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Does *Helicobacter pylori* infection affect indirect hepatic fibrosis tests?

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Abstract

Background and Aim: Early detection, accurate evaluation, and proper follow-up of fibrosis in chronic liver disease are crucial for improving disease prognosis. Indirect biochemical fibrosis tests, such as the AST-to-Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4) score, have been developed, incorporating parameters like AST, ALT, and platelet count. However, the influence of factors such as *Helicobacter pylori* (*H. pylori*) on fibrosis tests such as APRI and FIB-4 remains unclear, and this study aimed to evaluate its impact.

Materials and Methods: This study included 190 patients (aged ≥18 years) who underwent gastric and liver biopsies at a tertiary center between 2006 and 2021. Patients were categorized into three groups based on liver histopathological findings: mild (F0-1), moderate (F2-3), and advanced (F4-6) fibrosis. Additionally, patients were grouped based on *H. pylori* presence as determined by gastric histopathology. Demographic, clinical, laboratory, imaging, and histopathological characteristics were analyzed and compared between groups.

Results: Among the 190 patients, *H. pylori* was detected in 135 (71%) and was absent in 55 (29%). No significant differences were observed between *H. pylori*-positive and -negative groups in terms of AST, ALT, platelet count, INR, FIB-4, or APRI scores. For APRI, significant differences were found between mild-moderate and mild-advanced fibrosis groups ($p<0.001$), but not between moderate and advanced groups ($p>0.05$). For FIB-4, significant differences were observed across all fibrosis groups ($p<0.001$). The presence of *H. pylori* did not significantly affect the APRI or FIB-4 scores within any fibrosis group.

Conclusion: The presence of *H. pylori* did not significantly impact APRI or FIB-4 scores. These indices can reliably assess liver fibrosis, regardless of *H. pylori* status.

Keywords: APRI; FIB-4; *Helicobacter pylori*.

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Introduction

Chronic liver disease (CLD), a major global health burden, often progresses to cirrhosis and hepatocellular carcinoma (HCC).[1] Key causes include NAFLD (60%), HBV (29%), and HCV (9%).[2] Fibrosis, driven by hepatic stellate cells (HSC), leads to extracellular matrix accumulation and liver dysfunction.[3,4] Early diagnosis and monitoring improve prognosis.

The gold standard for hepatic fibrosis assessment is histopathological evaluation. However, its invasive nature and associated risks limit its practicality.[5] Various non-invasive tests, both biochemical and radiological, have been developed. Biochemical tests, especially indirect ones, are frequently used due to their accessibility and cost-effectiveness. These include APRI and FIB-4, among others, which rely on routine biochemical markers. Sensitivity and specificity vary depending on cutoff values and fibrosis etiology.[6,7] However, these tests can yield falsely low or high results due to factors like diabetes mellitus, obesity, and extrahepatic inflammation.[8–10]

The global prevalence of *H. pylori* is 43.1%.[11] This bacterium causes gastrointestinal inflammation and is associated with extraintestinal conditions, including elevated transaminases and thrombocytopenia.[12–15] Its potential impact on liver fibrosis tests, such as APRI and FIB-4, remains unclear. Thus, this study aimed to evaluate the effects of *H. pylori* on these indirect fibrosis tests.

Materials and Methods

A retrospective analysis was conducted on 2,511 patients who underwent liver biopsy at the Gastroenterology Outpatient Clinic of Dokuz Eylul University Hospital between 2006 and 2021, including 528 patients who had gastric biopsies performed via esophagogastroduodenoscopy (EGD). A total of 190 patients were included in the study within one year, who underwent liver biopsy for various reasons and gastric biopsy due to dyspeptic complaints, with the presence of *H. pylori* investigated (Fig. 1). Patients who were found to be *H. pylori* negative in the gastric biopsy performed after the liver biopsy and *H. pylori* positive in the gastric biopsy performed before the liver biopsy were included in the study.

The selected study group consisted of patients who had not received eradication therapy for *H. pylori*. Patients were questioned about recent antibiotic and PPI use before testing, and those who had used such medications within the past four weeks were excluded from the study. Demographic data, comorbidities, laboratory findings, and liver disease diagnoses for fibrosis assessment at the time of liver biopsy were ob-

tained from the medical records of the patients included in the study. Based on the liver biopsy pathology results and clinical evaluations, the patients were categorized into five etiological groups for fibrosis assessment. These groups included HBV, HCV, NASH, autoimmune liver disease, and an "other" group consisting of patients with no definitive diagnosis (those with nonspecific findings on pathology slides).

