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Global Prevalence and Clinical Outcome of Spontaneous Peptic Ulcer Perforation Related to *Helicobacter pylori* Infection: A Systematic Review and Meta-Analysis

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ABSTRACT

Helicobacter pylori play an important role in the pathogenesis of digestive tract diseases, including peptic ulcers. One of the severe complications of peptic ulcers is spontaneous perforation. This research aimed to analyze the incidence of spontaneous peptic ulcer perforation in patients infected with *H. pylori* compared to the uninfected patient. This reseach applied an analytical research with a systematic review and meta-analysis design using articles from the PubMed and Scopus databases until December 2024. The analysis was carried out using R software with the Meta and Metafor packages. The pooled prevalence of *H. pylori* infection in cases of spontaneous perforation of peptic ulcers was 57% (95%CI: 0.44–0.70) with the highest prevalence occurring in the Eastern Mediterranean. The results of the analysis showed that patients with spontaneous duodenal ulcer perforation, 59.0% were infected with *Helicobacter pylori* (95%CI: 0.29–0.83). Infected patients had a 0.48 times risk of dying postoperatively (OR = 0.48; 95%CI: 0.06–3.59) and a 0.50 times risk of experiencing postoperative complications (OR = 0.50; 95%CI: 0.02–11.07). Infected patients were treated for an average of 7.06 days shorter (95%CI: –63.00–48.89). The prevalence of *H. pylori* infection in patients with spontaneous peptic ulcer perforation was 57% with the highest prevalence in the Eastern Mediterranean region and the lowest in America. Patients infected with *H. pylori* had a lower risk of death and postoperative complications. Patients infected with *H. pylori* had a shorter average length of hospital stay than those not infected.

KEYWORDS: Peptic Ulcer Perforation, *H. pylori*, Infection, Prevalence, Systematic Review, Meta-Analysis

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INTRODUCTION

Five decades have passed since the *Campylobacter pyloridis* bacterium was first identified. Since then, numerous studies on the bacterium now known as *Helicobacter pylori* (*H. pylori*) have been conducted extensively worldwide. *H. pylori* were later found to play a crucial role in the pathogenesis of various gastrointestinal diseases, such as chronic gastritis, gastric ulcers, peptic ulcers, gastric cancer, and mucosal-associated lymphoid tissue (MALT) lymphoma (1). It is estimated that more than half the world's population is infected with H. pylori. Several studies using meta-analyses and systematic reviews confirm the wide variation in the prevalence of *H. pylori* infection among countries worldwide. A 2017 systematic review and meta-analysis found that the highest prevalence of *H. pylori* infection was found in Africa (79.1%), followed by South America and the Caribbean (63.4%), Asia (54.7%), North America (37.1%), Western Europe (34.3%), and Oceania (24.4%) (2).

Peptic ulcers often occur at the lesser curvature of the stomach. Although often associated with *H. pylori* infection, they can also cause by long-term consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) and antiplatelet agents. The diagnosis of peptic ulcers is based on symptoms, risk factors, and confirmation by endoscopy. In high prevalence area, peptic ulcers should be followed up with endoscopy and biopsy.

Peptic ulcers complication that causes high morbidity and mortality is spontaneous perforation. Spontaneous perforation of hollow organs such as the stomach and duodenum can lead to extravasation of gastric fluid and pathogens into the intra-abdominal space. This condition can lead to peritonitis, also known as complicated intra-abdominal infection (CIAI). This condition is a medical emergency that can be fatal if not treated promptly and appropriately. Treatment can include conservative measures or more aggressive surgical procedures to treat the underlying cause.

To date, spontaneous perforation of peptic ulcers has been widely associated with *H. pylori* infection. Various studies aimed to examine the relationship between the prevalence of *H. pylori* infection and the incidence of spontaneous perforation of peptic ulcers

had been conducted worldwide. However, there are no systematic reviews and meta-analyses that specifically address the relationship between the prevalence of *H. pylori* infection and the incidence of spontaneous perforation of peptic ulcers. Therefore, in this study, we aimed to conduct an analytical study with a systematic review and meta-analysis design to examine the relationship between the prevalence of *H. pylori* infection and the incidence of spontaneous perforation of peptic ulcers worldwide and linking it to clinical profiles and patient outcomes.

