Original Article | **Open Access**

Hepatoma Research

Fan *et al. Hepatoma Res.* 2026;12:24 **DOI:**10.20517/2394-5079.2026.01

Helicobacter pylori is associated with a higher risk of MAFLD prevalence and all-cause mortality: results from the NHANES III follow-up study

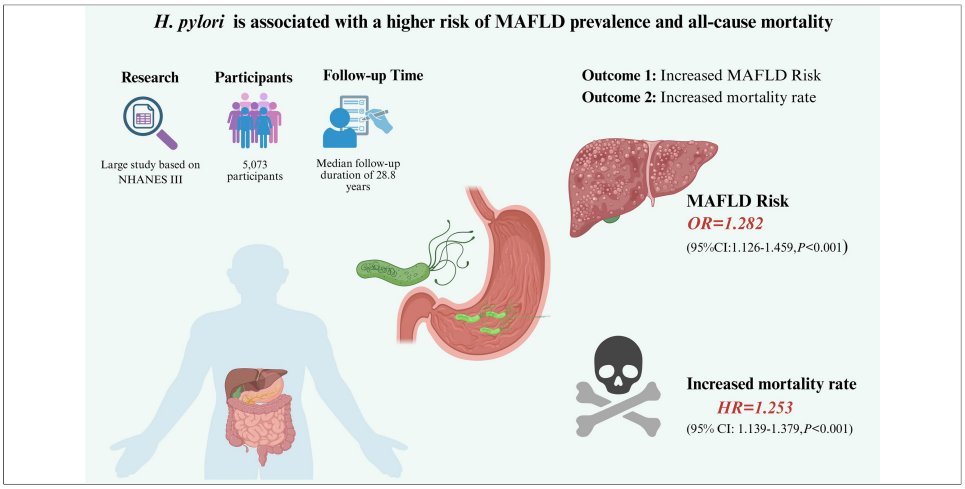
Qichao Fan[1,2,#], Yachun Chen[1,2,#], Junjin Liu[1,2], Liang Gao[1,2], Jiaofeng Huang[1,2]

Keywords:
Helicobacter pylori, MAFLD, mortality, NHANES

Citation: Fan Q, Chen Y, Liu J, Gao L, Huang J. *Helicobacter pylori* infection is associated with higher MAFLD prevalence and all-cause mortality: evidence from the NHANES III follow-up study. *Hepatoma Res.* 2026;12:24. https://dx.doi.org/10.20517/2394-5079.2026.01

Received: 1 Jan 2026
First Decision: 3 Apr 2026
Revised: 17 Apr 2026
Accepted: 7 May 2026
Published: 4 Jun 2026

Academic Editor: Yongbing Xiang
Copy Editor: Ting-Ting Hu
Production Editor: Ting-Ting Hu



Abstract

Aim: This study examined the relationship between *Helicobacter pylori* (*H. pylori*) and metabolic dysfunction-associated fatty liver disease (MAFLD) and concurrently evaluated their association with all-cause mortality risk.

Methods: Data were extracted from the Third National Health and Nutrition Examination Survey, which included 5,073 participants with available *H. pylori* IgG serology [enzyme-linked immunosorbent assay (ELISA)] results and mortality data. Logistic regression was used to assess the relationship between *H. pylori* seropositivity and MAFLD risk, while Cox proportional hazards regression was used to evaluate all-cause mortality risk, with adjustment for confounders.

Results: Among 5,073 participants, 2,394 (47.2%) tested positive for *H. pylori* and 1,610 (31.7%) had MAFLD; during a median follow-up of 28.8 years, 1,891 deaths occurred (overall mortality rate 37.3%). *H. pylori*-seropositive individuals exhibited significantly

[1]Department of Infectious Disease, The First Affiliated Hospital of Fujian Medical University, Fuzhou 350005, Fujian, China.
[2]Department of Infectious Disease, National Regional Medical Center, Binhai Campus of The First Affiliated Hospital of Fujian Medical University, Fuzhou 350212, Fujian, China.
[#]These authors contributed equally to this work.

Correspondence to: Prof. Jiaofeng Huang, Department of Infectious Disease, The First Affiliated Hospital of Fujian Medical University, Fuzhou 350005, Fujian, China. E-mail: huangjiaofeng@fjmu.edu.cn

higher mortality rates than seronegative individuals (43.5% *vs.* 31.7%, $P < 0.001$). Multivariate logistic regression confirmed *H. pylori* seropositivity as an independent risk factor for MAFLD [adjusted odds ratio (OR) = 1.282, 95% confidence interval (CI): 1.126-1.459, $P < 0.001$]. Multivariate Cox regression revealed that *H. pylori* seropositivity independently increased mortality risk (adjusted HR = 1.253, 95%CI: 1.139-1.379, $P < 0.001$), which was consistent across the MAFLD and non-MAFLD subgroups. Kaplan-Meier analysis corroborated significant survival divergence (log-rank, $P < 0.001$).

Conclusion: This study indicates that *H. pylori* seropositivity is independently associated with a higher prevalence of MAFLD and greater mortality risk in community-dwelling individuals.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a highly prevalent bacterial pathogen, affecting over 50% of the global population[1]. *H. pylori* infection is not only associated with a higher incidence of several gastric diseases, such as chronic gastritis, peptic ulcer disease, and gastric cancer[2], but also contributes to the risk of extragastric disorders[3]. Notably, *H. pylori* infection has been identified as a risk factor for cardiovascular diseases (e.g., coronary heart disease, arrhythmia, and acute myocardial infarction)[4], hepatobiliary system tumors and gallstones[5], as well as cholelithiasis[6]. The high global prevalence of *H. pylori* infection imposes a significant economic burden on national economies.

Metabolic dysfunction-associated fatty liver disease (MAFLD), a condition redefined to emphasize metabolic risk factors, has emerged as a "silent epidemic"[7]. The overall prevalence of MAFLD worldwide is estimated to be 32.4%[8], aligning with global trends projecting over 100 million cases in the U.S. by 2030[9]. Accumulating evidence indicates that MAFLD markedly increases the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma, particularly in individuals with comorbid metabolic disorders such as insulin resistance and obesity[10]. Moreover, MAFLD is associated with an increased incidence of extrahepatic conditions, including cardiovascular diseases[11], neurological disorders, and diverse malignancies beyond the liver, such as colorectal and breast cancer[12].

