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ORIGINAL ARTICLE

Case Control Study

Prevalence and risk factors associated with metabolic dysfunction-associated steatohepatitis in patients with *Helicobacter pylori* infection: A population-based study

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) is associated with the development of gastrointestinal disorders ranging from gastritis to gastric cancer. The evidence of the association between metabolic dysfunction-associated steatohepatitis (MASH) and *H. pylori* infection in the literature is scarce. Therefore, we aim to evaluate the risk of developing MASH in patients who have had a diagnosis of *H. pylori* infection independently of any confounding variables.

AIM
To evaluate the risk of developing MASH in patients who have had a diagnosis of *H. pylori* infection.

METHODS
This study used a validated multicenter research database of over 360 hospitals across 26 healthcare systems across the United States from 1999 to 2022. Multivariate regression analysis assessed the risk of developing MASH, adjusting for confounders including *H. pylori* infection, obesity, type 2 diabetes, hypertension, dyslipidemia, and male gender. A two-sided *P* value < 0.05 was considered as statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

RESULTS
A total of 79476132 individuals were screened in the database and 69232620 were selected in the final analysis after accounting for inclusion and exclusion criteria. Smokers (14.30%), patients with hyperlipidemia (70.35%), hypertension (73.86%), diabetes mellitus type 2 (56.46%), and obese patients (58.15%) were more common in patients with MASH compared to control. Using a multivariate regression analysis, the risk of MASH was increased in diabetics [odds ratio (OR): 3.55; 95%CI: 3.48-3.62], obese (OR: 5.93; 95%CI: 5.81-6.04), males (OR: 1.49; 95%CI: 1.46-1.52), individuals with hyperlipidemia (OR: 2.43; 95%CI: 2.38-2.49) and *H. pylori* infection (OR: 2.51; 95%CI: 2.31-2.73).

CONCLUSION
This is the largest population-based study in the United States illustrating an increased prevalence and odds of developing MASH in patients with *H. pylori* infection after adjusting for risk factors.

Key Words: Metabolic dysfunction-associated steatohepatitis; Metabolic dysfunction-associated steatotic liver disease; *Helicobacter Pylori*; Cirrhosis; Liver

Core Tip: *Helicobacter pylori* (*H. pylori*) is associated with the development of several gastrointestinal disorders ranging from gastritis to gastric cancer. The evidence of the association between metabolic dysfunction-associated steatohepatitis (MASH) and *H. pylori* infection in the literature is scarce. In this study, we evaluate the risk of developing MASH in patients who have had a diagnosis of *H. pylori* infection independently of any confounding variables. A validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the United States from 1999 to September 2022 was utilized to construct this study.

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INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH) is considered the most severe form of the metabolic dysfunction-associated steatotic liver disease (MASLD) spectrum and is characterized by the presence of chronic hepatitis (inflammation of the liver), hepatocellular injury, and variable degrees of fibrosis, in addition to the accumulation of fat in the liver that is present in all forms of MASLD[1-3]. In the United States, the prevalence of MASLD is estimated to be around 30%[4,5], while that of MASH is between 3%-5%[5]. The main sequelae of MASH are liver scarring, cirrhosis and liver cancer, and the main causes of death from MASLD/MASH are cardiovascular disease and extrahepatic malignancies. Besides lifestyle modifications, there is currently no approved therapy for MASLD[1,6].

Helicobacter pylori (*H. pylori*) is a Gram-negative, spiral-shaped, microaerophilic acidophilic bacterium that usually infects the mucinous surface of the stomach, with a prevalence in the United States of about 30%-50%. *H. pylori* infection is a major risk factor for the development of gastritis, gastric and duodenal ulcers, as well as gastric cancer. In addition, it can also cause manifestations outside the gastrointestinal system, most notably cardiovascular, hematological, respiratory, neurodegenerative, ophthalmological, otorhinolaryngologic, and endocrine diseases[7-9].

Despite the increasing number of studies investigating the association of *H. pylori* and MASH, conclusive evidence of an actual link between these two entities is scarce. Previous studies have proposed many mechanisms through which *H. pylori* can contribute to the pathogenesis of MASH; *H. pylori* can cause an increase in the levels of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin (IL)-6 by maintaining a chronic low-grade inflammation and can lead to the dysbiosis of the gastrointestinal microbiota with transport of their metabolites into the portal

circulation to activate Toll-Like Receptors. These factors promote insulin resistance and may favor the deposition of fat in the liver[10-12]. However, other studies concluded that *H. pylori* is not an independent risk factor for the development of MASH in many countries such as China, Japan, and Central Europe[13-15].