MATERIALS AND METHOD

This research is an analytical study with a systematic review design based on prospective cohort, cross-sectional, and randomized control trial articles. Data will be managed narratively and meta-analyzed. Journal selection was carried out using guidelines from the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis Protocol) flowchart and a PRISMA assessment sheet tailored to the objectives of this systematic review and meta-analysis. This research registration has been submitted to the International Prospective Register of Systematic Reviews/PROSPERO with registered status For the keywords, medical subject headings and free-text phrases which were; ((perforated peptic ulcer) OR (perforated gastric ulcer) OR (perforated duodenal ulcer)) AND (pylori)) AND (prevalence).

Inclusion criteria for this study included articles from the PubMed and Scopus databases until December 2024. Included studies included prospective cohort, cross-sectional, and randomized control trial designs. Exclusion criteria included studies published in languages other than English, articles not published in full-text form or only abstract publications, case studies, case series, and literature reviews. The risk of bias of included studies was assessed by using the Newcastle-Ottawa Scale (NOS) and Risk of Bias-2 (RoB-2) tool. Studies with NOS scores < 7 were considered to have a high risk of bias, whereas those with a score 7 were considered low risk of bias. Database search was performed by DD and CCG. Three independent reviewers read and extract the data (DD, CCG, KAF). The meta-analysis and synthesis were performed by DD, KAF, AW and ED. We collected the data of *Helicobacter pylori* infection status and clinical outcomes such as death and complication. The subjects age and gender of participants are also included.The statistical analysis was performed on the mean and risk ratio using R software with the Meta and Metafor packages. The analysis was performed using a coding system and applied to analyze the overall prevalence of infection and the association between outcomes and *H. pylori* infection status.

RESULTS

A total of 158 articles were identified from the Pubmed database and 37 articles were identified from the Scopus database. The flowchart of study selection was presented in Figure 1. Based on the inclusion and exclusion criteria, 23 articles from Pubmed and 7 articles from Scopus were included for the analysis of the prevalence of *H. pylori* infection. Of the 30 articles with *H. pylori* infection data, 2 articles with mortality rates data and 3 articles with post-operative complication rates data were used for further analyses. The 30 studies included in further analysis and their corresponding quality score were shown in Table 1.

