

Association Between *Helicobacter pylori* Infection and Ulcerative Colitis: A Meta-Analysis Study

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ABSTRACT

Background: Ulcerative colitis (UC), a chronic inflammatory disease causing bloody diarrhea, remains a major global disease burden. While *Helicobacter pylori* infection is postulated to be able to reduce the occurrence of UC, its role in the disease itself remains contentious. Hence, this meta-analysis aims to examine whether *H. pylori* infection can lower the chance of developing UC.

Method: A systematic search was conducted through three electronic databases, namely Cochrane, PubMed, and Embase, along with individual hand searching to analyze the association between ulcerative colitis and *H. pylori* infection in the adult population. Relevant articles selected through eligibility criteria were assessed for its quality by using the Newcastle-Ottawa Scale. Furthermore, a random-effects meta-analysis was conducted to estimate the pooled odd ratios (ORs) along with their 95% confidence intervals (CIs). Higgins test and funnel plots were also conducted.

Results: A total of 11,498 patients with UC and 356,130 controls from 22 studies were included in the meta-analysis. Included studies showed fair or good quality based on Newcastle-Ottawa Scale. Our findings indicated that *H. pylori* infection was associated with lower odds of UC [pooled ORs 0.51 (95% CI: 0.46-0.56)], albeit moderate heterogeneity ($I^2 = 54\%$, $p = 0.002$). Furthermore, publication bias was not found.

Conclusion: The present study adds to the growing body of evidence supporting the potential protective effects of *H. pylori* infection on the occurrence of UC. However, further primary research with prospective study design needs to be conducted to confirm our findings.

Keywords: *H. pylori* infection, ulcerative colitis, meta-analysis

ABSTRAK

Latar belakang: Kolitis ulseratif merupakan sebuah penyakit inflamasi kronik yang menyebabkan diare berdarah dan salah satu penyakit yang membebaskan dunia. Beberapa penelitian menunjukkan bahwa infeksi *Helicobacter pylori* dapat menurunkan resiko terjadinya kolitis ulseratif, tetapi peran protektif *H. pylori* pada penyakit tersebut masih diperdebatkan. Oleh karena itu, meta-analisis ini bertujuan untuk meneliti apakah infeksi *H. pylori* dapat menurunkan kemungkinan terjadinya kolitis ulseratif.

Metode: Pencarian sistematis dilakukan melalui pangkalan data elektronik Cochrane, PubMed, dan Embase serta pencarian literatur tambahan untuk menganalisa hubungan antara infeksi *H. pylori* dengan kolitis ulseratif

pada pasien dewasa. Artikel relevan yang terpilih melalui kriteria inklusi kemudian dianalisa kualitasnya menggunakan Skala Newcastle-Ottawa. Selanjutnya, meta-analisis efek acak dilakukan untuk memperkirakan angka rasio peluang (OR) dengan interval kepercayaan 95% (95% CI). Selain itu, funnel plot dan tes Higgins juga dilakukan.

Hasil: Sebanyak 11,498 pasien dengan kolitis ulseratif dan 356,130 kontrol dari 22 penelitian menjadi subjek pada meta-analisis ini. Studi yang disertakan dalam penelitian ini memiliki kualitas cukup atau bagus berdasarkan Skala Newcastle-Ottawa. Penelitian ini menunjukkan bahwa infeksi *H. pylori* dikaitkan dengan kemungkinan terkena kolitis ulseratif yang lebih rendah [pooled ORs = 0.51 (95% CI: 0.46-0.56)], walaupun heterogenitas sedang ditemukan ($I^2 = 54\%$, $p = 0.002$). Bias publikasi tidak ditemukan.

Simpulan: Penelitian ini menambah dan mendukung bukti yang ada terkait temuan infeksi *H. pylori* yang dapat menjadi faktor protektif terhadap munculnya kolitis ulseratif. Namun, penelitian primer lebih lanjut dengan desain penelitian prospektif perlu dilakukan untuk mengkonfirmasi temuan kami.

Kata kunci: Infeksi *H. pylori*, kolitis ulseratif, meta-analysis

INTRODUCTION

Ulcerative colitis (UC) is a condition caused by chronic inflammation, mainly originating and manifesting in the colon.^{1,2} It causes erosion and bleeding in the colorectum mucosal area. There are 9 - 20 cases of ulcerative colitis (UC) per 100,000 population in the world each year.^{3,4} In Asia the ratio ranges from 0.54-3.44 per 100,000 people each year. The peak age of onset of this disease is 30-40 years.⁵ In addition, the distribution of the disease is equal by sex, both to men and women, they are affected equally.⁵ In Indonesia, there is yet to be a national epidemiological study related to IB or ulcerative colitis.