Many of these previous studies have limited data and fail to provide sufficient information. Moreover, the results are inconsistent among different cohorts and different regions. Therefore, we aim to evaluate the risk of developing MASH in patients who have had a diagnosis of *H. pylori* infection independently of any confounding variables.

MATERIALS AND METHODS

Database

Explorys Inc., Cleveland, OH, United States is a validated multicenter and research platform database of more than 360 hospitals form 26 different healthcare systems across the United States consisting of data from 1999 to September 2022. Explorys was developed and has been prospectively maintained by IBM Corporation, Watson Health[16], including electronic health records from greater than 60 million unique patients and provide a broad regional distribution of the United States representing approximately 15% of the population. It was utilized to construct a retrospective cohort analysis. A systematized Nomenclature of medicine-clinical terms hierarchy[17] was used to select diagnosis, findings, and procedures. Prescription drug orders are mapped into SNOMED and RxNorm[18]. Institutional Review Board was not required as source data are de-identified. To protect patient confidentiality, Explorys rounds population count to the nearest 10 and treats all counts between zero and 10 as equivalent. The study was conducted in accordance to the Declaration of Helsinki (as revised in 2013). Access to the database is granted to participating healthcare systems. Use of Explorys platform has been validated in multiple fields including gastroenterology[19-21].

Patient selection

Patients aged 18 years and above were included in this study. Exclusion criteria included pregnancy, patients with cancer and patients with alcohol use disorder. The individuals included were from different socioeconomic backgrounds and ethnic groups.

Statistical analysis

Patients with MASH were compared to those who did not. The risk of developing MASH was calculated using a multivariate regression analysis to account for potential cofounders including a history of *H. pylori* infection, obese patients, those with type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and male individuals. A 2-sided P value ≤ 0.05 was considered as statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

RESULTS

Descriptive epidemiology

A total of 79476132 individuals were screened in the database and 69232620 patients were selected in the final analysis after applying the inclusion and exclusion criteria. Patients were divided into two subgroups: Patients who had been diagnosed with MASH, whether by ultrasound, fibroscan or liver biopsy, were considered cases; and patients without MASH were considered control. The baseline characteristics of patients with MASH are reported in Table 1. Smokers (14.30%), patients with hyperlipidemia (70.35%), hypertension (73.86%), T2DM (56.46%) and obesity (58.15%) were more common in patients of the case group category.

Risks of developing MASH using a multivariate regression analysis

Using a multivariate regression analysis, the risk of developing MASH was increased in diabetics [odds ratio (OR): 3.55; 95%CI: 3.48-3.62], obese patients (OR: 5.93; 95%CI: 5.81-6.04), males (OR: 1.49; 95%CI: 1.46-1.52), individuals with hyperlipidemia (OR: 2.43; 95%CI: 2.38-2.49) and those with a *H. pylori* infection (OR: 2.51; 95%CI: 2.31-2.73) as reported in Figure 1.

DISCUSSION

MASLD is the most common liver disease worldwide, and the leading cause of liver-related morbidity and mortality[22]. In 20%-30% of cases, MASLD can progress to MASH[6], which is the most severe and aggressive form of the disease, marked by chronic inflammation of the liver with possible progression to advanced scarring (cirrhosis) and hepatic failure[23]. It is estimated that 3% to 6% of Americans are affected by MASH with a rising prevalence, and a strong association with obesity, dyslipidemia, type 2 diabetes, as well as metabolic syndrome[24].