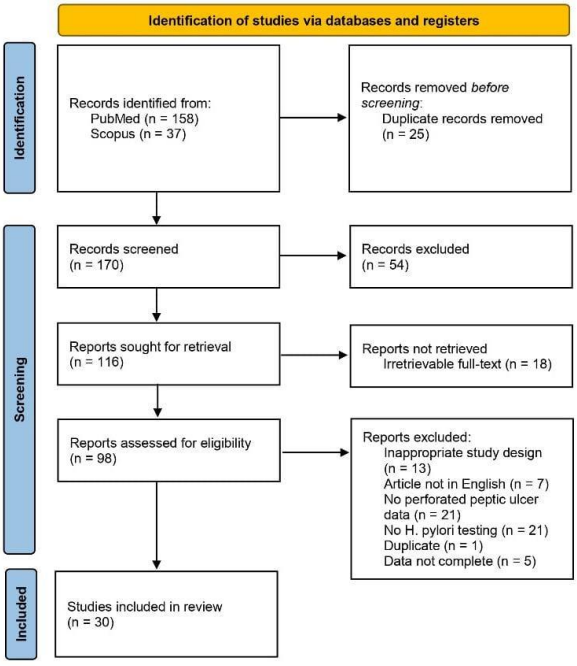

Figure 1. The flowchart of study selection

Table 1: Characteristics of included studies

No.	Author	Country	n	Quality score*	*H. pylori*-positive (n/N; %)	Citation
1	Yeh et al., 2024	Taiwan	7	7	2/7 (28.5)	(3)
2	Tadesse et al., 2021	Ethiopia	46	4	19/46 (41.3)	(4)
3	Thirupathaiah et al., 2020	India	48	7	6/48 (12.5)	(5)
4	Okidi et al., 2019	Uganda	28	4	4/28 (14.3)	(6)
5	Yan et al., 2019	China	20	4	42/79 (53.1)	(7)
6	Rasane et al., 2019	US	79	9	6/20 (30.0)	(8)
7	Yang et al., 2017	South Korea	174	7	78/174 (44.8)	(9)
8	Seow et al., 2017	Singapore	599	9	363/599 (60.6)	(10)
9	Casali et al., 2012	Brazil	14	5	11/14 (84.6)	(11)
10	Zelicson et al., 2011	USA	79	5	27.9%	(12)
11	El-Nakeeb et al., 2009	Egypt	77	Some concerns	65/77 (84.4)	(13)
12	Aman et al., 2008	Pakistan	50	4	34/50 (68.0)	(14)
13	Komen et al., 2008	Netherlands	30	6	18/30 (60.0)	(15)
14	Hua et al., 2007	China	52	7	4/52 (7.7)	(16)
15	Bobrzynski et al., 2005	Poland	91	6	58/91 (63.7)	(17)
16	Gisbert et al., 2004	Spain	16	9	10/16 (62.5)	(18)
17	Canoy et al., 2002	United Kingdom	5	5	2/5 (40.0)	(19)
18	Metzger et al., 2001	Switzerland	45	5	33/45 (73.3)	(20)
19	Sillakivi et al., 2001	Estonia	53	5	52/53 (98)	(21)
20	Ng et al., 2000	Hong Kong	129	Some concerns	99/129 (76.7)	(22)
21	Tokunaga et al., 1998	Japan	47	6	92%	(23)
22	Ng et al., 1996	Hong Kong	73	6	51/73 (69.9)	(24)
23	Reinbach et al., 1993	England	80	7	47%	(25)
24	Edyedu, et al 2024	Uganda	81	6	56/81 (69.1)	(26)
25	Hussain et al., 2012	Pakistan	75	5	75 (100)	(27)
26	Plummer et al., 2004	Jamaica	97	6	3/3 (100)	(28)
27	Hartin et al., 2009	United States	5	6	3/5 (60.0)	(29)
28	Dogra et al., 2014	India	50	7	46/50 (92)	(30)
29	Tunruttanakul et al., 2018	Thailand	136	9	94/136 (69.6)	(31)
30	Bhardwaj et al., 2016	India	75	5	38/75 (50.6)	(32)

*Case control and cohort studies were assessed using Newcastle-Ottawa Scale, while randomized-controlled trial was assessed using Risk of Bias-2 (RoB-2) tool

3.1. Prevalence of *H. pylori* infection in patients with spontaneous peptic ulcer perforation

We analyzed 30 articles reporting the prevalence of *H. pylori* infection in patients with spontaneous peptic ulcer perforation. The overall pooled prevalence of *H. pylori* infection in cases of spontaneous peptic ulcer perforation was 57% (95% CI: 0.44–0.70). Heterogeneity analysis showed significantly heterogeneous data distribution ($I2 = 90\%$; $p < 0.0001$). We also conducted subgroup analysis by dividing articles based on the regional divisions by the World Health Organization, subsequently divided into six regions: Western Pacific, Africa, Southeast Asia, America, Eastern Mediterranean, and Europe. In general, the analysis results showed differences in the prevalence of *H. pylori* infection in each region. In the Western Pacific region, eight articles were analyzed and the prevalence of infection was 52% (95% CI: 0.29 – 0.75). In the African region, there were three articles with a pool prevalence of infection of 41% (95% CI: 0.14 – 0.74). In the South and East Asia regions, four articles were analyzed with a pool prevalence of infection of 58% (95% CI: 0.20 – 0.89). In the Americas region, five articles were found with a prevalence of *H. pylori* infection of 37% (95% CI: 0.11 – 0.74). In the Eastern Mediterranean region, we analyzed three articles and found a total prevalence of 89% (95% CI: 0.50–0.99). In Europe, seven articles were analyzed, with a prevalence of 65% (95% CI: 0.51–0.77). Heterogeneity analysis showed that the prevalence distribution across all regions was significantly heterogeneous ($p < 0.05$ for all regions). The Forrest plot of the prevalence analysis is shown in Figure 2.