Recognition of the gut microbiome's contribution to MAFLD has shifted attention toward the role of *H. pylori* in modulating hepatic metabolism[13]. A systematic review and meta-analysis showed a mildly positive association between *H. pylori* infection and an increased incidence of MAFLD[14]. Another single-center study indicated that *H. pylori* infection was associated with a higher risk of MAFLD development and progression to fibrosis[15]. Furthermore, a Mendelian randomization study found no genetic evidence supporting a causal link between *H. pylori* and MAFLD, suggesting that the eradication or prevention of *H. pylori* infection might not confer benefits for MAFLD[16]. Therefore, the association between *H. pylori* infection and MAFLD remains unclear.

Therefore, this study utilized the Third National Health and Nutrition Examination Survey (NHANES III) database to conduct a cross-sectional analysis to investigate the potential relationships among *H. pylori* seropositivity, MAFLD, and all-cause mortality risk.

METHODS

Study population

NHANES III (1988-1994), a nationally representative survey coordinated by the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics (NCHS), provided the data for this study. De-identified data were retrieved from the CDC's public repository (https://wwwn.cdc.gov/nchs/nhanes/) following the protocols for the secondary analysis of population-based health surveys. We included adult

participants (age ≥ 20 years) from the NHANES III (1988-1994) with complete data on *H. pylori* IgG serology and hepatic ultrasonography. Participants with missing baseline anthropometric data or incomplete follow-up information in the NHANES III Linked Mortality File were excluded. Mortality outcomes through December 2019 were acquired from the National Death Index (NDI) linkage files (updated May 2022), using probabilistic matching of participant identifiers (https://ftp.cdc.gov/pub/Health_Statistics/NCHS/datalinkage/linked_mortality/). The original NHANES III protocol was approved by the NCHS Research Ethics Review Board, and written informed consent was obtained from all participants. Given that only anonymized, publicly available data were used, an individual ethics review was not required.

Definition

MAFLD

Hepatic steatosis was assessed using ultrasonography as the primary radiological modality. Data from two separate ultrasound examinations obtained from the NHANES III database were combined to form a unified analytical dataset. The severity of hepatic steatosis, determined using standard ultrasonographic criteria, was categorized as normal (no fat deposition), mild, moderate, or severe. For analytical purposes, cases exhibiting mild, moderate, or severe steatosis were grouped and classified as having clinically significant hepatic steatosis. MAFLD diagnosis adhered to the criteria specified in a recent international expert consensus[17]. This diagnostic framework mandates ultrasonographic evidence of hepatic steatosis coupled with the presence of at least one additional criterion: (1) overweight or obesity [body mass index (BMI) ≥ 25 kg/m^2]; (2) type 2 diabetes mellitus; or (3), in non-obese individuals (BMI < 25 kg/m^2), the presence of two or more metabolic risk abnormalities. For the NHANES III, race was classified into four distinct categories: non-Hispanic White, non-Hispanic Black, Mexican American, and Other.

H. pylori antibody test

Serological detection of *H. pylori* IgG antibodies was performed using a commercial enzyme-linked immunosorbent assay (ELISA) kit[18], following the manufacturer's instructions. This ELISA is designed for qualitative detection of *H. pylori* IgG in human serum and has demonstrated sensitivity, specificity, and reproducibility comparable to established serological techniques[19].

Operational definitions

Type 2 diabetes mellitus status was ascertained through three complementary approaches: self-reported physician diagnosis, current utilization of insulin or oral hypoglycemic agents, or fulfillment of biochemical thresholds [fasting plasma glucose (FPG) ≥ 7.0 mmol/L, glycosylated hemoglobin (HbA1c) ≥ 6.5%, or 2-h postprandial glucose ≥ 11.0 mmol/L]. Hypertension was characterized by meeting either of two conditions: (1) documented systolic blood pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg; OR (2) a prior clinical diagnosis of hypertension or active use of antihypertensive medications.

Laboratory assessment

Standardized clinical records provided an extensive array of biochemical indices, including complete blood count parameters, C-reactive protein (CRP) levels, glucose metabolism markers (FPG and HbA1c), hepatic transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], serum lipid profiles (total cholesterol and triglycerides), and serum creatinine concentrations. All laboratory assays were performed in accordance with rigorously controlled measurement protocols.

Statistical analysis

Categorical variables were presented as frequencies (percentages), whereas continuous variables were reported as mean values with standard deviations. Group comparisons for normally distributed variables were conducted using independent-samples *t*-tests, non-normally distributed parameters were analyzed

using Mann-Whitney *U*-tests, and categorical data were assessed using Pearson's chi-squared tests. The association between *H. pylori* seropositivity and MAFLD risk was investigated using logistic regression analysis. Kaplan-Meier curves were used to evaluate survival probability differences between *H. pylori* antibody-positive and antibody-negative groups. The relationship between *H. pylori* seropositivity and all-cause mortality was examined using the Cox proportional hazards regression model.

To address potential multicollinearity among the variables, we first assessed pairwise collinearity using the variance inflation factor and correlation coefficients. Strong multicollinearity was detected among the following variable pairs: BMI and waist circumference; FPG and HbA1c; ALT and AST; and serum cholesterol and triglycerides. Based on this criterion, waist, HbA1c, AST, and triglycerides were selected over their collinear counterparts (BMI, FPG, ALT, serum cholesterol, respectively) for inclusion in the multivariate Cox proportional hazards regression model. A two-tailed significance threshold of $P < 0.05$ was applied for all statistical tests. Data analyses were conducted using the R software version 4.3.3 (www.r-project.org). The survival analysis was performed with the R package "survival" employing the Kaplan-Meier method.