The main symptom of this condition is bloody diarrhea, which may be accompanied by tenesmus, abdominal pain, and malaise.^{1,6} Initial examinations in patients suspected of having ulcerative colitis can be in the form of stool examinations to screen for the infection of *Clostridium difficile*, blood tests and fecal calprotectin to see the degree of the disease and screen for IBD, however both method are not specific to ulcerative colitis diagnosis. To confirm the diagnosis of ulcerative colitis, a colonoscopy is required to see the inflammatory involvement of the colonic lining as well as a biopsy. In ulcerative colitis, the layers involved in the inflammatory process are from the mucosa to the submucosal area. The disease activity can vary from remission to severe relapse, therefore is necessary to grade the severity, based on the assessment of Montreal Classification.⁶ The classification could rate and provide proper grading of the severity of ulcerative colitis, an important finding needed when determining appropriate therapy for the patient.⁷ No definitive cure exists as of today, and thus, the therapy is targeted

towards lowering the symptoms and inflammation until achieving remission. The medication used is anti-inflammatory drugs such as sulfasalazine, but if the use of drugs does not give a positive effect, then surgical procedures such as colectomy can be proposed. Because of the extensive symptoms and medications, patients with UC may have lower quality of life. Furthermore, it has many complications such as toxic megacolon and colon cancer.^{1,6,8}

Until now, the exact cause of ulcerative colitis is unknown. Genetic and environmental factors may contribute towards the occurrence of UC as it disrupts the normal homeostasis in the colon. Environmental factors such as smoking, low fiber and high protein intake diets may play a role in UC. However, it is postulated that the genetic component is the most important risk factor in this disease. This disease is thought to be caused by an autoimmune process.⁹ Another theory states that changes in the composition of the gut microbiota and immune defects in the mucosa can cause ulcerative colitis, thus a combination of genetic, immune and environmental factors may cause ulcerative colitis.⁶ One of the theories being studied regarding the cause of ulcerative colitis is *H. pylori* infection. *H. pylori* is a gram-negative bacteria that can infect the gastrointestinal tract, causing various diseases, such as peptic ulcer and gastritis. About 50% of the world's population is infected with *H. pylori*.¹⁰ The role of *H. pylori* in ulcerative colitis is controversial. According to Mansour et al, these bacteria may elicit a chronic systemic inflammatory process, triggering an autoimmune response so that infection by these bacteria is implicated in having a role in the emergence of ulcerative colitis.¹¹ In theory, *H.*

pylori infection can interfere with the immune system, causing the process of autoimmunity. However, several recent studies have shown that the prevalence of *H. pylori* infection is actually lower in IBD patients compared to patients without IBD, so it is considered a protective factor for IBD including ulcerative colitis.^{12–14} *H. pylori* is theorized to protect IBD by promoting immune tolerance and suppressing the inflammatory response. In addition, experts interpret that *H. pylori* infection can protect against IBD based on the “Hygiene Hypothesis”, stating that *H. pylori* infection can help develop the immune system and therefore prevent allergic and autoimmune diseases from occurring.¹⁰ From these controversial results, this evidence-based case report will examine whether infection with *H. pylori* can reduce or increase the risk of ulcerative colitis based on case reports with *H. pylori* infection and ulcerative colitis.^{10,11} Thus allowing the physician to educate the patient in regards to the possible causative or protective factors of ulcerative colitis.

METHOD

This meta-analysis follows the guidelines from the preferred reporting items for systematic reviews and meta-analyses (PRISMA). Rigorous article search for this meta-analysis was conducted through various available online databases. The databases used for the research were Cochrane, PubMed and Embase. To combine search terms, Boolean search operators “AND” and “OR” were utilized to expand the search. Keywords included in the search were “adult patients”, “*H. pylori* infection”, and “ulcerative colitis” along with the synonyms for each keyword. The strategy also utilized Medical Subject Heading (MeSH) terms and keyword combinations based on aforementioned keywords. Furthermore, additional hand-searching of gray literature was also conducted to retrieve more studies.