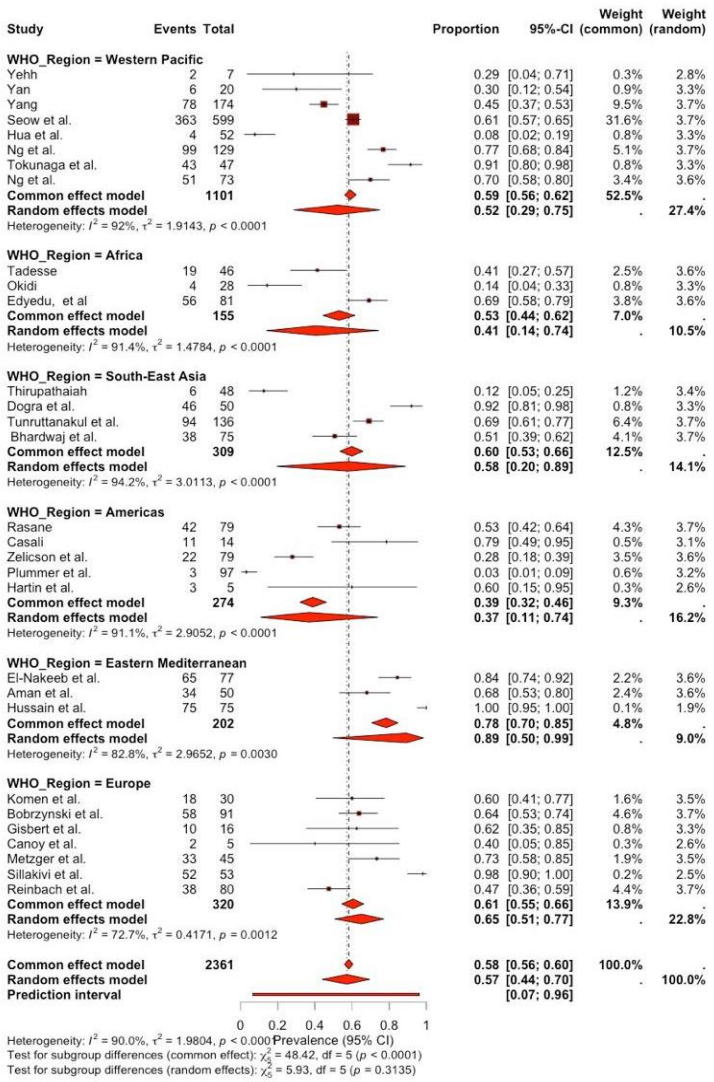

Figure 2. Forest plot of prevalence of *H. pylori* infection in spontaneous peptic ulcer perforation events

Prevalence of *H. pylori* infection in patients with spontaneous duodenal ulcer perforation

We analyzed the prevalence of spontaneous duodenal ulcer perforation without patients who had gastric ulcer perforation. Eight studies investigating cases of duodenal ulcer perforation were identified. The analysis showed that among all patients with spontaneous duodenal ulcer perforation, 59.0% were infected with H pylori (95% CI: 0.29–0.83). Further analysis was also carried out by categorizing studies on peptic ulcer perforation according to regional divisions (Figure 3). In the Eastern Mediterranean region, two articles were analyzed, showing an infection prevalence of 77.0% (95% CI: 0.57–0.89). In the European region, two articles were analyzed, with an infection prevalence of 47.0% (95% CI: 0.37–0.58). In the Western Pacific region, two articles were analyzed, showing a prevalence of 84.0% (95% CI: 0.63–0.94). In the Americas region, two articles were identified, with an *H. pylori* infection prevalence of 17.0% (95% CI: 0.00–0.90).