RESULTS

Baseline characteristics

A total of 5,946 participants who completed both ultrasound examination and *H. pylori* antibody testing were initially screened for this study [Figure 1]. Following the exclusion of 413 participants lacking follow-up data and 460 with missing baseline clinical characteristics, 5,073 individuals were included in the final analytical cohort. Of these, 2,630 (51.8%) were male, with a mean age of 43.3 ± 15.9 years. Hypertension and diabetes were present in 2,378 (46.9%) and 685 (13.5%) participants, respectively. A total of 2,394 (47.2%) participants were seropositive for *H. pylori* antibodies. Among the population, 1,610 cases met the MAFLD diagnostic criteria, with a prevalence of 31.7%.

Comparison by H. pylori serological status

Based on *H. pylori* antibody test results, the participants were categorized as seropositive or seronegative. Comparative analysis of baseline characteristics [Table 1] revealed that the seropositive group was significantly older (46.2 ± 16.0 years *vs.* 40.8 ± 15.4 years; $P < 0.001$) and had a greater percentage of male participants (55.3% *vs.* 48.8%; $P < 0.001$). Furthermore, the seropositive group exhibited a higher prevalence of diabetes, hypertension, and markers of metabolic dysregulation, including elevated BMI, waist circumference, FPG, HbA1c, and serum cholesterol and triglycerides. Indicators of liver injury (ALT and AST) were also elevated more frequently in the seropositive group. Notably, the prevalence of MAFLD was significantly higher among seropositive individuals than among their seronegative counterparts (36.6% *vs.* 27.4%).

H. pylori association with MAFLD

As shown in Table 2, univariate logistic regression revealed that *H. pylori* seropositivity was a significant risk factor for MAFLD [unadjusted OR = 1.535, 95% confidence interval (CI): 1.363-1.729, $P < 0.001$]. This association persisted in multivariable analyses accounting for prespecified confounders. In Model 1 (adjusted for sex, age, race, diabetes, and hypertension), the OR was 1.422 (95%CI: 1.260-1.605, $P < 0.001$). After further adjustment for BMI, Platelets (PLT), CRP, FPG, serum cholesterol, ALT, and creatinine levels (Model 2), the OR remained significant at 1.282 (95%CI: 1.126-1.459, $P < 0.001$). These results confirm that *H. pylori* seropositivity is an independent predictor of MAFLD risk.

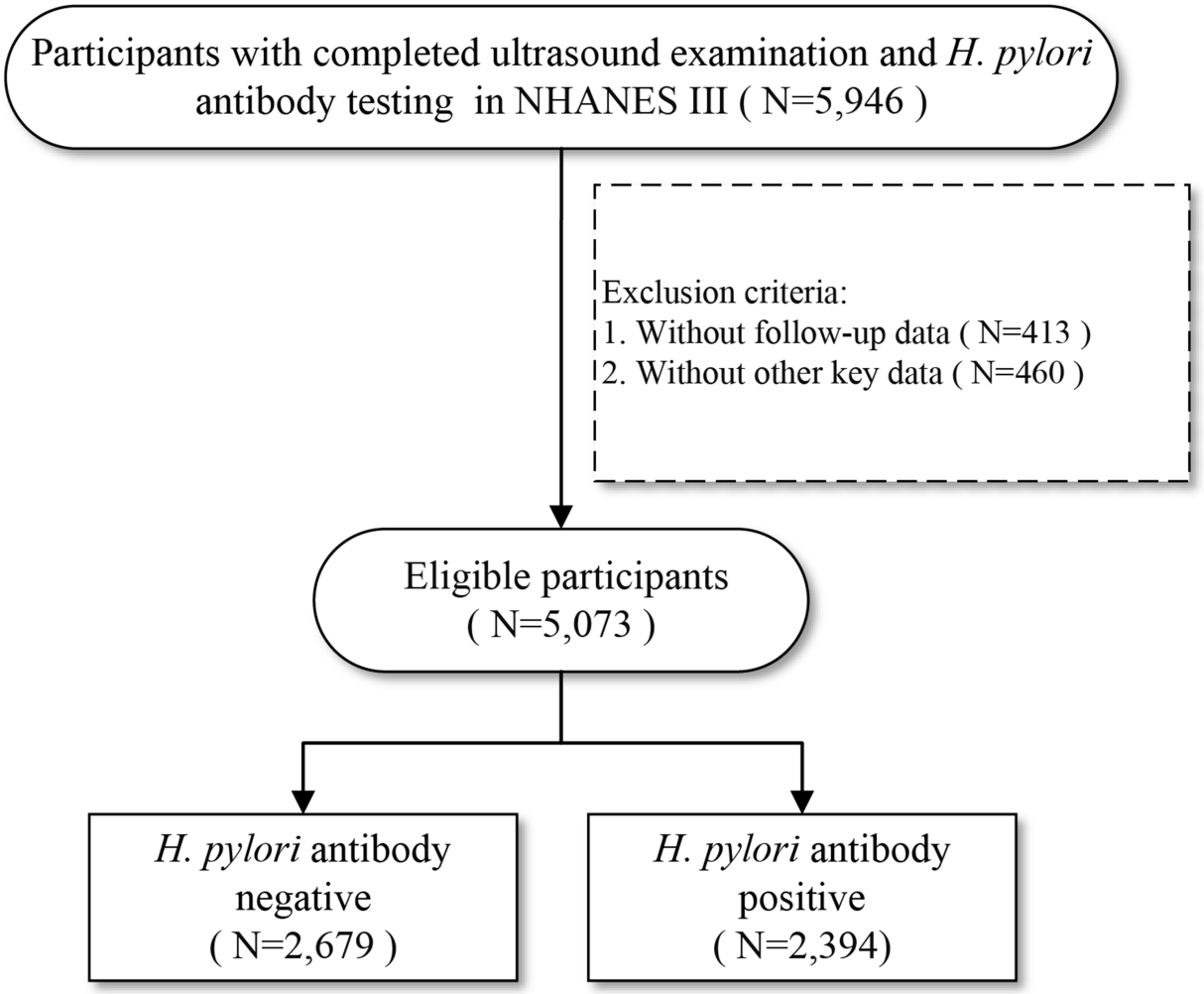


Figure 1. The flow chart of case selection. *H. pylori*: *Helicobacter pylori*; NHANES III: the Third National Health and Nutrition Examination Survey.

