Helicobacter pylori *Infection and Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis*

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ABSTRACT

Since numerous studies have stated that there may be a relationship between Helicobacter pylori infection and nonalcoholic fatty liver disease, and because of the high prevalence of both conditions worldwide, this study investigated the risk of non-alcoholic fatty liver disease in patients infected with H. pylori. Following a systematic review of PubMed, Scopus, Web of Science and Embase, and a search in Google Scholar using MeSH terms such as H. pylori and non-alcoholic fatty liver disease, the relevant papers up to November 2020 were reviewed. All cohort, case-control, and cross-sectional studies that examined the risk of developing non-alcoholic fatty liver disease in patients infected with H. pylori entered this study. A meta-analysis was conducted in STATA 11. This systematic review examined 22 papers with 117 117 participants (33 711 patients infected with H. pylori and 83 406 participants as control) and 20 studies were subjected to meta-analysis The results indicated a 22% to 27% increase in the risk of developing non-alcoholic fatty liver disease in patients infected with H. pylori (crude odds ratio: 1.27, 95% CI: 1.17-1.33; and adjusted odds ratio: 1.22, 95% CI: 1.09-1.35). According to the subgroup analysis, the study region, sample size, and the method of diagnosing H. pylori were the factors contributing to the high heterogeneity. The meta-analysis revealed the increased risk of developing non-alcoholic fatty liver disease in patients infected with H. pylori. This indicates that H. pylori is a serious risk factor in patients susceptible to NAFLD.

Keywords: *Fatty liver, Helicobacter, meta-analysis, steatohepatitis*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide.[1] The estimated prevalence of NAFLD worldwide is approximately 25%, and its highest prevalence rates are observed in the Middle East (32%), followed by South America (31%).[2-4] Based on current literature, there is no proven treatment for NAFLD. However, lifestyle modification and exercise to reduce 7-10% of weight can help to improve liver fat content, inflammation, and fibrosis.[5] Non-alcoholic fatty liver disease is known as a major global health concern and governments incur high costs for its research and treatment.[6] The risk of NAFLD is associated with and increased by conditions such as type 2 diabetes, cardiovascular disease, and chronic kidney and liver diseases.[7-9] In addition, given the strong relationship between NAFLD and obesity, dyslipidemia, insulin resistance, type 2 diabetes, and hypertension, it is also known as the hepatic manifestation of metabolic syndrome.[10] Given the significant prevalence of NAFLD around the world, special attention is paid to risk factors and factors affecting the prevalence and exacerbation of the disease.

Helicobacter pylori is a gram-negative bacterium which colonizes the gastric mucosa and increases the risk of developing chronic gastritis, gastric ulcer, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma.[11] About 50% of the global population is infected with this pathogen. Prevalence varies according to geographical location. It is more prevalent in

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developing countries and less prevalent in developed nations.[12,13] Numerous clinical and animal studies have highlighted the relationship between *H. pylori* infection and the progression of liver fibrosis, cirrhosis, and hepatocellular carcinoma.[14-16] Several global[17-20] and regional[21] meta-analyses have investigated the relationship between *H. pylori* infection and the progression of NAFLD. In this meta-analysis, subgroup analysis was conducted to examine the sources of heterogeneity in the early studies. Several quality studies have emerged in the past 2 years, which have been used in the present study for a structural analysis on the relationship between *H. pylori* infection and prevalence of NAFLD.

MATERIALS AND METHODS

The protocols of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline were followed for study design, search approach, screening, and reporting. We performed a systematic review and meta-analysis of cohort, case-control, and cross sectional studies.

Search Strategy

The title and abstract fields of electronic databases including PubMed, Scopus, and Embase, and the title, abstract, and keyword fields of Web of Science were investigated, without limitation in publication date until November 2020. Our systematic search was conducted using the following keywords: "Helicobacter pylori" OR "Campylobacter pylori" OR "H pylori" OR "HP" and "Non-alcoholic Fatty Liver Disease" OR "Nonalcoholic Steatohepatitis" OR "fatty liver" OR "NAFLD" OR "NASH".

A manual search was conducted by investigating the reference list of articles included and reference list of the related review studies. The Google Scholar search engine was also used at this stage.

Eligibility Criteria

The inclusion criteria used to select the articles were as follows:

- Cohort, case–control, or cross-sectional studies;
- Studies including patients with NAFLD;
- Studies evaluating *H. pylori* infection in patients;
- Studies in English (or available in English too) and published by November 2020; and
- Studies with no restriction on place of study.

The exclusion criteria used to eliminate articles were as follows:

- Studies with other designs, including clinical trials, case series, and case reports; .
- Laboratory and animal studies; and
- Studies performed only among elderly patients or children.

Study Selection

This phase consisted of 3 sections. Initially, duplicates were removed by EndNote software. Then, 2 researchers (KH and MY) independently screened the articles obtained following the search based on the criteria listed by title and abstract. In case the eligibility of an article was doubtful according to title and abstract, the full version of the paper was acquired and then decided upon. A third researcher (RAN) as a referee was questioned about any disagreement between KH and MY. The current study investigated the risk of developing NAFLD in patients with *H. pylori* infection.

Quality Assessment

The Newcastle–Ottawa Quality Assessment checklists were used for evaluating the quality of the included studies. Two researchers in the team performed quality assessment of the studies independently. A third team member resolved any disagreements at this stage.

The studies included were classified into 3 categories. Studies with scores of 1, 2, and 3 were classified as poor, those with scores of 4, 5, and 6 were considered as moderate, and studies with scores of 7, 8, and 9 were regarded as good.