As for the prevalence of *H. pylori*, it also differs amongst nations globally. In industrialized countries, it is roughly 30%, but it can reach as high as 80% in developing nations[25,26]. Given the evidence that *H. pylori* infection has been associated with a wide spectrum of gastrointestinal tract disorders, such as peptic ulcer, mucosa associated lymphoid

Table 1 Baseline characteristics of patients with metabolic dysfunction-associated steatohepatitis and control, *n* (%)

	MASH	No MASH
Smoker	8650 (14.03)	3629290 (5.24)
Male	26020 (42.21)	31483000 (45.51)
Hyperlipidemia	43360 (70.35)	11634530 (16.82)
Hypertension	45520 (73.86)	13997560 (20.23)
T2DM	34800 (56.46)	5552250 (8.02)
Obesity	35840 (58.15)	5123940 (7.40)
H. pylori infection	570 (0.92)	79420 (0.11)
Total	61630	69170990

H. pylori infection: *Helicobacter pylori* infection; T2DM: Type 2 diabetes mellitus; MASH: Metabolic dysfunction-associated steatohepatitis.

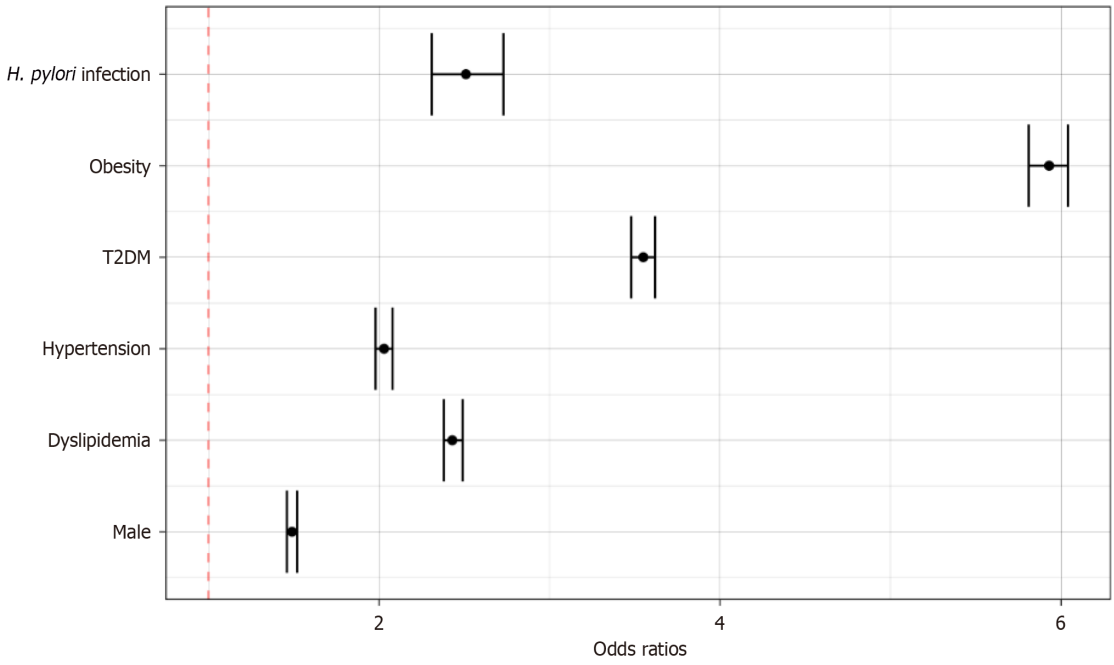

Figure 1 Forest plot for risk of developing metabolic dysfunction-associated steatohepatitis *vs* control. Reference line for an odds ratio of 1.0, indicating no association. *H. pylori* infection: *Helicobacter pylori* infection; T2DM: Type 2 diabetes mellitus.

tissue lymphoma, gastric adenocarcinoma and others, there has been speculation regarding the possible association of *H. pylori* infection with the development of non-alcoholic fatty liver disease[27].

In our present study, we examined whether there is a link between the incidence of MASH and *H. pylori* infection. We found that the risk of developing MASH was indeed increased in people infected with *H. pylori*. Our results were statistically significant, even after correcting for several mediators or confounders, including smoking, gender, hyperlipidemia, hypertension, diabetes mellitus, and obesity.

The proportion of subjects infected with *H. pylori* was significantly higher in our group of MASH positive patients (0.92%) than in the MASH-negative patients (0.11%). This is in accordance with Chen *et al*'s study[28] conducted in China, which noted a prevalence of 26.6% of MASH among 2263 subjects, 53% of which were also diagnosed with *H. pylori* infection, whilst in the 1660 non-MASH subjects, only 43.6% were diagnosed with *H. pylori* infection (P value = 4.9×10^{-4}) [28]. Furthermore, in Sumida *et al*'s study[29] conducted in Japan, the prevalence of MASH was (80.8%) in the *H. pylori*-positive subjects and 50.7% (P value = 8×10^{-3}) in the *H. pylori* negative subjects[29,30].

