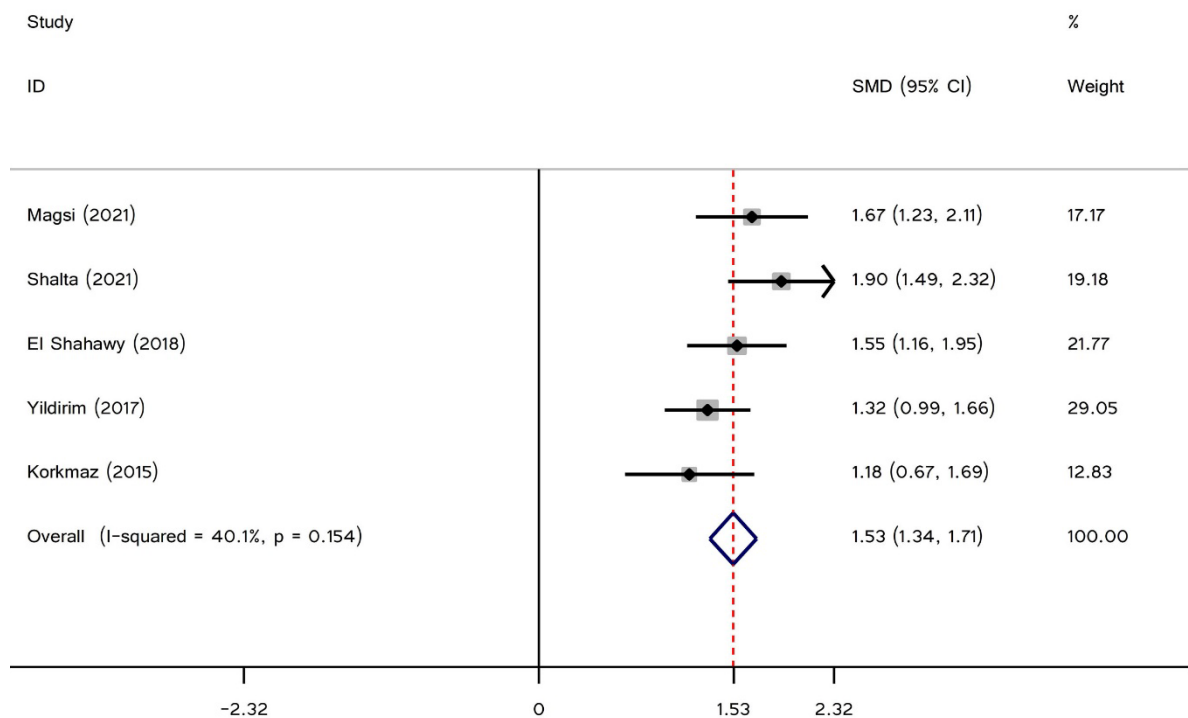
**Figure 3.** A) Sensitivity analysis results; B) Publication bias test

**The association between *Helicobacter pylori* eradication and vitamin D**

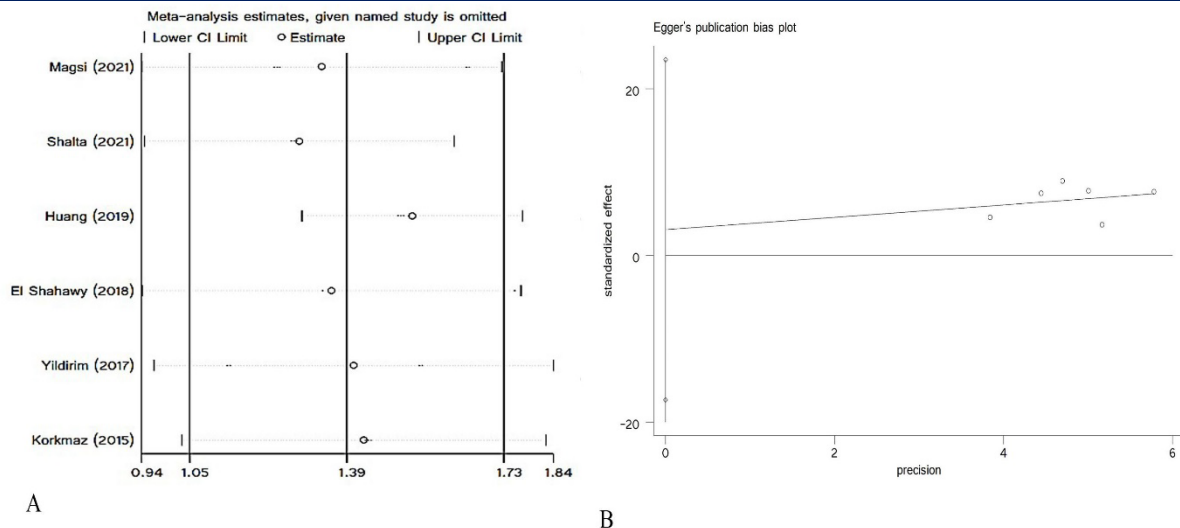
Due to the heterogeneity among the studies ( $I^2 = 76.1\%$ ,  $Q = 20.96$ ,  $p\text{-value} = 0.001$ ), a random effects model was used to estimate the standardized mean difference (SMD) between the means of vitamin D in the two groups. The results showed that the mean of vitamin D in patients with successful eradication was  $1.39 \text{ ng/mL}$  (95% CI:  $1.05\text{-}1.73$ ) more than the unsuccessful eradication patients (Figure 4). According to the results of sensitivity analysis (Figure 5A), it was observed that with the omission of Huang study, the