Data Extraction

Data were extracted from the full text of eligible articles. Information of all papers, including the name of first author, year of publication, type of study, mean age of patients, number of participants, number of patients with NAFLD, number of patients with *H. pylori* infection, diagnostic method of NAFLD and *H. pylori*, and the adjusted and crude odds ratios for developing NAFLD in patients with *H. pylori* infection were extracted.

Data Analysis

The heterogeneity of the studies was evaluated using the I^2 statistic. Based on the Cochrane Handbook for Systematic Reviews of Interventions,[22] the I^2 value was interpreted as follows: 0-40%: might not be important; 30-60%: may represent moderate heterogeneity;

50-90%: may represent substantial heterogeneity; and 75-100%: considerable heterogeneity. In the case of zero frequency, a correction value of 0.1 was used. According to the results and in the case of I^2, more than 40% of the random effect model was used to combine the results of the studies. Data were analyzed using STATA version 11 software and a forest plot chart.

To identify the potential source of heterogeneity, a subgroup analysis based on location of study, design, sample size, case-to-control ratio, diagnostic method of *H. pylori* and NAFLD, and quality assessment score was performed.

The odds ratio (OR) was used for outcome estimation, whenever appropriate, with 95% CI.

RESULTS

Study Selection Process

The database search yielded 1931 results. After exclusion of duplicated results and initial screening, 1332 papers were assessed for eligibility. Twenty-two papers were selected for qualitative synthesis. Finally, 18 papers entered the meta-analysis. Two articles were obtained by a manual search of different sources. The screening process is shown in the PRISMA flow diagram (Figure 1).

Study Characteristics

The sample size of the studies ranged from 53 to 21 456, with a total of 33 711 cases with NAFLD and 83 406 healthy controls. The characteristics of the studies that entered into the systematic review are shown in Table 1.

Quality Assessment

According to the quality assessment performed by the Newcastle–Ottawa Quality Assessment Form, 10 studies were of good quality and the other 8 studies were of moderate quality.

META-ANALYSIS FINDINGS

Non-Alcoholic Fatty Liver Disease and H. pylori Infection

The meta-analysis indicated that odds of developing NAFLD increased by 27% in individuals with *H. pylori* infection (crude OR: 1.27, 95% CI: 1.17-1.33). After adjusting OR for potential confounders, the meta-analysis showed 22% increase in the development of NAFLD in patients with *H. pylori* infection (adjusted OR: 1.22, 95% CI: 1.09-1.35) (Figures 2 and 3).

Odds of Non-Alcoholic Fatty Liver Disease Based on Region

Pooled estimates of the studies revealed a narrow range of odds of developing NAFLD, across countries (Table 2). The highest and the lowest rates were for Egypt (crude OR: 1.71, 95% CI: 0.82-2.60) and South Korea (crude OR: 1.17, 95% CI: 0.89-1.45). After adjusting the odds ratio for confounders, the combination analysis showed similar odds ratios regarding China and the United States (adjusted OR: 1.30, 95% CI: 1.11-1.49, and adjusted OR: 1.23, 95% CI: 0.89-1.57, respectively) (Table 2).

Odds of Non-alcoholic Fatty Liver Disease Based on Diagnostic Methods

The urea breath test (UBT) was the most common method used to evaluate the *H. pylori* infection (9 studies), followed by serology (8 studies), histology (3 studies), and other methods (3 studies). The pooled odds ratios for developing NAFLD in *H. pylori*-positive patients detected by the UBT (crude OR: 1.22, 95% CI: 1.09-1.34, adjusted OR: 1.11, 95% CI: 1.03-1.18), serology (crude OR: 1.36, 95% CI: 1.19-1.53, adjusted OR: 1.27, 95% CI: 0.90-1.64), and histology (crude OR: 1.02, 95% CI: 0.49-1.56), as shown in Table 2.

Ultrasonography and histology were the most frequently used diagnostic test methods for NAFLD. The lowest odds ratio for developing NAFLD was for histology (crude OR: 1.03, 95% CI: −0.48-2.54) and the highest odds ratios were for other methods (various criteria were used to detect NAFLD in some studies) (crude OR: 1.71, 95% CI: 1.02-2.39 and adjusted OR: 1.35, 95% CI: 0.91-1.80) (Table 2).

Odds of Non-alcoholic Fatty Liver Disease Based on Study Design

Meta-analysis demonstrated a considerable difference in odds ratio for developing NAFLD in people with *H. pylori* infection based on study design. The highest odds ratios were for case-control studies (crude OR: 2.24, 95% CI: 0.51-3.97, and adjusted OR: 2.02, 95% CI: 0.35-3.68), and the lowest odds ratios were for cross-sectional studies (crude OR: 1.23, 95% CI: 1.12-1.34, and adjusted OR: 1.21, 95% CI: 0.86-1.18) (Table 2).