Using AST, ALT, and platelet values at the time the biopsy was taken from the patients, APRI and FIB-4 scores were calculated. The correlation between the APRI and FIB-4 scores and the Ishak fibrosis score,[16] as reported in the patients' pathology reports, was examined. The patients were then divided into two groups based on their Ishak scores: 0–1 and 2–6. The discriminative performance of the APRI and FIB-4 scores was evaluated for these groups. Subsequently, gastric pathology reports were reviewed, and patients were categorized as *H. pylori* positive or negative. The effect of *H. pylori* on APRI and FIB-4 scores was assessed in patients across different fibrosis groups.

Ethical approval was obtained from the Dokuz Eylul University Ethics Committee (Approval Date: 02.06.2021, Approval No: 2021/17-07), and informed consent was secured from all participants. The study adhered to the Helsinki Declaration and followed Good Laboratory and Clinical Practices.

Statistical Analysis

The analysis yielded a statistical power of 87%, indicating that the study was adequately powered to detect meaningful differences between the *H. pylori*-positive and -negative groups. The Shapiro–Wilk test assessed data normality. Descriptive statistics were presented as mean ± SD for normally distributed data, median (IQR) for non-normal data, and n (%) for categorical variables. Categorical data were compared using Pearson's chi-square or Fisher's Exact test, while Mann–Whitney U and Kruskal–Wallis tests were used for non-parametric continuous data. ROC analysis evaluated APRI and FIB-4 scores in distinguishing fibrosis stages, with AUC, sensitivity, specificity, and optimal cut-off points determined via the Youden index. AUCs were compared using the DeLong method.[17] Statistical analysis was performed with SPSS v23.0 (IBM Corp., Armonk, NY), and $p<0.05$ was deemed significant.

Results

Of the 190 patients included in the study, *H. pylori* was detected in 135 (71%) patients and was absent in 55 (29%). The proportion of female patients (52.6%) was higher than that of males (47.4%), but gender distribution did not significantly differ across groups (p=0.073). A comparison of patient characteristics based on *H. pylori* presence revealed no significant differences in demographic, clinical, or laboratory findings. The median age was 56 years (IQR: 49–62) in the *H. pylori*-negative group and 54 years (IQR: 46–62) in the *H. pylori*-positive group (p=0.204). No significant associations were found between *H. pylori* status and comorbidities, including hypertension (p=0.828), diabetes mellitus (p=0.463), hyperlipidemia (p=0.747), chronic kidney disease (p=0.139), and coronary artery disease (p=0.514). Similarly, the laboratory findings did not differ significantly between *H. pylori*-positive and -negative groups. The AST levels were comparable (p=0.567), with a median of 33 U/L (IQR: 24–74) in the *H. pylori*-negative group and 34 U/L (IQR: 23–54) in the *H. pylori*-positive group. ALT values also showed no significant difference (p=0.819), with median values of 34 U/L in both groups. Platelet counts, INR, APRI, and FIB-4 scores were also similar across the groups (p>0.05). Regarding fibrosis etiology, no statistically significant differences were observed between the *H. pylori* groups in terms of HBV (p=0.972), HCV (p=0.191), NASH (p=0.071), autoimmune liver disease (p=0.055), or other causes (p=0.323) (Table 1).