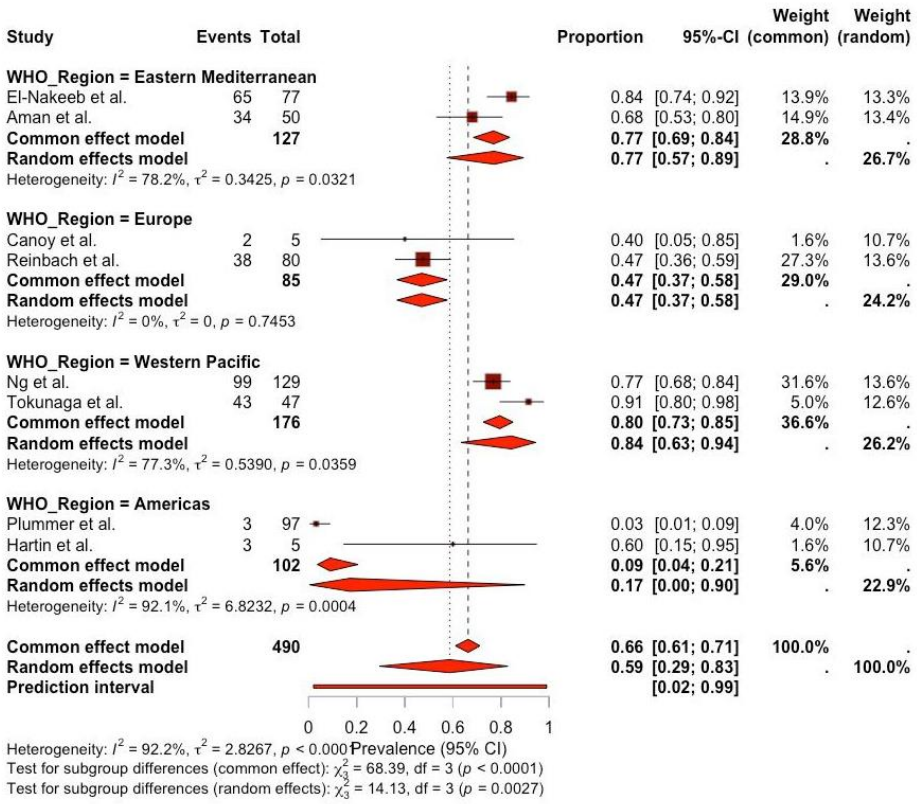

Figure 3. Prevalence of *H. pylori* infection in spontaneous duodenal ulcer perforation

3.2 Relationship between *H. pylori* infection and clinical outcomes

In this study, we analyzed the relationship between *H. pylori* infection status and patient outcomes. Of the 30 articles, only two included data related to patient mortality rates in the group of patients infected and those not infected with *H. pylori*. The results of the analysis showed that patients infected with *H. pylori* had a 0.48 times risk of dying postoperatively due to spontaneous perforation of peptic ulcers (OR = 0.48; 95% CI = 0.06 – 3.59). Heterogeneity analysis showed that both articles in this analysis were homogeneous and there was no significant difference between them (I^2 = 0.0%, p = 0.887). The Forrest plot of the relationship between *H. pylori* infection and mortality is shown in Figure 4.

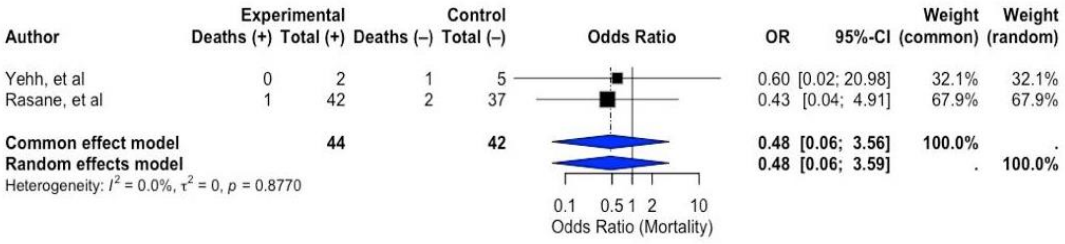

Figure 4. The Forrest plot of the relationship between *H. pylori* infection and mortality

We analyzed the relationship between *H. pylori* infection and the incidence of post-operative complications. Of the 30 articles, three studies were included for further analysis. Patients infected with *H. pylori* had a 0.50 times greater risk of experiencing post-operative complications due to spontaneous perforation of peptic ulcers (OR = 0.50; 95% CI = 0.02 – 11.07). Heterogenity analysis showed that both articles in this analysis were homogeneous and there was no significant difference between them (I^2 = 0.0%, p = 0.384). A Forrest plot of the relationship between *H. pylori* infection and post-operative complications is shown in Figure 5.