Odds of Non-alcoholic Fatty Liver Disease Based on Sample Size

Most of the included studies had a sample size less than 10 000 patients (16 studies). The pooled estimates

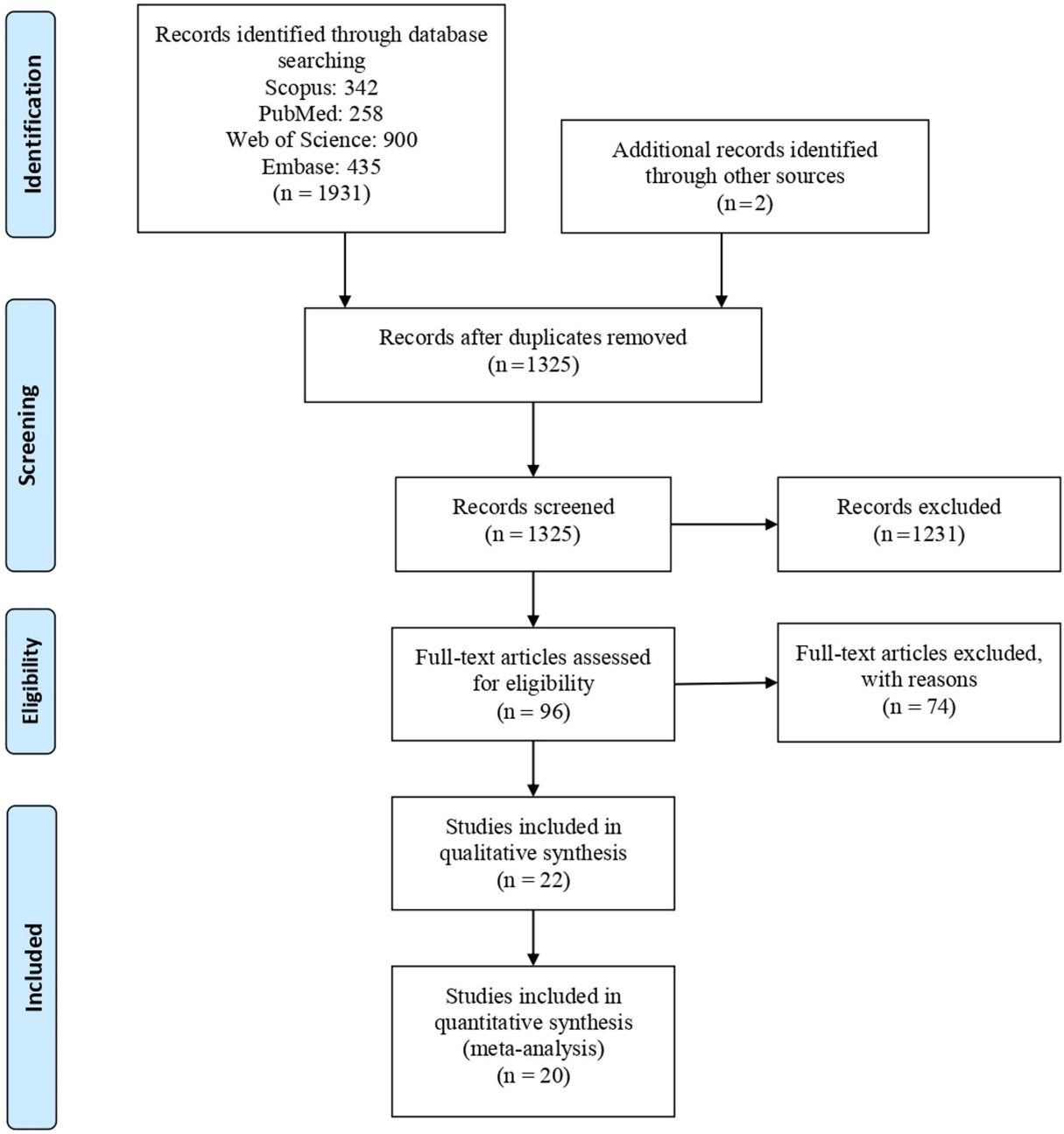

Figure 1. PRISMA flowchart for study selection process.

of studies with sample size less than 10 000 patients revealed a lower odds ratio for developing NAFLD in *H. pylori*-positive patients (crude OR: 1.26, 95% CI: 1.13-1.40, and adjusted OR: 1.16, 95% CI: 1.03-1.29) in comparison with studies with sample size greater than 10 000 patients (crude OR: 1.30, 95% CI: 1.11-1.50, and adjusted OR: 1.27, 95% CI: 1.04-1.50) (Table 2).

Odds of Non-alcoholic Fatty Liver Disease Based on Publication Status

Twenty out of the 22 included studies were full-text and the combined odds ratios of these studies were smaller than other conference abstracts (crude OR: 1.27, 95% CI: 1.16-1.39, and adjusted OR: 1.22, 95% CI: 1.09-1.35 vs crude OR: 2.49, 95% CI: –1.32-6.30) (Table 2).