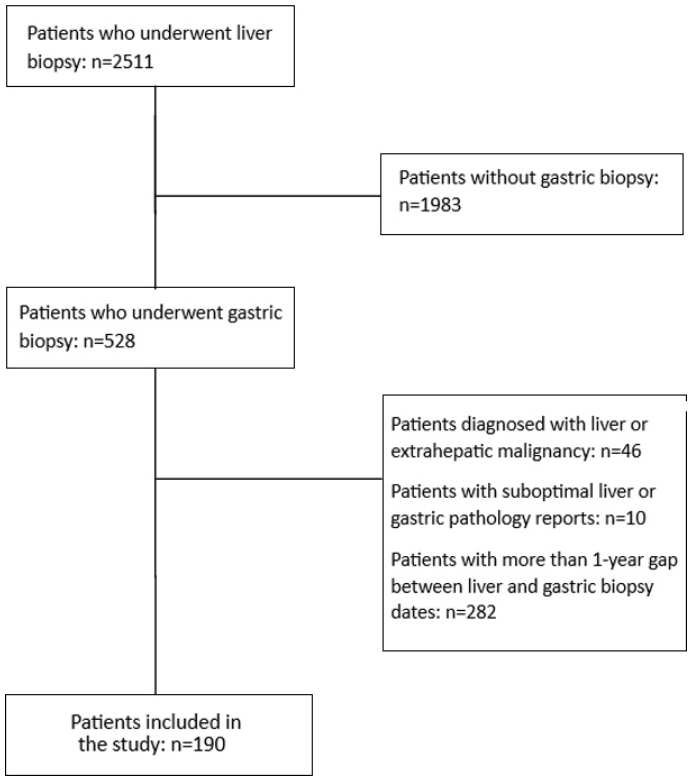

Figure 1. Flowchart of patient inclusion in the study.

APRI scores showed significant differences between mild–moderate and mild–advanced fibrosis groups ($p<0.001$) but not between moderate and advanced groups ($p>0.05$). The FIB-4 scores differed significantly across all fibrosis groups ($p<0.001$). *H. pylori* presence did not significantly impact APRI or FIB-4 scores in any fibrosis group or etiological subgroup ($p>0.05$) (Table 2, 3).

Discussion

The FIB-4 and APRI tests are non-invasive hepatic fibrosis tools frequently used in clinical practice. While these tests reliably predict hepatic fibrosis, their values can be influenced by comorbidities and extrahepatic inflammation.[8] Consequently, the effects of various factors, including *H. pylori* infection, on these tests should be explored. Studies have shown that *H. pylori* impacts AST, ALT, and platelet counts, which are parameters used in calculating FIB-4 and APRI.[13,14] However, no data exist on the direct impact of *H. pylori* on these fibrosis tests. Our study of 190 patients examined this association, finding no statistically significant effect of *H. pylori* on FIB-4 and APRI scores.

The 2013 TURHEP study in Turkey reported an *H. pylori* prevalence of 82.5% nationwide and 80.3% in the Western region.[18] In our study, the prevalence was 71%, with no significant gender difference (p=0.345). This lower prevalence likely reflects the higher socioeconomic status of the urban population studied, aligning with the literature.

The relationship between *H. pylori* and thrombocytopenia was first identified in a case study in 1992. Subsequent research has demonstrated that the eradication of *H. pylori* in patients with immune thrombocy-

Table 1. Patient characteristics based on the presence of *H. pylori*

Variables	*H. Pylori* absent (n=55)	*H. Pylori* present (n=135)	p
Age, median (IQR)	56 (49–62)	54 (46–62)	0.204
Gender (female/male), n (%)	26 (47.3) / 29 (52.7)	74 (54.8) / 61 (45.2)	0.345
Comorbidities, n (%)			
Hypertension	18 (32.7)	42 (31.1)	0.828
Diabetes mellitus	18 (32.7)	37 (27.4)	0.463
Hyperlipidemia	4 (7.3)	8 (5.9)	0.747
Chronic kidney disease	7 (12.7)	8 (5.9)	0.139
Coronary artery disease	2 (3.6)	9 (6.7)	0.514
Laboratory findings			
AST, (median, IQR)	33 (24–74)	34 (23–54)	0.567
ALT, (median, IQR)	34 (21–99)	34 (21–70)	0.819
Platelets (PLT, median, IQR)	210 (146–266)	220 (160–276)	0.522
INR, (median, IQR)	1 (1–1.1)	1 (1–1.1)	0.356
APRI, (median, IQR)	0.51 (0.27–1.07)	0.38 (0.23–0.89)	0.251
FIB-4, (median, IQR)	1.68 (1.07–2.82)	1.33 (0.91–2.26)	0.103
Diagnosis, n (%)			
HBV	19 (34.5)	47 (34.8)	0.972
HCV	10 (18.2)	15 (11.1)	0.191
NASH	6 (10.9)	30 (22.2)	0.071
Autoimmune	12 (21.8)	15 (11.1)	0.055
Other	8 (14.5)	28 (20.7)	0.323