heterogeneity in the studies was significantly reduced ( $I^2 = 40.1\%$ ,  $Q = 6.68$ ,  $p\text{-value} = 0.154$ ). After deleting the study and using the fixed effects model, the SMD of vitamin D in the successful eradication group was  $1.53 \text{ ng/mL}$  (95% CI:  $1.34\text{-}1.71$ ) more than the unsuccessful eradication group.

Publication bias was tested among all articles describing the association between vitamin D deficiency and H pylori infection and its eradication. The publication bias of the studies using Egger's ( $p=0.699$ ) and Begg's ( $p=0.573$ ) test methods was not significant (Figure 5B).



**Figure 4.** SMD of vitamin D level in H pylori successful and unsuccessful eradication individuals.



**Figure 5.** A) Sensitivity analysis results B) Publication bias test

## Discussion

The relationship between vitamin D and H pylori infection and especially the effect of vitamin D on the eradication of this infection is still controversial in clinical studies. Therefore, in order to provide sufficient evidence, relevant published articles were reviewed and a meta-analysis was conducted. The results of this study showed that the level of vitamin D in patients with H pylori infection was lower than in those without infection. Research indicated that vitamin D can reduce the risk of infections by several mechanisms. Vitamin D strengthens the innate immune system by up-regulating the expression of antimicrobial peptides and defense in immune cells.<sup>29</sup> Therefore, vitamin D deficiency may increase immune system disorders and be a risk factor for the development of an infectious disease.<sup>45</sup> The results of the present study confirmed that the level of vitamin D in people with successful eradication was higher than in those with unsuccessful eradication. H pylori infection was also more likely to be eradicated in people with normal vitamin D levels than in most people with vitamin D deficiency. The results of a study showed that vitamin D3 decomposition product (VDPI) selectively affects H pylori.<sup>46</sup> When VDPI comes in contact with dimyristoyl phosphatidylethanolamine (DMPE), which is a major component of H pylori cell membrane, it dissolves.<sup>47</sup> Vitamin D plays its biological role by combining with VDR in tissues such as kidney, thyroid, intestine, skin, immune cells, nonparenchymal hepatocytes, and biliary

epithelial cells.<sup>48</sup> Therefore, VDR is involved in a variety of biological reactions and is able to reduce infection due to its antibacterial effects against H pylori.<sup>49</sup> Guo believes that vitamin D can have antimicrobial effects due to its important role in gastric mucosa homeostasis and host protection from H pylori.<sup>50</sup> In vitamin D deficiency, infected macrophages are unable to produce 1,25(OH)D<sub>2</sub>, so cathelicidin and  $\beta$ -defensin are not produced to kill H pylori strains. Vitamin D deficiency may be a risk factor for failure to treat H pylori and may require vitamin D supplementation before the eradication of H pylori.<sup>29</sup>

## Conclusions

The results of this study showed that there is a relationship between vitamin D deficiency and H pylori infection and its unsuccessful eradication and it seems necessary to consider the level of vitamin D in patients with H pylori infections. Prospective studies are also needed to confirm these results.

## Acknowledgment

None.

## Competing interests

The authors declare that they have no competing interests.

## Abbreviations

National Institute of Health Consensus Development Conference: NIH/CDC;

Proton pump inhibitor: PPI;  
Newcastle-Ottawa Scale: NOS;  
Standardized mean difference: SMD.

### Authors' contributions

RGG, VB, and RS contributed to designing and performing this systematic review. RGG and ANA checked the data and conduct data analyses. ANA and RGG contributed to writing and editing the paper. All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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### Availability of data and materials

The data used in this study are available from the corresponding author on request.

### Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval was obtained.

### Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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