All-cause mortality grouped by *H. pylori* antibody

With a median follow-up of 28.8 years (interquartile range: 21.7-29.9), 1,891 deaths occurred within the cohort, resulting in an overall cumulative mortality rate of 37.3%. As shown in Table 1, individuals seropositive for *H. pylori* had significantly higher mortality rates than seronegative individuals (43.5% *vs.* 31.7%, $P < 0.001$). A significant difference in survival probability between the *H. pylori*-positive and negative groups was demonstrated by Kaplan-Meier analysis (log-rank $P < 0.001$; Figure 2A). This survival disadvantage associated with *H. pylori* seropositivity became apparent within the initial ten years of follow-up and continued to increase over time. By the 30-year mark, the absolute difference in survival was 11.8% (seropositive: 56.5% *vs.* seronegative: 68.3%). Consistently, the Kaplan-Meier curves showed significantly greater survival probabilities in *H. pylori*-negative individuals, a pattern evident in both the non-MAFLD [Figure 2B] and MAFLD [Figure 2C] subgroups (log-rank $P < 0.001$ for each).

Cox regression analysis

To assess the relationship between *H. pylori* seropositivity and all-cause mortality within the entire cohort, Cox proportional hazards regression analysis was conducted. The findings are presented in Table 3 and Figure 3. The initial unadjusted analysis indicated a significant association between seropositivity for *H. pylori* antibodies and elevated all-cause mortality risk (HR = 1.525, 95%CI: 1.393-1.670). To further

Table 1. Baseline demographic and clinical characteristics of the study population according to *H. pylori* serological status

Variables	*H. pylori* antibody			*P*-value
	Total	Negative	Positive	
N	5,073	2,679	2,394	
All-cause mortality, *n* (%)	1,891 (37.3)	849 (31.7)	1,042 (43.5)	< 0.001
Follow-up time (years)	28.8 (21.7, 29.9)	29.1 (25.5, 30.1)	28.6 (18.7, 29.7)	< 0.001
Race, *n* (%)				< 0.001
Non-Hispanic white	2,026 (39.9)	1,421 (53.0)	605 (25.3)	
Non-Hispanic black	1,318 (26.0)	592 (22.1)	726 (30.3)	
Mexican-American	1,545 (30.5)	578 (21.6)	967 (40.4)	
Other	184 (3.6)	88 (3.3)	96 (4.0)	
Male (%)	2,630 (51.8)	1,307 (48.8)	1,323 (55.3)	< 0.001
Age (years)	43.3 ± 15.9	40.8 ± 15.4	46.2 ± 16.0	< 0.001
Type 2 diabetes, *n* (%)	685 (13.5)	278 (10.4)	407 (17.0)	< 0.001
Hypertension, *n* (%)	2,378 (46.9)	1,131 (42.2)	1,247 (52.1)	< 0.001
BMI (kg/m^2)	26.8 ± 5.5	26.4 ± 5.5	27.3 ± 5.5	< 0.001
Waist (cm)	92.6 ± 14.3	91.3 ± 14.6	94 ± 13.8	< 0.001
Platelets (× 10^9/L)	284.4 ± 71.0	283.7 ± 69.6	285.1 ± 72.6	0.495
CRP (mg/dL)	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.2 (0.2, 0.4)	< 0.001
FPG (mmol/L)	5.4 ± 2.0	5.2 ± 1.7	5.6 ± 2.2	< 0.001
HbA1c (%)	5.4 ± 1.1	5.3 ± 1.0	5.6 ± 1.2	< 0.001
Cholesterol (mmol/L)	5.3 ± 1.1	5.2 ± 1.1	5.4 ± 1.2	< 0.001
Triglyceride (mmol/L)	1.6 ± 1.4	1.5 ± 1.4	1.7 ± 1.3	< 0.001
AST (U/L)	19 (16, 24)	19 (16, 23)	20 (17, 25)	< 0.001
ALT (U/L)	13 (10, 19)	13 (10, 19)	14 (10, 20)	< 0.001
Creatinine (μmol/L)	93.7 ± 25.3	92.9 ± 22.7	94.7 ± 27.8	0.012
MAFLD	1610 (31.7)	733 (27.4)	877 (36.6)	< 0.001

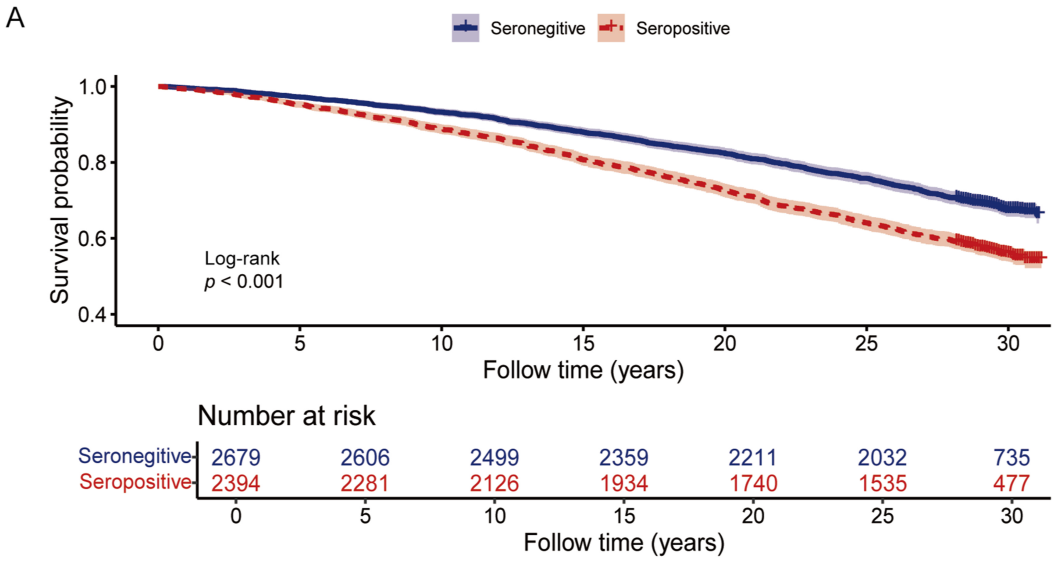
ALT: Alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CRP: C-reactive protein; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; *H. pylori*: *Helicobacter pylori*; MAFLD: metabolic dysfunction-associated fatty liver disease.