This association was furthermore supported by many studies in different regions in the world[29-32]. Similarly, two other studies from Turkey and Japan respectively pointed to *H. pylori* infection as one of the independent risk factors for the emergence of MASH[27,30]. These results have been supported by additional findings among Asian populations, and further data from outside Asia has also replicated these findings[31-33].

In Guatemalan people who tested positive for Cytotoxic-associated gene A (*CagA*) and Vacuolating Toxin (*VacA*), Alvarez *et al*[33] showed a positive connection between MASH and *H. pylori*. *CagA* and *VacA* have been found to be more

virulent, with a change in the gut microbiota and permeability, an increase in the inflammation state and a critical involvement in the development of gastric cancer[34,35].

However, Kang *et al*[36] found that in *H. pylori*-infected individuals, MASH was more common in *CagA*-negative individuals than in *CagA*-positive individuals. Additionally, despite adjusting for numerous conventional risk variables, *CagA* negative *H. pylori* positivity was strongly related with MASH, demonstrating a clinically important association between these two disorders. They also showed a slight, significant correlation in a recent meta-analysis with an odds ratio of 1.21 (95%CI: 1.07-1.37)[32,36].

In our study, the calculated odds ratio between *H. pylori* and MASH was 2.51 (95%CI: 2.31-2.73), suggesting a strong association between these two disorders.

Given that there are numerous theories explaining the link between *H. pylori* infection and MASH, and as no clear-cut evidence for any one pathway has been found, the pathophysiology is likely complex and multifactorial. In a meta-analysis conducted by Mantovani *et al*[37], *H. pylori* infection was found to be mildly associated with an increased risk of both prevalent and incident MASLD. The meta-analysis included 13 observational studies involving a total of 81162 middle-aged individuals, predominantly of Asian ethnicity. The results showed that *H. pylori* infection was linked to a higher risk of prevalent MASLD (random-effects OR 1.20, 95%CI: 1.07-1.35) and incident MASLD (random-effects hazard ratio 1.14, 95%CI: 1.05-1.23). The study suggested that chronic *H. pylori* infection may play a role in the development of MASLD, possibly through mechanisms involving systemic inflammation, insulin resistance, and changes in gut microbiota. During *H. pylori* infection, inflammatory cytokines, and vasoactive substances such as IL-6, IL-8, and TNF-α are released. They induce chronic low-grade systemic inflammation which may accelerate the progression to MASH and cause insulin resistance. A comprehensive review of nine studies also examined and confirmed this relationship[36].

The inflammatory process, which is characterized by several kinases including JNK, IKK/NF-kB, upregulates Ser phosphorylation or suppresses the autophosphorylation of the tyrosyl group of the insulin receptor substrate-137 Leading to insulin resistance[36,38]. In addition, TNF-α can increase free fatty acids by accelerating lipolysis resulting in hepatocyte dysfunction, which is a part of the pathway to MASH[38,39].

A hormonal link has also been hypothesized, specifically focusing on the hormones of the adipose tissue such as adiponectin which is decreased in patients with MASH and MASLD. This hormone protects against inflammation and fibrosis by lowering lipid storage in the liver[38,39]. According to this, *H. pylori* infection may result in decreased adiponectin levels and, eventually, decreased protection against fibrosis and MASH.

Furthermore, many common gene bases were discovered across *H. pylori* at the genomic level. These 95 genes significantly enriched 108 pathways according to pathway analysis (P value < 0.001), many of which have been linked to both *H. pylori* and MASH. Examples of these pathways include the response to LPS (lipopolysaccharide), the inflammatory response, aging, the response to hypoxia, and cytokine activity[28].

These findings imply that multiple genetic pathways exist between *H. pylori* and MASH, through which many genes interact to affect the pathogenic progression of both diseases.

Despite all the positive findings discussed, some studies have reported somewhat conflicting results[30,40-42]. Some findings were made in China, where a sizable cross-sectional study of 21456 people demonstrated no link between *H. pylori* infection and MASH as identified by ultrasound[42]. According to a cross-sectional study conducted in Japan on 13737 patients, *H. pylori* infection may not even be a risk factor for MASH[41].