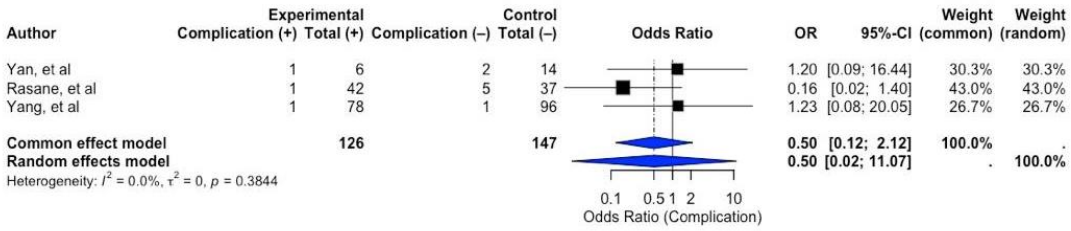

Figure 5. The Forrest plot of the relationship between *H. pylori* infection and post-operative complications

In this meta-analysis, we included two studies comparing the length of hospital stay between *H. pylori*-positive and *H. pylori*-negative patients with perforated peptic ulcers. The pooled mean difference was –7.06 days (95% CI: –63.00 – 48.89), indicating a shorter length of stay in the *H. pylori*-positive group, but this result was not statistically significant. Heterogenity was high (I^2 = 90.4%, p = 0.0012), indicating significant differences between the studies. These findings should be interpreted with caution, and further research is needed for more definitive conclusions. The analysis of length of stay is shown in Figure 6.

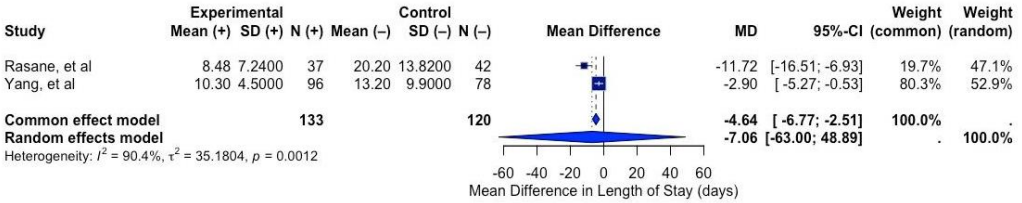

Figure 6. Forrest plot of the relationship between *H. pylori* infection and length of stay

DISCUSSION

The research examined the prevalence of *H. pylori* infection in spontaneous peptic ulcer perforation cases according to the WHO regional classification. We found that the prevalence of *H. pylori* infection varied between regions, with the lowest prevalence in the Americas and the highest in the Eastern Mediterranean. Previous studies have shown that the prevalence of infection in Eastern Mediterranean countries is relatively high, reaching 88.7% in Egypt (33) and 57% in Pakistan (34). Prevalence in developing countries with high population density and limited hygiene is a risk factor often associated with the transmission mechanism of this bacterial infection (35; 36). The high prevalence of *H. pylori* infection in this region may be related to the pathogenesis of peptic ulcers.

Spontaneous peptic ulcer perforation can be caused by various factors, but NSAID and *H. pylori* infection are believed to be the two main causes. These two conditions can occur independently or simultaneously. The risk factors that increase the risk of gastroduodenal perforation remain controversial, as various studies have reported conflicting results. One study reported that 70% of patients with duodenal or pre-pyloric ulcer perforation were infected with *H. pylori*. However, when stratifying these patients based on NSAID use, 80% (48 of 60 patients) of non-NSAID-related perforations were found to be infected with *H. pylori*, compared with only 3 of 13 patients in the NSAID group. Thus, among non-NSAID users, *H. pylori* infection is likely an important cause of ulcer formation and perforation (24). This study suggests that *H. pylori* infection is a risk factor for perforation, whether or not NSAID use is present.