Table 1. Characteristics of Studies Selected for the Meta-analysis

Study	Country	Study Design	Type of Publication	HP Diagnostic Method	NAFLD Diagnostic Method	Total Sample Size	NAFLD		Control		Q/A Score	Adjusted by
							HP +	HP –	HP +	HP –		
S. A. Polyzos 2012[29]	Greece	CS	Full text	Serology	Histologic	53	23	5	14	11	6	-
Z. Shen 2013[30]	China	CS	Conference abstract	Serology	US	9091	566	1804	1307	5411	-	-
K. Okushin 2015[31]	Japan	CS	Full text	Serology	US	5489	523	1279	926	2561	6	-
A. Lecube 2016[32]	Spain	CS	Full text	Histologic	Histologic	416	264	110	25	17	6	-
C. Zhang 2016[33]	China	CC	Full text	UBT	Histologic	1200	300	300	144	456	8	Sex, age, smoking status
M. K. Baeg 2016[34]	South Korea	CS	Full text	UBT	Other *	3663	469	385	1167	1642	6	Sex, BMI, insulin resistance, liver enzyme levels
C. X. Chen 2017[35]	China	CC	Full text	UBT	Chinese criteria**	2663	313	290	723	937	7	Unclear
T. J. Kim 2017[36]	South Korea	Cohort	Full text	Serology	US	17028	2080	1201	7838	5809	8	-
R. Kumar 2017[37]	India	CS	Conference abstract	UBT	US	120	11	16	20	73	-	-
O. Cai 2018[38]	China	CS	Full text	UBT	US	2051	145	143	500	1118	6	-
N. Fan 2018[39]	China	CS	Full text	UBT	US	21456	6150	3580	11173	553	7	Age, sex
A. Abdel-Razik 2018[40]	Egypt	Cohort	Full text	Serology	US	369	12	0	159	198	9	HOMA-IR
S. J. Kang 2018[41]	USA	CS	Full text	Serology	US	5404	658	1065	1115	2566	7	Age, sex, race-ethnicity, income, diabetes, hypertension, smoking status, waist circumference, alcohol consumption, caffeine consumption, TG, HDL-C, transferrin saturation
Y. Y. Yu 2018[42]	China	CS	Full text	UBT	US	20389	3132	4460	4716	8081	7	Age, sex, smoking, HP infection, WBC, HS-CRP, HbA1c, FPG, HOMA-IR, TG, LDL-C, systolic blood pressure, diastolic blood pressure
L. J. Lu 2018[43]	China	CS	Full text	UBT	US	1867	199	397	390	881	7	-
L. Y. Yu 2019[44]	Taiwan	CS	Full text	Histologic	US	2402	583	851	379	589	6	-

(*Continued*)

Table 1. Characteristics of Studies Selected for the Meta-analysis *(Continued)*

Study	Country	Study Design	Type of Publication	HP Diagnostic Method	NAFLD Diagnostic Method	Total Sample Size	NAFLD		Control		Q/A Score	Adjusted by
							HP +	HP –	HP +	HP –		
D. M. Tang 2019[45]	USA	CS	Full text	Multi method	US	270	-	-	-	-	7	Age, sex, statin use
T. Jiang 2019[7]	China	CS	Full text	UBT	US	4081	1022	842	1115	1102	7	Sex, age, education level, smoking, hypertension, diabetes, dyslipidemia, BMI, ALT, AST, AKP, TBIL
M. Y. Xu 2020[46]	China	CS	Full text	Serology	US	17971	-	-	-	-	6	Age, sex, underlying diseases, metabolic syndrome
Y. E. E. Abo-Amer 2020[47]	Egypt	CS	Full text	Stool antigen	US	646	442	82	82	40	7	-
C. S. Alvarez 2020[24]	Guatemala	CS	Full text	Serology	US	424	-	-	-	-	7	Age, sex, education, residence, smoking, alcohol intake
M. Doulberis 2020[26]	Switzerland	CS	Full text	Histologic	Histologic	64	0	9	15	40	6	-

HP, *Helicobacter pylori*; NAFLD, non-alcoholic fatty liver disease; QA, quality assessment; CS, cross-sectional; CC, case-control; UBT, urease, breath test; US, ultrasonography; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; WBC, white blood cell; HS-CRP, high-sensitivity C-reactive protein; HbA1C, hemoglobin A1c; FPG, fasting plasma glucose; TG, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; TBIL, total bilirubin.

*Diagnosis of NAFLD was based on a previously published noninvasive steatosis formula.[48,49]

**Diagnosis of NAFLD was based on the criteria suggested by the Chinese Liver Disease Association.[50]

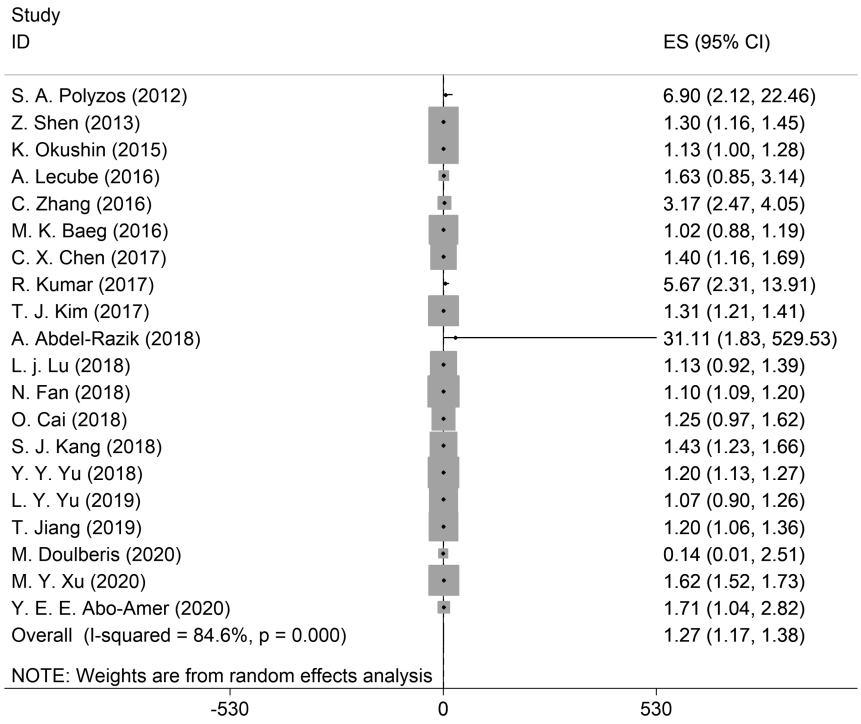

Figure 2. Forest plot evaluating the overall risk of non-alcoholic fatty liver disease with *Helicobacter pylori* infection (crude odds ratio).