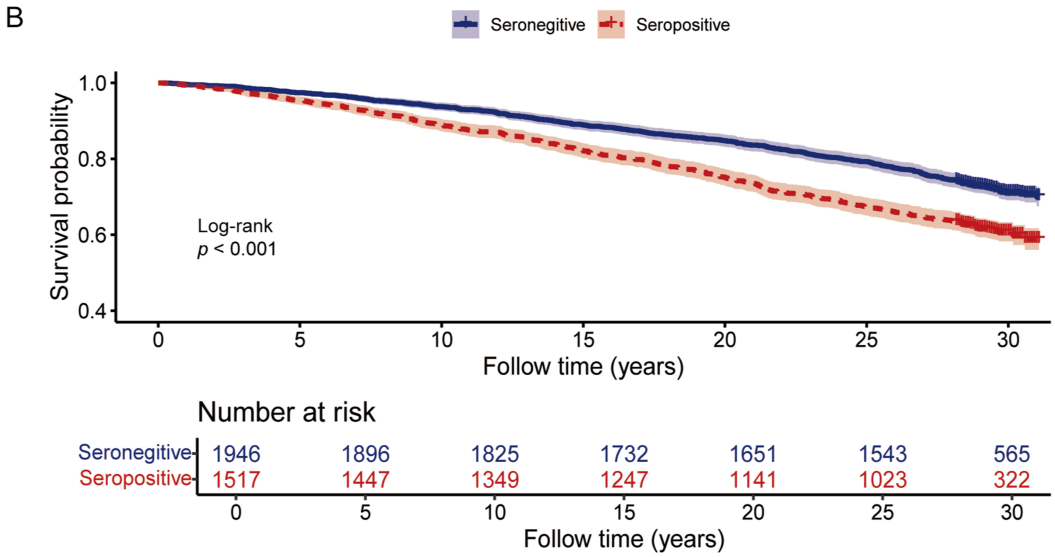
Table 2. Logistic regression analysis of *H. pylori* seropositivity and MAFLD risk

Model	OR (95%CI)	*P*-value
Crude	1.535 (1.363-1.729)	< 0.001
Model 1	1.422 (1.260-1.605)	< 0.001
Model 2	1.282 (1.126-1.459)	< 0.001

Model 1 was adjusted for sex, age, race, diabetes, and hypertension; Model 2 was adjusted for all the variables in Model 1, plus BMI, PLT, CRP, FPG, serum cholesterol, ALT, and creatinine levels. ALT: Alanine aminotransferase; BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; FPG: fasting plasma glucose; *H. pylori*: *Helicobacter pylori*; MAFLD: metabolic dysfunction-associated fatty liver disease; OR: odds ratio; PLT: platelet count.

investigate this potential association and account for confounding factors, two multivariable models were constructed. Model 1 was adjusted for sex, age, race, diabetes, and hypertension. Model 2 included all variables in Model 1, with additional adjustments for BMI, PLT, CRP, FPG, serum cholesterol, ALT, and creatinine levels. The positive association between *H. pylori* seropositivity and all-cause mortality persisted in both adjusted models (Model 1: HR = 1.236, 95%CI: 1.123-1.360, $P < 0.001$; Model 2: HR = 1.253, 95%CI: 1.139-1.379, $P < 0.001$). This suggests that the observed relationship is independent of the evaluated confounders. Notably, this significant association persisted in the analyses stratified by MAFLD and non-MAFLD subgroups.


A
Seronegitive
Seropositive
Survival probability
1.0
0.8
0.6
0.4
Log-rank
p < 0.001
0
5
10
15
20
25
30
Follow time (years)
Number at risk
Seronegitive 2679 2606 2499 2359 2211 2032 735
Seropositive 2394 2281 2126 1934 1740 1535 477
Follow time (years)


B
Seronegitive
Seropositive
Survival probability
1.0
0.8
0.6
0.4
Log-rank
p < 0.001
0
5
10
15
20
25
30
Follow time (years)
Number at risk
Seronegitive 1946 1896 1825 1732 1651 1543 565
Seropositive 1517 1447 1349 1247 1141 1023 322
Follow time (years)

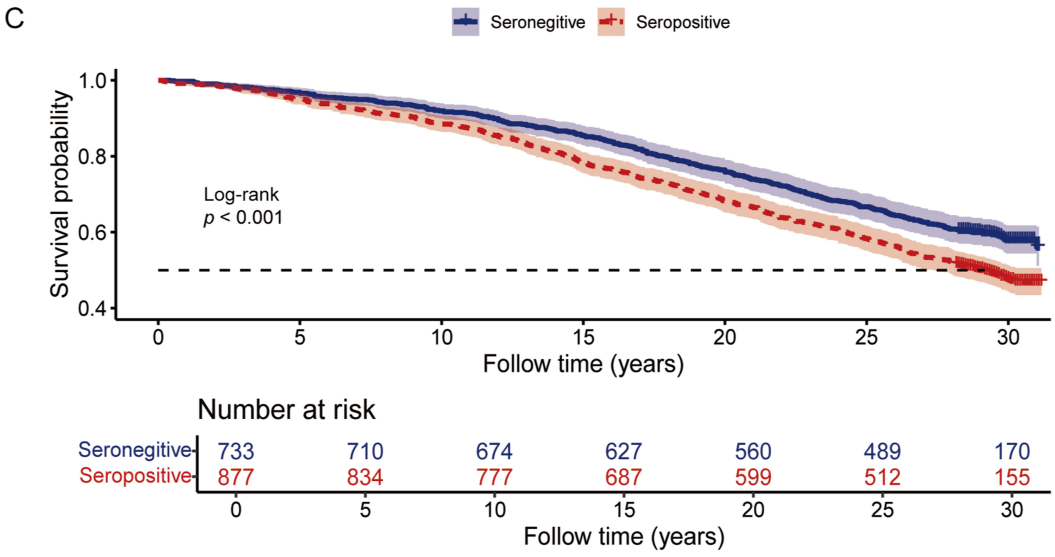

C
Seronegitive
Seropositive
Survival probability
1.0
0.8
0.6
0.4
Log-rank
p < 0.001
0
5
10
15
20
25
30
Follow time (years)
Number at risk
Seronegitive 733 710 674 627 560 489 170
Seropositive 877 834 777 687 599 512 155
Follow time (years)

Figure 2. Kaplan-Meier analysis comparing *H. pylori*-seropositive and seronegative participants. (A) Total population; (B) non-MAFLD group; and (C) MAFLD group. Log-rank test *P*-values are shown. *H. pylori*: *Helicobacter pylori*; MAFLD: metabolic dysfunction-associated fatty liver disease.