Eligibility Criteria

To determine which articles can be included in this meta analysis, eligibility criteria were created which were further divided into 2, inclusion and exclusion criteria. Inclusion criteria for this meta analysis includes articles using meta-analyses or systematic reviews of randomized controlled trials, cohort studies, or case-control studies, and/or randomized controlled trials, primary cohort

studies, and primary case-control studies as methods. In addition, the inclusion criteria also included adult patients, *H. pylori* infection, and ulcerative colitis. Meanwhile, articles in languages other than English and Indonesian, articles whose full texts are unavailable, articles that are still in process for publication, and articles published before 1994 are part of the exclusion criteria.

Article Selection

The strategy for selecting the articles is summarized in Figure 1. The number of articles obtained from hand searching, PubMed, Cochrane, and Embase is 127. A total of 114 full-text articles were screened for eligibility using the eligibility criteria, yielding 25 studies in the process for qualitative screening. Of the 25 studies, only 22 studies remained for this meta analysis.

Risk of Bias

For the risk of bias assessment, the Newcastle Ottawa Scale was used. Good quality was achieved with the minimum score of 3 stars for selection, 1 star for comparability, and 2 stars for outcome/exposure, while fair quality was achieved with the minimum score of 2 stars for domain, 1 star for comparability, and 2 stars for outcome/exposure.

Statistical Analysis

After selecting 22 articles and assessing its risk of bias, a random-effects meta-analysis was conducted to estimate the pooled odd ratios (ORs) along with their 95% confidence intervals (CIs). A forest graph was also plotted by the combined effect size. Statistical heterogeneity was assessed using the Higgins test (I^2). Low heterogeneity, moderate heterogeneity, and high heterogeneity are considered when $I^2 < 25\%$, I^2 25–75%, $I^2 > 75\%$ respectively. In addition, funnel plots were conducted in order to assess the publication bias for this study.

RESULTS

A total of 127 studies were identified through the aforementioned database and gray literature searches. A total of 13 records were excluded because they were duplicates. After screening the titles and abstracts, a total of 25 articles were retrieved for the qualitative process. Afterwards, 22 articles were chosen for the meta-analysis process. The other 102 records were

excluded due to their unavailability in terms of full text, unclear reports of the cases, as well as not fulfilling the eligibility criteria. The detailed flow diagram can be seen in Figure 1. In the 22 studies that were included for the meta-analyses, the total sample size was 367,628 with 11,498 UC patients and 356,130 controls.¹⁷ of the studies were made with case-control study design and the other 5 were a cohort study. The included studies had 6 studies and 16 studies with fair scores and good scores respectively based on the risk of bias assessment. The detailed characteristics of the studies included can be seen in Table 1.

In this meta-analysis 11,498 (3,22%) of the patients who had UC, were also infected with *H. pylori*

infection. The pooled OR on the data shows that *H. pylori* infection is associated with lower odds of UC [pooled ORs 0.51 (95% CI: 0.46-0.56)]. The pooled OR was statistically significant because the diamond did not intersect with the line of no effect and therefore, the CI did not exceed 1, except for several studies that were made with a very limited population. These details can be seen in Figure 2.

In the funnel plot below (Figure.3), it shows that the distribution of studies were symmetrical. In addition, the Begg and Egger Test ($I^2 = 54\%$, $p = 0.002$). Furthermore, publication bias was not found in the analysis of ulcerative colitis and *H. pylori* infection.