Other investigations have found no correlation between MASH and *H. pylori* serology positivity in highly endemic locations[41,42]; this was also confirmed in a recent American investigation using data from the Third National Health and Nutrition Examination Survey[34]. Furthermore, after controlling for confounding variables, Fan *et al*'s findings[42] that the prevalence of MASH was considerably greater in participants with *H. pylori* infection (36.0% *vs* 33.3%, P value 0.05) was disproved.

Measurement of these markers at a single time point may not be able to accurately predict the inflammatory condition of the disease, as these negative results must be related to the variation of serum aminotransferases during MASH[33].

Although there have been conflicting results, studies examining the impact of *H. pylori* eradication on MASH may offer stronger proof that there is, in fact, a link between them. This is consistent with a recent meta-analysis that demonstrated a positive association between *H. pylori* infection and fatty liver disease with an improvement in the markers of MASLD as well as the MASLD fibrosis score following eradication of *Pylori*[35,37].

One of the drawbacks of our study was the inclusion of subjects aged 18 years and above. Therefore, using elder subject group alone would be beneficial and could lessen the influence of age on the results, since young subjects are less likely to develop MASLD.

Moreover, our study relied on different methods for the detection of *H. pylori* infection. Some used the ELISA test which frequently overestimates the number of positive individuals. Its reliability is lower than other diagnostic tools used in other patients such as histology or rapid urease test or urea breath test.

In addition, there was no uniform standard used for diagnosis of MASH in these patients. Some were diagnosed using ultrasonography which has inevitable limitations and may provide an improper diagnosis. Others were assessed using Fibroscan, and others underwent liver biopsy which is the gold standard for evaluation of MASH.

However, our study has several strengths worth noting. This case-control study is a large representative sample from the United States general population. It covered patients from 360 hospitals across the nation for a considerable amount of time-roughly 23 years. The individuals included were from different socioeconomic backgrounds and ethnic/racial groups, and thus, the results are generalizable. The large number of patients with *H. pylori* infection and MASH has provided high statistical power to assess the magnitude of the relationship between these two common conditions. Additionally, analyses were performed after adjusting potential confounding variables, which increased the validity of our findings and made our results more credible.

H. pylori infection is implicated in several systemic disorders. Based on clinical investigations demonstrating higher rates of MASH in *H. pylori* positive patients in our study, a link between them has recently been suggested, although it is worth noting that there have been conflicting results in other studies.

Although the pathophysiology underlying this association is still not fully understood, potential mechanisms involve a systemic pro-inflammatory state, which favors a lipogenic profile, as well as an effect on hormonal levels that affects fibrosis and lead to insulin resistance. An implication in common gene pathways was also found. Furthermore, the elimination of *H. pylori* has demonstrated decreases in markers of MASLD activity as well as liver fat scores, supporting the evidence for this association.

CONCLUSION

To our knowledge, this is the first and most recent case-control study integrating large sample size population to explore possible association between *H. pylori* and MASH as previous studies exploring this association have been constrained by several significant limitations, including smaller and regionally restricted sample sizes. Our study could offer new insights into the current field of *H. pylori*-MASH correlation study and if confirmed, treating *H. pylori* might be a brand-new, specific therapeutic strategy for MASH. Although our current study does not delve into genetic analyses, future research should aim to explore specific genetic markers, such as single nucleotide polymorphisms or other genomic variations, that could modulate the relationship between *H. pylori* infection and MASH. Understanding these genetic underpinnings could provide crucial insights into the mechanisms driving this association, particularly in pathways related to inflammation, insulin resistance, and lipid metabolism. This would also complement our findings on hormonal influences and gene enrichment pathways implicated in the progression of MASH.

FOOTNOTES

Author contributions: Abdel-Razeq R, Onwuzo S and Boustany A designed the research study; Abdel-Razeq R, Onwuzo S, Bitar L, Bitar ER, Onwuzo C, Abu-Hammour MN, Mohamed I, Johnson A and Eren B ;contributed to the writing of the manuscript and critically revised the draft for important intellectual content; Boustany A performed the statistical analysis and interpreted the data; Asaad I supervised and reviewed manuscript for accuracy and completeness; All authors have read and approved the final manuscript.

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