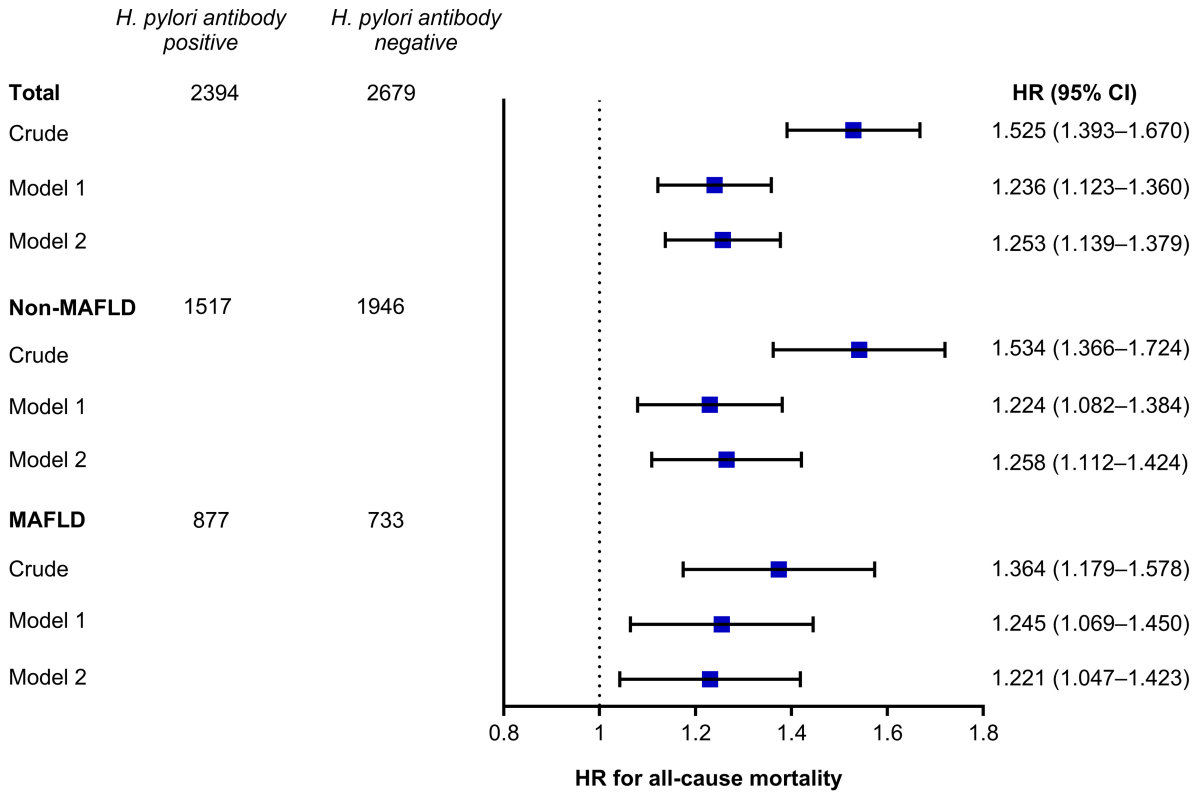


Figure 3. Forest plot of estimated HRs for mortality according to *H. pylori* status based on Cox regression analysis. HRs: Hazard ratios; *H. pylori*: *Helicobacter pylori*; CI: confidence interval; MAFLD: metabolic dysfunction-associated fatty liver disease.

Table 3. Cox regression analysis of the association between *H. pylori* seropositivity and all-cause mortality

Model	Total		non-MAFLD		MAFLD	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Crude	1.525 (1.393-1.670)	< 0.001	1.534 (1.366-1.724)	< 0.001	1.364 (1.179-1.578)	< 0.001
Model 1	1.236 (1.123-1.360)	< 0.001	1.224 (1.082-1.384)	0.001	1.245 (1.069-1.450)	0.005
Model 2	1.253 (1.139-1.379)	< 0.001	1.258 (1.112-1.424)	< 0.001	1.221 (1.047-1.423)	0.011

Model 1 was adjusted for sex, age, race, diabetes, and hypertension; Model 2 was adjusted for all the variables in Model 1, plus BMI, PLT, CRP, FPG, serum cholesterol, ALT, and creatinine levels. ALT: Alanine aminotransferase; BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; FPG: fasting plasma glucose; *H. pylori*: *Helicobacter pylori*; HR: hazard ratio; MAFLD: metabolic dysfunction-associated fatty liver disease; PLT: platelet count.

The results are presented for the total population, the non-MAFLD group, and the MAFLD group across three adjustment models: crude (unadjusted), Model 1 (adjusted for sex, age, race, diabetes, and hypertension), and Model 2 (additionally adjusted for BMI, PLT, CRP, FPG, serum cholesterol, ALT, and creatinine levels).

DISCUSSION

The present study demonstrated a notable association between *H. pylori* seropositivity and MAFLD, along with an elevated risk of all-cause mortality, independent of conventional metabolic and inflammatory confounders. These findings add to the expanding body of literature connecting *H. pylori* to systemic health outcomes beyond its recognized involvement in gastrointestinal disorders.