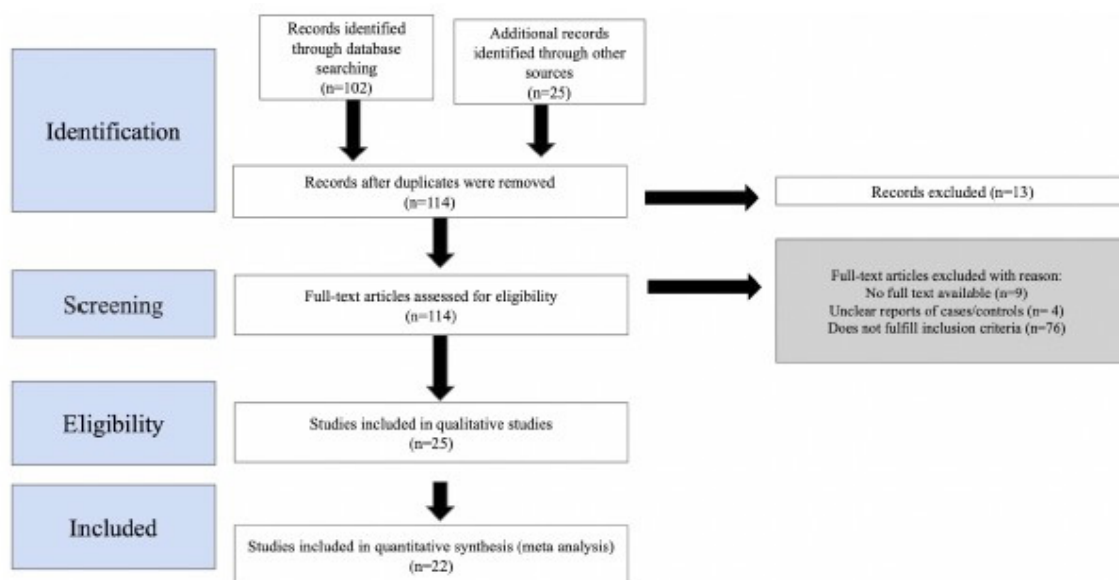


Figure 1. PRISMA flow chart describing the identification process of included studies

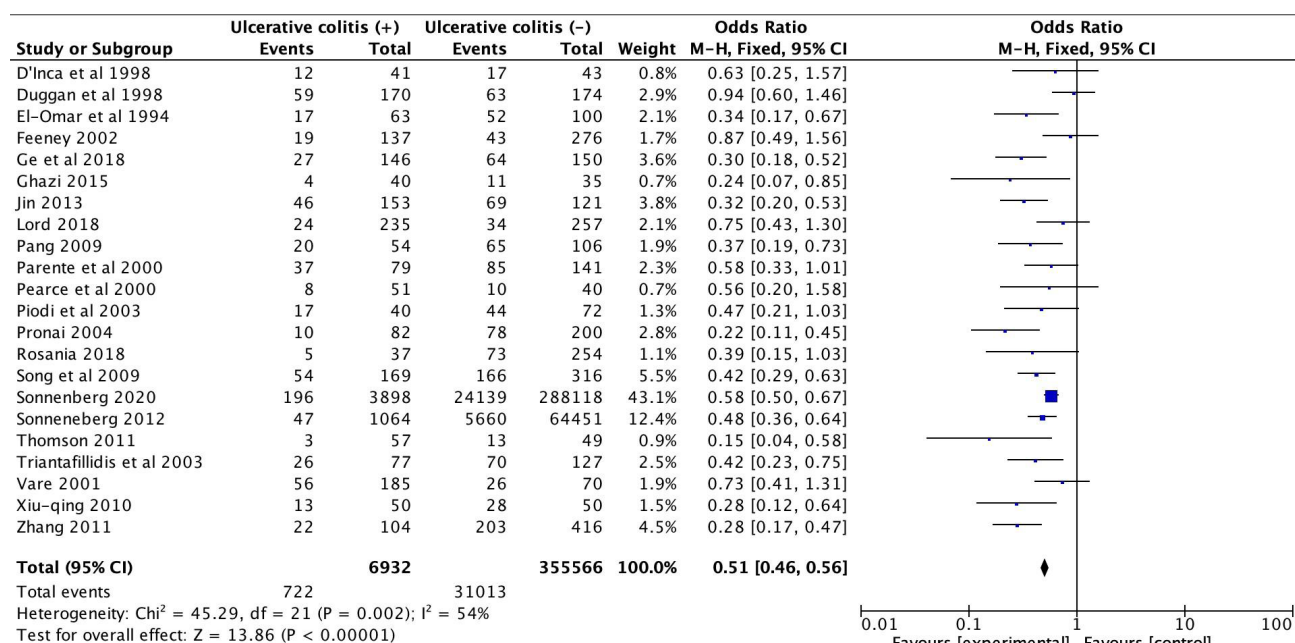


Figure 2. Forest plot showing the pooled odds ratio of the occurrence of ulcerative colitis in patients with *H. pylori* infection