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; APRI: AST-to-Platelet Ratio Index; FIB-4; Fibrosis-4; *H. pylori: Helicobacter pylori*; HBV: Hepatitis B virus; HCV: Hepatitis C virus; INR: International normalized ratio; NASH: Non-alcohol-associated steatohepatitis.

topenic purpura (ITP) leads to a significant increase in platelet counts.[19] In a multicenter prospective study conducted in Italy involving 244 pediatric patients with chronic immune thrombocytopenia, *H. pylori* was identified in 50 patients. Successful eradication of *H. pylori* was achieved in 33 patients, and notably, 13 of them (39%) experienced a significant increase in platelet counts following eradication.[20] In our study, there was no statistically significant difference in platelet counts between groups with and without *H. pylori* infection (p=0.522).

In a study published in 2019 involving 58 patients with HCV, the effect of *H. pylori* infection on liver function tests was investigated. In the group of 32 patients who were co-infected with HCV and *H. pylori*, the levels of AST, ALT, and ALP were found to be significantly higher compared to the 26 patients who were infected solely with HCV.[21] In a retrospective study published in 2014, *H. pylori* eradication was performed in 108 patients with unexplained elevated transaminases. The study found that in patients with elevated AST, 46.6% experienced normalization of their levels post-eradication, while 45.7% of patients with elevated ALT also showed normalization after treatment.[13] In our study, no significant difference was found between the groups with and without *H. pylori* in terms of AST and ALT levels (p=0.567, p=0.819). While an association between *H. pylori* and elevated transaminases has been previously demonstrated, the studies in the literature often involve small sample sizes. The absence of data on transaminase levels after *H. pylori* eradication in our study, combined with the inclusion of cirrhotic patients who generally do not exhibit elevated transaminases, may have contributed to the discordant results compared to existing literature.

Recent studies have suggested a potential association between *Helicobacter pylori* infection and liver fibrosis, particularly in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). While our study did not demonstrate a significant effect of *H. pylori* colonization on FIB-4 and APRI scores, suggesting that colonization alone may not be sufficient to influence these indices, other studies have reported contrasting results. For instance, Gulati et al.[22] found a significant association between *H. pylori* positivity and higher non-invasive fibrosis scores (FIB-4, APRI, and NAFLD fibrosis score; p<0.05) in 584 severely obese individuals undergoing bariatric surgery. These patients also exhibited increased liver stiffness, steatosis, and NAFLD activity scores, with biopsy-confirmed fibrosis across all stages (p<0.05). Similarly, a large-scale population-based study from 2023 involving 12,931 participants reported elevated AST levels and FIB-4 scores in *H. pylori*-positive individuals.[15] However, the absence of liver biopsy data in that study limits the ability to confirm whether elevated scores truly reflect fibrosis or represent potential false positives. These findings suggest that *H. pylori* may contribute to fibrosis progression, especially in metabolically high-risk groups, potentially accounting for discrepancies between our findings and those of previous studies.

Table 2. Effect of *H. pylori* infection on APRI and FIB-4 scores in patients with fibrosis 0–1 by etiology

Etiology	*H. Pylori* present	*H. Pylori* absent	p
HBV			
n	23	7	
APRI, (median, IQR)	0.22 (0.17–0.31)	0.42 (0.25–0.6)	0.061
FIB-4, (median, IQR)	0.98 (0.84–1.4)	1.42 (0,92–1.57)	0.245
HCV			
n	7	4	
APRI, (median, IQR)	0.2 (0.2–0.3)	0.35 (0.25–0.5)	0.315
FIB-4, (median, IQR)	1.33 (0.72–1.41)	1.32 (0.91–1.79)	0.788
NASH			
n	21	2	
APRI, (median, IQR)	0.4 (0.27–0.61)	0.84 (0.56–1.11)	0.237
FIB-4, (median, IQR)	0.91 (0.71–1.21)	1.87 (1.31–2.43)	0.095
Autoimmune liver disease			
n	10	7	
APRI, (median, IQR)	0.29 (0.21–0.4)	0.29 (0.25–0.51)	0.813
FIB-4, (median, IQR)	1.11 (0.8–1.24)	1.07 (0.65–1.43)	0.962

APRI: AST-to-Platelet Ratio Index; FIB-4: Fibrosis-4; *H. pylori: Helicobacter pylori;* HBV: Hepatitis B virüs; HCV: Hepatitis C virus; NASH: Non-alcohol-associated steatohepatitis.