Our results revealed a 36.6% prevalence of MAFLD in *H. pylori*-seropositive individuals, significantly higher than the 27.4% prevalence observed in their seronegative counterparts. This association persisted after adjusting for metabolic factors and inflammatory markers, suggesting that *H. pylori* may exacerbate hepatic lipid accumulation through mechanisms independent of conventional metabolic derangements. Several meta-analyses have demonstrated that *H. pylori* infection is associated with an elevated risk of prevalent MAFLD, with odds ratios (OR) ranging from 1.20 to 1.27[14,20,21]. A cross-sectional study has reported a positive association between *H. pylori* seropositivity and triglyceride levels (OR = 1.231)[22]. In a case-control study, *H. pylori*-infected individuals exhibited elevated low-density lipoprotein cholesterol and reduced high-density lipoprotein cholesterol concentrations[23]. The prevalence of *H. pylori* infection was significantly higher among participants with diabetes than in those without diabetes[24]. Population-based studies have indicated that *H. pylori* infection may exacerbate insulin resistance, leading to elevated lipid and glucose levels and subsequently triggering metabolic abnormalities[25], thereby increasing the risk of MAFLD. Experimental animal studies have shown that *H. pylori* aggravates MAFLD progression by modulating hepatic lipid metabolism through its virulence factor, the cytotoxin-associated gene A (CagA) protein[26]. Another study revealed dynamic alterations in the gut microbiota consistent with *H. pylori*-induced metabolic phenotype changes[27]. Therefore, the mechanisms underlying *H. pylori*-induced metabolic disturbances remain complex and warrant further investigations to validate these preliminary findings.

Even after rigorous adjustment for metabolic and inflammatory variables, *H. pylori* seropositivity was associated with an 11.8 percentage point higher all-cause mortality rate. This suggests that *H. pylori* infection poses a systemic health threat. This survival disadvantage emerged early (within 10 years) and widened over time, which is consistent with the cumulative effects of chronic inflammation and microvascular damage. Notably, the mortality gap persisted in both the MAFLD and non-MAFLD subgroups, suggesting that *H. pylori*-driven pathways influence mortality through multiple parallel routes. Potential mechanisms include accelerated atherosclerosis (via endothelial dysfunction or procoagulant states), enhanced oxidative stress, or synergistic interactions with comorbid conditions (e.g., diabetes and hypertension)[28]. Our findings align with those of prior studies linking *H. pylori* to cardiovascular and overall mortality; however, this study uniquely highlights its relevance across metabolic strata, including non-MAFLD populations. Public health initiatives should consider integrating *H. pylori* screening into metabolic syndrome management protocols, particularly in regions with high prevalence.

In light of the potential association between *H. pylori* seropositivity and increased MAFLD prevalence, researchers have begun preliminary studies to examine whether *H. pylori* affects MAFLD. Despite these efforts, the body of literature remains sparse, and the findings are inconclusive. Yu *et al.* demonstrated that the eradication of *H. pylori* could further ameliorate metabolic indices and reduce the degree of hepatic steatosis in patients with MAFLD[29]. Conversely, a separate randomized, open-label clinical trial indicated that the eradication of *H. pylori* might not significantly influence liver fat content, liver function tests, blood lipid profiles, or insulin resistance in patients with MAFLD[30]. Considering the practicality and cost-effectiveness of eradicating *H. pylori*, further research is necessary to determine whether targeted treatment can mitigate MAFLD-related complications and enhance survival.

A key strength of this study is its large, population-based cohort, combined with long-term follow-up (median 28.8 years), enabling a robust assessment of temporal trends in mortality. Additionally, adjustment for multiple confounders (e.g., BMI, CRP, and lipid profiles) strengthens the validity of our conclusions. Nevertheless, several limitations should be noted. First, the observational design precludes causal inferences, and residual confounding by unmeasured factors (e.g., smoking, diet, socioeconomic status) cannot be

excluded. Second, *H. pylori* seropositivity reflects past exposure rather than active infection, and data on eradication therapy were unavailable, limiting insights into reversibility. Third, the lack of direct measurements of liver histology or advanced fibrosis precludes detailed mechanistic conclusions. Future studies should prioritize prospective designs, incorporate *H. pylori* DNA detection or the ^{13}C-urea breath test to confirm active infection[31], and explore the mediators[32] (e.g., interleukin-6 and adiponectin) linking *H. pylori* to metabolic and hepatic outcomes.

Conclusions

In summary, this population-based epidemiological follow-up study demonstrated a significant correlation between *H. pylori* seropositivity and an increased risk of MAFLD and all-cause mortality. These findings highlight the enduring public health impact of *H. pylori* as a chronic bacterial infection, indicating the need for further research to ascertain whether eradication of *H. pylori* could reduce the risk of MAFLD and mortality in the general population.

DECLARATIONS

Acknowledgments

The Graphical Abstract was created in BioRender. Fan, Q. (2026) https://BioRender.com/2ecggp1.

Authors' contributions

Conceived the study design, supervised the project, and critically revised the manuscript for important intellectual content: Huang J

Performed the statistical analysis and was responsible for manuscript preparation: Fan Q

Conducted the primary data analysis and visualization: Chen Y

Contributed to the clinical interpretation of the findings and assisted in the literature review: Liu J, Gao L

Availability of data and materials

Publicly available datasets were analyzed in this study. The raw data used in the article are available on the National Health and Nutrition Examination Survey website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tools Gemini 3 Pro and DeepSeek-V3.2 were used solely for language editing. The tools did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

Financial support and sponsorship

This study was supported by the Joint Funds for the Innovation of Science and Technology, Fujian Province (No. 2024Y9131).