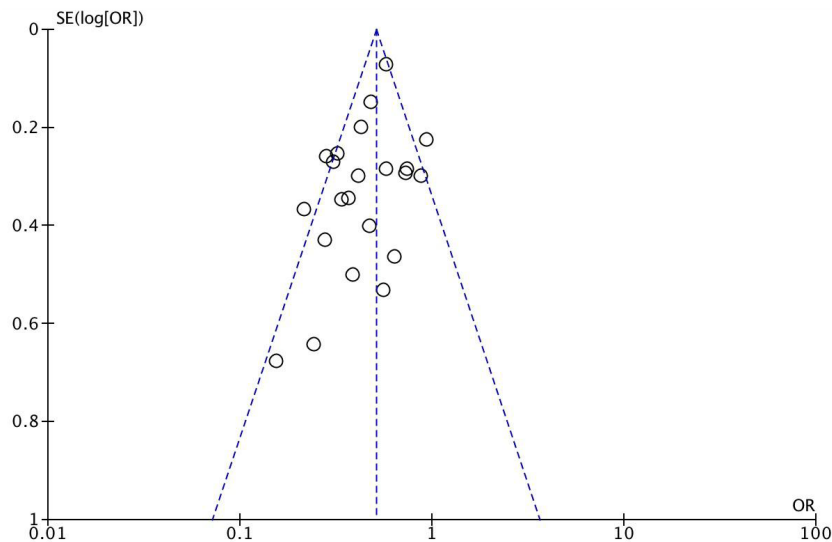


Figure 3. Funnel plot shows the distribution of studies

Table 1. Study characteristics

Author, year	Study design	Risk of bias assessment	Ulcerative colitis group (n)	Control group (n)	<i>H. pylori</i> diagnostic test
Pang et al, 2009 ¹⁶	Case control	Good	54	106	Serology
El-Omar et al, 1994 ¹⁷	Case control	Fair	47	100	Serology
Duggan, et al 1998 ¹⁸	Case control	Good	213	337	Serology
Pearce, et al 2000 ¹⁹	Cohort	Good	51	40	Serology, UBT
Feeney, et al 2002 ²⁰	Case control	Fair	137	276	Serology
Zhang, et al 2011 ²¹	Case control	Good	104	416	UBT
Jin, et al 2013 ²²	Case control	Fair	153	121	UBT/Biopsy sample culture
Ge, et al 2018 ²³	Case control	Good	146	150	RUT/Histology
D'Inca et al 1998 ²⁴	Cohort	Good	41	151	Histology
Parente, et al 2000 ²⁵	Cohort	Good	79	361	UBT/Histology
Piodi et al, 2003 ²⁶	Case control	Good	40	72	UBT
Triantafyllidis et al, 2003 ²⁷	Case control	Good	77	127	Serology
Vare et al, 2001 ²⁸	Cohort	Good	185	70	Serology
Rosania et al, 2018 ²⁹	Case control	Good	37	257	Serology
Pronai et al, 2004 ³⁰	Cohort	Good	82	200	UBT
Lord et al, 2018 ³¹	Case control	Fair	235	257	PCR/Culture
Song et al, 2009 ³²	Case control	Good	169	316	UBT
Xiu-qing, et al 2010 ³³	Case control	Fair	50	50	UBT
Sonnenberg, et al 2020 ³⁴	Case control	Good	3898	288,188	IHC
Ghazi et al, 2015 ³⁵	Case control	Good	40	35	IHC
Sonnenberg et al, 2012 ³⁶	Case control	Good	5603	64,451	IHC
Thomson et al, 2011 ³⁷	Case control	Fair	57	49	PCR

DISCUSSION

Ulcerative colitis (UC), a chronic inflammatory disease that can cause bloody diarrhea, remains a major global disease burden. It is a chronic and lifelong disease that leads to lower quality of life. It requires extensive treatment towards treating the symptoms due to the fact that there is no definitive medication except removing the colon by surgery. However, removing the colon itself may have complications and also require the lifelong use of a stoma. Hence, preventive acts have been proposed to lower the chance of having UC. Previous studies have shown that UC are less likely to be found in patients with *H. pylori* infection.^{1,6,8}

The role of *H. pylori* bacteria in the development of ulcerative colitis is still controversial, however recent studies have shown that *H. pylori* infection can be a protective factor against ulcerative colitis.¹²⁻¹⁴ It could be seen from all of the 22 studies included in this meta-analysis, there is an inverse association (*negative correlation*) between *H. pylori* infection and IBD. The pooled odds ratio is 0.51 (95% CI: 0.46-0.56) indicates that *H. pylori* infection could lower down the risk of obtaining ulcerative colitis in patients. Furthermore, meta analysis by Shirzad-Aski et al supports our findings, showing that the probability of *H. pylori* infection in patients with ulcerative colitis was OR

= 0.51 (95% CI: 0.42-0.63).³⁸ There was another meta-analysis by Luther et al which showed negative association between *H. pylori* infection with UC (RR = 0.75; 95% CI: 0.62–0.90).³⁹ Likewise, meta-analysis by Rokkas et al also supported our finding with pooled RR value of UC 0.53 (0.42–0.67).⁴⁰ These previous meta analysis strengthened the notion that *H. pylori* infection may have the protective effect towards UC.