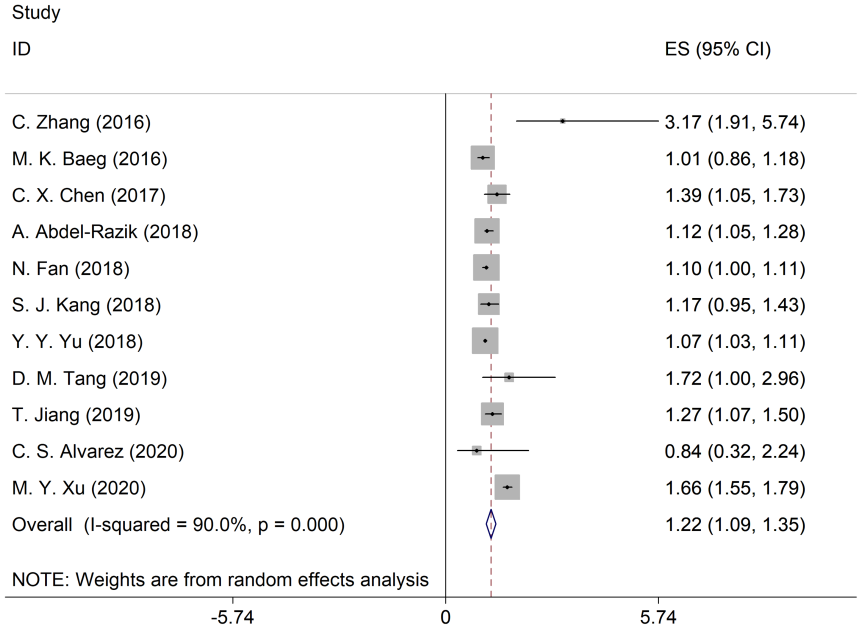

Figure 3. Forest plot evaluating the overall risk of non-alcoholic fatty liver disease with *Helicobacter pylori* infection (adjusted odds ratio).

Odds of Non-alcoholic Fatty Liver Disease Based on Quality Assessment Score

Ten studies had scores greater than 6 and the pooled estimates of these studies were patients (crude OR: 1.29, 95% CI: 1.17-1.40, and adjusted OR: 1.34, 95% CI: 0.69-1.98) in comparison with studies with lower scores (crude OR: 1.23, 95% CI: 1.01-1.44, and adjusted OR: 1.12, 95% CI: 1.06-1.18) (Table 2).

Table 2. Subgroup Analysis of Included Studies

Subgroup	Number of Studies	Crude Pooled OR (95% CI)	Heterogeneity		Number of Studies	Adjusted Pooled OR (95% CI)	Heterogeneity	
			I^2	*P*			I^2	*P*
Year of publication								
≤2016	6	1.38 (1.08-1.68)	84.9	.00	2	1.87 (–0.20-3.94)	79.4	.02
>2016	14	1.27 (1.15-1.39)	85.5	.00	9	1.24 (1.10-1.38)	91.5	.00
Type of publication								
Full text	18	1.27 (1.16-1.39)	85.8	.00	11	1.22 (1.09-1.35)	90.0	.00
Conference abstract	2	2.49 (–1.32-6.30)	54.2	.14	-	-	-	-
Study design								
Cross-sectional	16	1.23 (1.12-1.34)	84.0	.00	8	1.21 (1.06-1.37)	92.5	.00
Case-control	2	2.24 (0.51-3.97)	94.3	.00	2	2.02 (0.35-3.68)	68.9	.07
Cohort	2	1.31 (1.20-1.41)	0.0	.82	-	-	-	-
Area								
China	9	1.33 (1.18-1.49)	91.9	.00	6	1.30 (1.11-1.49)	94.8	.00
USA	-	-	-	-	2	1.23 (0.89-1.57)	12.4	.28
Egypt	2	1.71 (0.82-2.60)	0.0	.82	-	-	-	-
South Korea	2	1.17 (0.89-1.45)	88.5	.00	-	-	-	-
Sample size								
> 10 000	4	1.30 (1.11-1.50)	96.0	.00	3	1.27 (1.04-1.50)	97.7	.00
≤ 10 000	16	1.26 (1.13-1.40)	69.3	.00	7	1.16 (1.03-1.29)	45.4	.08
HP diagnostic method								
Serology	7	1.36 (1.19-1.53)	83.0	.00	4	1.27 (0.90-1.64)	93.4	.00
Urease breath test	9	1.22 (1.09-1.34)	79.8	.00	6	1.11 (1.03-1.18)	58.9	.00
Biopsy/ histology	3	1.02 (0.49-1.56)	34.4	.21	-	-	-	-
NAFLD diagnostic method								
Ultrasonography	14	1.26 (1.15-1.36)	85.2	.00	7	1.22 (1.07-1.37)	93.3	.00
Biopsy/histology	3	1.03 (–0.48-2.54)	53.3	.11				
Other methods	3	1.71 (1.02-2.39)	93.5	.00	4	1.35 (0.91-1.80)	70.2	.01
NOS score								
≤ 6	8	1.20 (0.94-1.47)	88.8	.00	2	1.34 (0.69-1.98)	97.7	.00
> 6	10	1.29 (1.17-1.40)	81.3	.00	9	1.12 (1.06-1.18)	42.0	.08

Odds of Non-alcoholic Fatty Liver Disease Based on Publication Year

Meta-analysis shows similar odds ratios for developing NAFLD in people with *H. pylori* infection based on studies published in 2016 and earlier, and those published after 2016 (crude OR: 1.38, 95% CI: 1.08-1.68, and adjusted OR: 1.27, 95% CI: 1.15-1.39 vs crude OR: 1.27, 95% CI: 1.15-1.39, and adjusted OR: 1.24, 95% CI: 1.10-1.38) (Table 2).