Conflicts of interest

Huang J is a Junior Editorial Board Member of *Hepatoma Research*. Huang J was not involved in any part of the editorial process for this manuscript, including reviewer selection, manuscript handling, or decision-making. The other authors declare that they have no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Li Y, Choi H, Leung K, Jiang F, Graham DY, Leung WK. Global prevalence of *Helicobacter pylori* infection between 1980 and 2022: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2023;8:553-64. DOI PubMed
2. Duan Y, Xu Y, Dou Y, Xu D. Helicobacter pylori and gastric cancer: mechanisms and new perspectives. *J Hematol Oncol.* 2025;18:10. DOI PubMed PMC
3. Tsay FW, Hsu PI. *H. pylori* infection and extra-gastroduodenal diseases. *J Biomed Sci.* 2018;25:65. DOI PubMed PMC
4. Yaslianifard S, Sameni F, Kazemi K, et al. Beyond the gut: a comprehensive meta-analysis on *Helicobacter pylori* infection and cardiovascular complications. *Ann Clin Microbiol Antimicrob.* 2025;24:18. DOI PubMed PMC
5. Penaflorida JLGR, Requesto JRU, Romero KYB, et al. Association between Helicobacter pylori and hepatobiliary cancer: a meta-analysis and systematic review. *Asian Pac J Cancer Prev.* 2024;25:3363-70. DOI PubMed PMC
6. Fabbri N, Greco S, Pesce A, Virgilio F, Romeo D, Feo CV. Role of *Helicobacter pylori* infection and the risk of cholelithiasis. *World J Gastroenterol.* 2025;31:102024. DOI PubMed PMC
7. Lazarus JV, Colombo M, Cortez-Pinto H, et al. NAFLD - sounding the alarm on a silent epidemic. *Nat Rev Gastroenterol Hepatol.* 2020;17:377-9. DOI
8. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2022;7:851-61. DOI PubMed
9. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology.* 2018;67:123-33. DOI PubMed PMC
10. Guo W, Ge X, Lu J, et al. Diet and risk of non-alcoholic fatty liver disease, cirrhosis, and liver cancer: a large prospective cohort study in UK biobank. *Nutrients.* 2022;14:5335. DOI PubMed PMC
11. Mostafa AM, Pan Z, Yu ML, Örmeci N, Fouad Y, Eslam M. MAFLD: a comprehensive review of the link between metabolic dysfunction and cardiovascular risk. *Hepat Med.* 2025;17:75-90. DOI PubMed PMC
12. Yuan X, Wang X, Wu S, et al. Associations between metabolic dysfunction-associated fatty liver disease and extrahepatic cancers: a cohort in China. *Hepatobiliary Surg Nutr.* 2023;12:671-81. DOI PubMed PMC
13. Dong TS, Luu K, Lagishetty V, et al. Gut microbiome profiles associated with steatosis severity in metabolic associated fatty liver disease. *Hepatoma Res.* 2021;7:37. DOI PubMed PMC
14. Heydari K, Yousefi M, Alizadeh-Navaei R, et al. Helicobacter pylori infection and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Turk J Gastroenterol.* 2022;33:171-81. DOI PubMed PMC
15. Gulati A, Roytman M, Lin J, et al. Association between Helicobacter pylori infection, MASLD, and liver fibrosis in patients with severe obesity: a single-center experience. *Surg Endosc.* 2024;38:6873-9. DOI PubMed
16. Liu Y, Xu H, Zhao Z, Dong Y, Wang X, Niu J. No evidence for a causal link between *Helicobacter pylori* infection and nonalcoholic fatty liver disease: A bidirectional Mendelian randomization study. *Front Microbiol.* 2022;13:1018322. DOI PubMed PMC
17. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol.* 2020;73:202-9. DOI PubMed
18. Centers for Disease Control and Prevention. NHANES 1999-2000 Laboratory Methods. Available from https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?BeginYear=1999. [accessed 4 June 2026].
19. Centers for Disease Control and Prevention. Questionnaires, Datasets, and Related Documentation-NHANES III. Available from https://wwwn.cdc.gov/nchs/nhanes/nhanes3/datafiles.aspx. [accessed 4 June 2026].
20. 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;52:386-91. DOI PubMed
21. Mantovani A, Turino T, Altomari A, et al. Association between *Helicobacter pylori* infection and risk of nonalcoholic fatty liver disease: an updated meta-analysis. *Metabolism.* 2019;96:56-65. DOI PubMed
22. Xie J, Wang J, Zeng R, Xie Y. Association between *Helicobacter pylori* infection and triglyceride levels: a nested cross-sectional study. *Front Endocrinol.* 2023;14:1220347. DOI PubMed PMC
23. Zhao MM, Krebs J, Cao X, et al. *Helicobacter pylori* infection as a risk factor for serum bilirubin change and less favourable lipid profiles: a hospital-based health examination survey. *BMC Infect Dis.* 2019;19:157. DOI PubMed PMC
24. Mansori K, Dehghanbanadaki H, Naderpour S, Rashti R, Moghaddam AB, Moradi Y. A systematic review and meta-analysis of the prevalence of Helicobacter pylori in patients with diabetes. *Diabetes Metab Syndr.* 2020;14:601-7. DOI PubMed
25. Polyzos SA, Kountouras J, Zavos C, Deretzi G. The association between *Helicobacter pylori* infection and insulin resistance: a systematic review. *Helicobacter.* 2011;16:79-88. DOI PubMed
26. Chen X, Peng R, Peng D, Liu D, Li R. *Helicobacter pylori* infection exacerbates metabolic dysfunction-associated steatotic liver disease through lipid metabolic pathways: a transcriptomic study. *J Transl Med.* 2024;22:701. DOI PubMed PMC

27. He C, Yang Z, Cheng D, et al. *Helicobacter pylori* infection aggravates diet-induced insulin resistance in association with gut microbiota of mice. *EBioMedicine.* 2016;12:247-54. DOI PubMed PMC
28. Candelli M, Franza L, Cianci R, et al. The interplay between *Helicobacter pylori* and gut microbiota in non-gastrointestinal disorders: a special focus on atherosclerosis. *Int J Mol Sci.* 2023;24:17520. DOI PubMed PMC
29. Yu YY, Tong YL, Wu LY, Yu XY. *Helicobacter pylori* infection eradication for nonalcoholic fatty liver disease: a randomized controlled trial. *Sci Rep.* 2022;12:19530. DOI PubMed PMC
30. 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:e14679. DOI PubMed PMC
31. Kamboj AK, Cotter TG, Oxentenko AS. *Helicobacter pylori*: the past, present, and future in management. *Mayo Clin Proc.* 2017;92:599-604. DOI PubMed
32. Yildirim Z, Bozkurt B, Ozol D, et al. Increased exhaled 8-isoprostane and interleukin-6 in patients with Helicobacter pylori infection. *Helicobacter.* 2016;21:389-94. DOI PubMed