Table 3. Effect of *H. pylori* infection on APRI and FIB-4 scores in patients with fibrosis 2–6 by etiology

Etiology	*H. Pylori* present	*H. Pylori* absent	p
HBV			
n	24	12	
APRI, (median, IQR)	0.78 (0.41–1.17)	0.85 (0.3–2.74)	0.830
FIB-4, (median, IQR)	1.91 (1.35–3.72)	2.63 (1.33–4.63)	0.704
HCV			
n	8	6	
APRI, (median, IQR)	1.55 (0.85–2.25)	1.1 (0.4–1.7)	0.282
FIB-4, (median, IQR)	4.77 (2.47–5.66)	3.1 (1.98–4.36)	0.228
NASH			
n	9	4	
APRI, (median, IQR)	1 (0.88–1.34)	0.78 (0.51–0.9)	0.148
FIB-4, (median, IQR)	3.51 (1.67–3.79)	1.48 (1.15–3.76)	0.604
Autoimmune liver disease			
n	5	5	
APRI, (median, IQR)	0.94 (0.44–1.66)	0.93 (0.51–2.28)	0.841
FIB-4, (median, IQR)	2.28 (1.61–5.47)	1.68 (1.68–3.36)	0.753

APRI: AST-to-Platelet Ratio Index; FIB-4: Fibrosis-4; *H. pylori: Helicobacter pylori*; HBV: Hepatitis B virüs; HCV: Hepatitis C virus; NASH: Non-alcohol-associated steatohepatitis.

Additionally, our study found no significant difference in the APRI scores between patients with moderate and advanced fibrosis. Notably, while the FIB-4 score appeared to be more effective in distinguishing between moderate (F2–3) and advanced (F4–6) fibrosis stages, APRI failed to demonstrate such discriminatory capacity. This may be attributed to APRI's greater reliance on AST levels, which can plateau or increase only slightly in advanced disease, especially in cases progressing to cirrhosis, where chronic hepatocyte damage leads to less pronounced enzyme fluctuations. Furthermore, although platelet count is a critical component of the APRI score, the expected decline due to splenomegaly and portal hypertension may not be uniformly present in all patients, limiting APRI's sensitivity in detecting advanced fibrosis. These physiological and biochemical nuances likely underlie the observed limitations of APRI in our cohort.

The limitations of this study include its retrospective design, single-center nature, and small sample size for subgroup analysis by etiology. Additionally, the lack of data on eradication outcomes in the group with *H. pylori* positivity represents another significant limitation. Future studies should aim to address these limitations by utilizing larger sample sizes, multicenter designs, and including post-eradication follow-up data to provide a more comprehensive understanding of the relationship between *H. pylori* and liver fibrosis.

Our study found no significant effect of *H. pylori* on FIB-4 and APRI scores, regardless of etiology or fibrosis stage ($p>0.05$). When patients were grouped into mild (F0–1), moderate (F2–3), and advanced (F4–6) fibrosis stages, the presence of *H. pylori* did not significantly influence these scores in any group. Similarly, when categorized by etiology (HBV, HCV, NASH, autoimmune liver disease) and fibrosis severity ($F<2$ vs. $F\geq2$), no significant impact of *H. pylori* was observed on FIB-4 or APRI scores in any subgroup ($p>0.05$).

In conclusion, our study evaluated the impact of *H. pylori* presence on the FIB-4 and APRI tests, and the results indicated that *H. pylori* does not have a statistically significant effect on either FIB-4 or APRI scores. The likely reason for this finding is that, while *H. pylori* infection is widespread in the population, its impact on ALT, AST, and platelet values occurs less frequently. No studies in the literature have investigated the effect of *H. pylori* on the evaluation of hepatic fibrosis using APRI and FIB-4 scores. This study is the first of its kind in the literature. Based on the data we obtained, the APRI and FIB-4 scores can be reliably used in clinical practice for the evaluation of hepatic fibrosis, regardless of the presence of *H. pylori*. However, further studies involving larger patient cohorts with diverse etiologies are needed for more definitive results.

Ethics Committee Approval: The Dokuz Eylul University Ethics Committee granted approval for this study (date: 02.06.2021, number: 2021/17-07).

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