DISCUSSION

This systematic review and meta-analysis combined the data on 117 117 participants in 22 studies that examined the chances of developing non-alcoholic fatty liver disease in patients with *H. pylori* infection. The results suggested a 22% increased risk of developing NAFLD in patients infected with *H. pylori*. To examine the statistical heterogeneity in the studies included in

this meta-analysis, the chances of developing NAFLD were investigated based on different variables including *H. pylori* and NAFLD diagnostic methods, design of the study, sample size, location of study, and the quality assessment score. In general, the heterogeneity of the studies was significant. According to the subgroup analysis, the region under study, sample size, and the *H. pylori* diagnostic method were the factors that contributed to the high heterogeneity. However, in all of the mentioned subgroup analyses, the risk of developing NAFLD in patients with *H. pylori* infection was higher than in the other participants. In the raw and specific analyses, only 1 study indicated that the chance of developing NAFLD in the patients with *H. pylori* was lower than that in the normal participants.[23,24]

The results of this study complied with those of the previous systematic reviews and meta-analyses.[17-19,21] In one of them, which reported the results of 6 studies, the chance of developing NAFLD in patients with *H. pylori* infection was 1.21 (1.07-1.37).[18] They reviewed the full text and conference abstract of studies similar to the present study. In the present study, all relevant papers including full texts and conference abstracts were included. To examine heterogeneity, they were analyzed separately and the results indicated a significant difference in the results of the 2 studies. The OR obtained from the conference abstracts was almost twice that of the full-text studies. In a study which collected the results of 12 studies, the reported OR was 1.36 (1.22-1.53).[17] In the meta-analyses conducted by Zhou et al[19] and Xu et al[21] who examined the same issue, the chances of developing NAFLD in patients with *H. pylori* infection were 1.19 (1.29-1.11) and 1.20 (1.28-1.13), respectively. The study by Xu et al[21] was a regional one, conducted only on Chinese participants. The present study included papers from all around the world and provided more reliable results. Lie et al[20] conducted the most comprehensive study in Chinese databases that has ever been carried out. It was the only review study which reported a higher chance compared to that of the present one. The meta-analysis in the present study includes a larger sample size compared to previous studies and it is the most up-to-date.

The relationship between *H. pylori* and NAFLD can be investigated from various aspects. There are theories which associate NAFLD with *H. pylori*. For example, disruption of the gastrointestinal epithelium and the transport of *H. pylori*-related metabolites through portal flow to the liver activate the inflammatory process by toll-like receptors, which may progress to NAFLD.[25,26]

To the best of our knowledge, there are a limited number of studies that evaluate the effect of *H. pylori* eradication on NAFLD, and the results of these studies are inconsistent. Jamali et al[27] have compared liver fat content in a group of patients with NAFLD who received a *H. pylori* eradication regimen (n = 48) with a group of patients with NAFLD. without any treatment for *H. pylori* eradication (n = 50). The results of this study reveal no significant difference between liver fat content, laboratory parameters, and changes in the anthropometric measurements between the 2 groups.[27] Another study that evaluated 13 patients with biopsy-proven NAFLD showed *H. pylori* eradication had no significant long-term effect on hepatic steatosis.[28] Based on our study, *H. pylori* infection increases the risk of developing NAFLD. Hence, it would be more logical to expect better improvement in patients with NAFLD who receive *H. pylori* eradication therapy. However, the available evidence does not support this theory. Therefore, more comprehensive studies with a greater sample size are needed to attain more consistent results.

This study encountered several limitations, as follows. (1) data were limited in some studies, and therefore, they could not be included in the meta-analysis; (2) some eligible studies based on inclusion and exclusion criteria failed to provide sufficient information to calculate the intended effect size in the study; (3) since the prevalence rates of *H. pylori* infection varied in different regions, and because genetics plays a major role in the prevalence of diseases, it was not possible to examine the studies geographically for a more dedicated analysis; and (4) most studies had a cross-sectional design; therefore, it is suggested to design and conduct prospective cohort studies to better investigate various aspects of the relationship between *H. pylori* infection and NAFLD.

CONCLUSION

According to this meta-analysis, *H. pylori* infection increases the risk of developing non-alcoholic fatty liver disease and can be considered an independent risk factor for NAFLD. Given the strong role of *H. pylori* infection in developing NAFLD, it is suggested that future research investigates screening and eradication of this infection in patients who are at high risk of NAFLD and/or are in the early stages of this disease.

Ethics Committee Approval: The proposal of this systematic review and meta-analysis has been registered in the research committee of Mazandaran University of Medical Sciences with the ethical approval number: IR.MAZUMS.REC.1400.9215.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept – K.H., M.Y., R.A.; Design – R.A., K.H., M.Y., P.L.; Supervision – R.A., M.M; Materials – K.H., M.Y., R.A., F.S.; Data Collection and/or Processing – A.H., F.S.H., M.R., F.G.H. ; Analysis and/or Interpretation – K.H., H.M., R.A., M.M.; Literature Search – K.H., M.Y., P.L.; Writing Manuscript – K.H., S.R., A.V.; Critical Review – All authors.