In this meta-analysis, the clinical outcomes that can be further analyzed include post-operative patient mortality, post-operative complications, and length of hospital stay. We found that patients infected with *H. pylori* had a lower incidence of post-operative mortality and post-operative complications. This might be caused by the mechanism of low gastric acid in patients with pangastritis due to *H. pylori* colonization in the gastric mucosa (37;38). Lower gastric acid production is one of the conditions that support the healing process of peptic ulcers, including primary post-suturing wounds due to spontaneous perforation (Huang and Hunt, 1996). This can reduce the risk of post-suturing leakage and also reduce the risk of early post-surgical complications such as surgical wound infection, bleeding, and ongoing septic shock.

In terms of length of hospital stay, patients infected with *H. pylori* had a shorter average length of stay than those not infected. A study by Rasane et al. showed that the uninfected group had a length of stay in the ICU nearly 10 times longer, four times longer ventilator days, and more than twice as long a hospital stay as the *H. pylori*-infected group. In this study, the infected group had a higher comorbidity index and lower albumin levels than the uninfected group, suggesting that the pathophysiology of perforation may differ between the infected and uninfected groups (8). This may be related to the fact that the incidence of post-operative complications in *H. pylori*-infected patients is also lower than in uninfected patients, resulting in shorter post-operative care.

Another important issue related to patients with perforated peptic ulcer is the prevention of postoperative complications. Postoperative pneumonia and slow physical recovery are major complications following emergency laparotomy. These complications are reported to significantly associated with higher healthcare expenses, prolonged hospitalization, greater risk of mortality, and slower recovery (39). Early postoperative rehabilitation should be performed to prevent postoperative pulmonary complication. Rehabilitation such as early ambulation and respiratory exercises, assisted mobilization, and guided session of deep-breathing and coughing exercises (40; 41; 42). Previous study reported the high prevalence of prolonged ventilator used and postoperative pneumonia in patients underwent abdominal surgery, caused by a reduction of 20–50% in respiratory muscle strength, which continues for the first five days after the operation (43). Respiratory physiotherapy such as diaphragmatic breathing exercises, inspiratory muscle training, spirometry, effective coughing techniques, and positive expiratory pressure, as well as an early mobilization protocol that includes sitting on the edge of the bed, standing, and walking with daily progression are widely used rehabilitation methods (44; 45). In addition, postoperative pain management is important to consider, either pharmacological intervention or non-pharmacological intervention such as preoperative patient education and mind-body modalities (46). Adequate postoperative pain management may reduce discomfort and improving mobility.

In developed countries, preventing pulmonary complications in patients undergoing major abdominal surgery is a key role and duty of hospital physiotherapists. Unfortunately, in regions where physiotherapy is not yet well established, the perioperative measures is still the feasible option to prevent complication. Physiotherapists could educate patients on the risk of postoperative complication and explain how breathing exercises and early movement can help prevent it, followed by instruction and practice in deep-breathing and coughing techniques (41). However, perioperative rehabilitation has limitation to be used in emergency case such as spontaneous peptic ulcer perforation. Therefore, the optimalization of postoperative rehabilitation should be performed to increase patient recovery.

This study has several limitations. First, the studies analyzed further in this systematic review and meta-analysis could not rule out the possibility of spontaneous peptic ulcer perforation caused by factors other than *H. pylori* infection, such as long-term use of aspirin, naproxen, and NSAIDs, excessive alcohol consumption, smoking, and stress, which could potentially contribute to the study's bias. Second, the limited number of studies included in the outcome analysis was due to a lack of information on outcomes in both *H. pylori*-infected and uninfected patient groups. However, despite these limitations, this study can serve as a reference for describing the relationship between spontaneous peptic ulcer perforation and *H. pylori* infection status globally.

CONCLUSION

The prevalence of *H. pylori* infection in patients with spontaneous peptic ulcer perforation was 57% with the highest prevalence in the Eastern Mediterranean region and the lowest in America. Patients infected with *H. pylori* have a lower risk of death and postoperative complications. Patients infected with *H. pylori* have a shorter average length of hospital stay than those not infected.

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