The exact mechanism of how *H. pylori* infection may lower the chance of obtaining UC remains unclear however there are many possible mechanisms that have been studied. *H. pylori* bacteria ignite a certain cellular immune response in the mucosal line, their ability to interact with dendritic cells allow them to upregulate the T-cells. This will result in a high production of interleukin (IL)-12, leading to a T helper type 1 (Th1)-polarized response and will decrease the pro-inflammatory cytokine level in the body. The protective role might also be elicited from the alteration of the host immunologic response that also acts towards the proinflammatory Th1/Th17 response that *H. pylori* is attributed to, thus leading to an increased level of T-regulatory cell immune response, such as the increase of gastric mucosal expression of Foxp3. It is also postulated that *H. pylori* infection may induce the production of antibacterial peptides and compete with other pathological bacteria for the same ecological niche in the upper gastrointestinal tract.^{12,44}

The occurrence of UC is contributed by many factors, not only genetic but also environmental. As seen in this meta analysis, which includes patients who originated from various regions of the World, the occurrence of UC varies. The study conducted by Konkel showed that the regional variation happening in patients from East Asia could be attributed to the environmental and socioeconomic factors of the region, such as the role of diet and lifestyle choices.⁴⁴ In countries that have low intake of fiber and high intake of refined carbohydrate and refined meat, IBD or ulcerative colitis could easily be found due to these factors.⁴¹ The increase of IBD incidence in East Asia could be caused by the adoption of western diet into the everyday life of people residing in the region. Nonetheless, it was found that despite the lifestyle modifications, the protective factor of *H. pylori* towards ulcerative colitis is still significant in East Asian population.³⁹⁻⁴¹ In a study mentioned by Imawana et al, the beneficial effects of *H. pylori* on the risk of IBD are greater for eastern than for western populations. This could happen due to the seropositive

component of CagA *H. pylori* strain in East Asian compared to western populations.^{15,40} The expression of CagA might increase the production of beta-defensins in IBD pathogenesis and act as a protective factor. Another theory that supports the finding of *H. pylori* as a protective factor for ulcerative colitis or IBD is the *H. pylori* presence in the gastrointestinal tract could significantly suppress the secretion of gastric acid in inflammatory bowel diseases.³⁹⁻⁴¹ These occurrences might also change the composition of bacteria in the upper and lower region of the gastrointestinal tract. Those changes would be beneficial in patients who were suffering from IBD since the inflammatory response in the bowel could be lowered down with the presence of *H. pylori* in the gut. The variation of protective effect could also be different between the East Asian population and the Western population in the research. The cases in East Asia tend to be attributed to sporadic occurrences rather than genetic factors such as those in Europe or North America.³⁹⁻⁴¹ These findings supported the idea that despite patients with *H. pylori* infection have lower chance of having UC, there are other factors that may induce the occurrence of UC.

There are several studies included in this meta analysis that show a less statistically significant outcome since the CI is exceeding the line of no-effect (>1). This could happen due to the low number of research populations or samples. Studies by D'Inca et al, Xiu-qing, Pearce, Feeney and Duggan show that the research was done only with an affected population that ranges from 8 to 50 people. The small population size could lead to a statistically insignificant p-value. However, if compared with the other 17 studies where the p-value shows a very significant outcome both statistically and clinically, the findings from those five studies might not affect the overall result of the research.^{15,43,44} The protective value of *H. pylori* infection towards ulcerative colitis can still be proven in this meta-analysis. All of the studies included in this meta-analysis were graded as fair and good according to the Newcastle-Ottawa scale. Hence, the publication bias and confounding bias are very minimal in this meta-analysis. Overall, all studies have consistently shown that *H. pylori* infection reduces the risk of developing ulcerative colitis, thus has the potential to be a protective factor. This meta-analysis has several advantages such as having a moderate heterogeneity in the results and a clear result on the potential protective factor of *H. pylori* infection in ulcerative colitis cases.^{15,42,43}

CONCLUSION

In conclusion, the present study adds to the growing body of evidence supporting the potential protective effects of *H. pylori* infection on the occurrence of UC. However, the exact protective mechanism of *H. pylori* towards UC remains unclear. Hence, to confirm the findings in this study, further primary research with prospective study design needs to be conducted. The prospective study design should also take into account possible confounding factors such as diet or socioeconomic factors that may contribute to the emergence of UC. Furthermore, future studies need to highlight how *H. pylori* infection can be incorporated to be the preventive mechanism towards UC.

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