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REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84. [CrossRef]

2. Moghaddasifar I, Lankarani KB, Moosazadeh M, et al. Prevalence of non-alcoholic fatty liver disease and its related factors in Iran. Int J Organ Transplant Med. 2016;7(3):149-160.

3. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11-20. [CrossRef]

4. Younossi Z, Tacke F, Arrese M, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2019;69(6):2672-2682. [CrossRef]

5. Brunner KT, Henneberg CJ, Wilechansky RM, Long MT. Nonalcoholic fatty liver disease and obesity treatment. Curr Obes Rep. 2019;8(3):220-228. [CrossRef]

6. Allen AM, Van Houten HK, Sangaralingham LR, Talwalkar JA, McCoy RG. Healthcare cost and utilization in nonalcoholic fatty liver disease: real-world data from a large US claims database. Hepatology. 2018;68(6):2230-2238. [CrossRef]

7. Jiang T, Chen X, Xia C, et al. Association between Helicobacter pylori infection and non-alcoholic fatty liver disease in North Chinese: a cross-sectional study. Sci Rep. 2019;9(1):4874. [CrossRef]

8. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313(22):2263-2273. [CrossRef]

9. Yang MH, Sung J, Gwak GY. The associations between apolipoprotein B, A1, and the B/A1 ratio and nonalcoholic fatty liver disease in both normal-weight and overweight Korean population. J Clin Lipidol. 2016;10(2):289-298. [CrossRef]

10. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD single topic conference. Hepatology. 2003;37(5):1202-1219. [CrossRef]

11. McColl KE. Clinical practice: Helicobacter pylori infection. N Engl J Med. 2010;362(17):1597-1604. [CrossRef].

12. Moosazadeh M, Lankarani KB, Afshari M. Meta-analysis of the prevalence of Helicobacter pylori infection among children and adults of Iran. Int J Prev Med. 2016;7:48. [CrossRef]

13. Zamani M, Ebrahimtabar F, Zamani V, et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. Aliment Pharmacol Ther. 2018;47(7):868-876. [CrossRef]

14. Abdel-Razik A, Mousa N, Elhelaly R, et al. Helicobacter pylori as an initiating factor of complications in patients with cirrhosis: a single-center observational study. Front Med. 2020;7:96. [CrossRef]

15. Goo MJ, Ki MR, Lee HR, et al. Helicobacter pylori promotes hepatic fibrosis in the animal model. Lab Invest. 2009;89(11):1291-1303. [CrossRef]

16. Ki MR, Goo MJ, Park JK, et al. Helicobacter pylori accelerates hepatic fibrosis by sensitizing transforming growth factor-β 1-induced inflammatory signaling. Lab Invest. 2010;90(10):1507-1516. [CrossRef]

17. Ning L, Liu R, Lou X, et al. Association between Helicobacter pylori infection and nonalcoholic fatty liver disease: a systemic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31(7):735-742. [CrossRef]

18. Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Manatsathit W, Jaruvongvanich V, Ungprasert P. Helicobacter pylori and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis. J Clin Gastroenterol. 2018;52(5):386-391. [CrossRef].

19. Zhou BG, Yang HJ, Xu W, Wang K, Guo P, Ai YW. Association between Helicobacter pylori infection and nonalcoholic fatty liver disease: a systematic review and meta-analysis of observational studies. Helicobacter. 2019;24(3):e12576. [CrossRef].

20. Liu R, Liu Q, He Y, et al. Association between Helicobacter pylori infection and nonalcoholic fatty liver: a meta-analysis. Medicine. 2019;98(44):e17781. [CrossRef]

21. Xu X, Li W, Qin L, Yang W, Yu G, Wei Q. Relationship between Helicobacter pylori infection and obesity in Chinese adults: a systematic review with meta-analysis. PLoS One. 2019;14(9):e0221076. [CrossRef]

22. J HJPTTJC. Cochrane Handbook for Systematic Reviews of Interventions Version 6.0. 2nd ed. Chichester: John Wiley & Sons; 2019.

23. Doulberis M, Polyzos SA, Papaefthymiou A, Katsinelos P, Kiosses C, Kountouras J. Treatment of nonalcoholic fatty liver disease: from adult trials to perspectives in the management of children and adolescents. Expert Opin Pharmacother. 2020;21(3):247-251. [CrossRef]

24. Alvarez CS, Florio AA, Butt J, et al. Associations between Helicobacter pylori with nonalcoholic fatty liver disease and other metabolic conditions in Guatemala. Helicobacter. 2020;25(6):e12756. [CrossRef]

25. Polyzos SA, Kountouras J. Novel Advances in the Association between Helicobacter pylori Infection, Metabolic Syndrome, and Related Morbidity. New York: Wiley Online Library; 2015.

26. Doulberis M, Srivastava S, Polyzos SA, et al. Active Helicobacter pylori infection is independently associated with nonalcoholic steatohepatitis in morbidly obese patients. J Clin Med. 2020;9(4). [CrossRef]

27. Jamali R, Mofid A, Vahedi H, Farzaneh R, Dowlatshahi S. The effect of Helicobacter pylori eradication on liver fat content in subjects with non-alcoholic fatty liver disease: a randomized open-label clinical trial. Hepat Mon. 2013;13(12):e14679. [CrossRef]
28. Polyzos SA, Nikolopoulos P, Stogianni A, Romiopoulos I, Katsinelos P, Kountouras J. Effect of Helicobacter pylori eradication on hepatic steatosis, NAFLD fibrosis score and HSENSI in patients with nonalcoholic steatohepatitis: a MR imaging-based pilot open-label study. Arq Gastroenterol. 2014;51(3):261-268. [CrossRef]
29. Polyzos SA, Kountouras J, Papatheodorou A, et al. Helicobacter pylori infection in patients with nonalcoholic fatty liver disease. Metabolism. 2013;62(1):121-126. [CrossRef]
30. Shen Z, Qin Y, Lu Y, Yu C, Li Y. Association between Helicobacter pylori infection diagnosed by serological status and nonalcoholic fatty liver disease: a cross-sectional study. U Eur Gastroenterol J. 2013;1(1):A99.
31. Okushin K, Takahashi Y, Yamamichi N, et al. Helicobacter pylori infection is not associated with fatty liver disease including non-alcoholic fatty liver disease: a large-scale cross-sectional study in Japan. BMC Gastroenterol. 2015;15(1). [CrossRef]
32. Lecube A, Valladares S, López-Cano C, et al. The role of morbid obesity in the promotion of metabolic disruptions and non-alcoholic steatohepatitis by Helicobacter pylori. PLoS One. 2016;11(11):e0166741. [CrossRef]
33. Zhang C, Guo L, Qin Y, Li G. Correlation between Helicobacter pylori infection and polymorphism of adiponectin gene promoter –11391G/A, superoxide dismutase gene in nonalcoholic fatty liver disease. Zhong Nan Da Xue Bao Yi Xue Ban. 2016;41(4):359-366. [CrossRef]
34. Baeg MK, Yoon SK, Ko SH, Noh YS, Lee IS, Choi MG. Helicobacter pylori infection is not associated with nonalcoholic fatty liver disease. World J Gastroenterol. 2016;22(8):2592-2600. [CrossRef]
35. Chen CX, Mao YS, Foster P, Zhu ZW, Du J, Guo CY. Possible association between Helicobacter pylori infection and nonalcoholic fatty liver disease. Appl Physiol Nutr Metab. 2017;42(3):295-301. [CrossRef]
36. Kim TJ, Sinn DH, Min YW, et al. A cohort study on Helicobacter pylori infection associated with nonalcoholic fatty liver disease. J Gastroenterol. 2017;52(11):1201-1210. [CrossRef]
37. Kumar R, Dixit VK, Shukla SK, Sachan S, Agarwal S. The association of Helicobacter pylori infection in non-alcoholic fatty liver disease patients. Indian J Gastroenterol. 2017;36(1):A33.
38. Cai O, Huang ZP, Li M, Zhang CQ, Xi FB, Tan SY. Association between Helicobacter pylori infection and nonalcoholic fatty liver disease: a single-center clinical study. Gastroenterol Res Pract. 2018;2018:8040262. [CrossRef]
39. Fan N, Peng L, Xia Z, Zhang L, Wang Y, Peng Y. Helicobacter pylori infection is not associated with non-alcoholic fatty liver disease: a cross-sectional study in China. Front Microbiol. 2018;9. [CrossRef]
40. Abdel-Razik A, Mousa N, Shabana W, et al. Helicobacter pylori and non-alcoholic fatty liver disease: a new enigma? Helicobacter. 2018;23(6):e12537. [CrossRef]
41. Kang SJ, Kim HJ, Kim D, Ahmed A. Association between cagA negative Helicobacter pylori status and nonalcoholic fatty liver disease among adults in the United States. PLoS One. 2018;13(8):e0202325. [CrossRef]
42. Yu YY, Cai JT, Song ZY, Tong YL, Wang JH. The associations among Helicobacter pylori infection, white blood cell count and non-alcoholic fatty liver disease in a large Chinese population. Medicine. 2018;97(46):e13271. [CrossRef]
43. Lu LJ, Hao NB, Liu JJ, Li X, Wang RL. Correlation between Helicobacter pylori infection and metabolic abnormality in general population: a cross-sectional study. Gastroenterol Res Pract. 2018;2018:7410801. [CrossRef]
44. Yu LY, Hu KC, Liu CJ, et al. Helicobacter pylori infection combined with non-alcoholic fatty liver disease increase the risk of atherosclerosis: focus in carotid artery plaque. Medicine. 2019;98(9):e14672. [CrossRef]
45. Tang DM, Chascsa DM, Chou JY, et al. Helicobacter pylori infection is strongly associated with metabolic syndrome, and weakly associated with non-alcoholic fatty liver disease, in a US Hispanic population. GastroHep. 2019;1(6):325-331. [CrossRef]
46. Xu MY, Ma JH, Du J, et al. Nonalcoholic fatty liver disease is associated with Helicobacter pylori infection in north urban Chinese: a retrospective study. Gastroenterol Res Pract. 2020;2020:9797841. [CrossRef]
47. Abo-Amer YE, Sabal A, Ahmed R, et al. Relationship between Helicobacter pylori infection and nonalcoholic fatty liver disease (NAFLD) in a developing country: a cross-sectional study. Diabetes Metab Syndr Obes. 2020;13:619-625. [CrossRef]
48. Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010;42(7):503-508. [CrossRef]
49. Kotronen A, Peltonen M, Hakkarainen A, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology. 2009;137(3):865-872. [CrossRef]
50. Fan JG, Jia JD, Li YM, et al. Guidelines for the diagnosis and management of nonalcoholic fatty liver disease: update 2010: (published in Chinese on Chinese Journal of Hepatology 2010; 18:163-166). J Dig Dis . 2011;12(1):38-44. [CrossRef]