Medical Science and Discovery
ISSN: 2148-6832

Helicobacter pylori and ischemic liver injury in heart failure: A new clinical association?

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ABSTRACT

Objective: This study aimed to investigate the association between Helicobacter pylori (H. pylori) scolonisation and ischemic hepatitis in patients with heart failure.

Material Methods: A retrospective analysis was conducted on the medical records of 80 patients with heart failure who had undergone liver function tests. The patients were divided into two groups based on their liver function tests: those who developed ischemic hepatitis and those who did not. H. pylori scolonisation status was determined using serum immunoglobulin G antibody testing.

Results: Of the 80 patients, 47 (58.75%) had H. pylori colonisation. H. pylori scolonisation was more prevalent in the group of patients who developed ischemic hepatitis compared to those who did not (36.2% vs 63.8%, $p<0.05$). These findings suggest that H. pylori scolonisation may contribute to developing ischemic hepatitis in patients with heart failure.

Conclusion: This study provides evidence for an association between H. pylori scolonisation and ischemic hepatitis in patients with heart failure. The results suggest that H.pylori may contribute to this condition's development and that further research is needed to understand the mechanisms involved fully. These findings have important implications for healthcare professionals in managing heart failure and liver disease patients.

Keywords: ischemic hepatitis, heart failure, H. pylori, inflammation

INTRODUCTION

Heart failure (HF) is a chronic and progressive cardiovascular disease affecting millions worldwide. Patients with HF often experience a variety of comorbidities, including liver dysfunction, which can further complicate their condition (1-3). Ischemic hepatitis, also known as shock liver, is a rare condition characterised by sudden liver dysfunction due to decreased blood flow to the liver. It is commonly observed in patients with severe heart failure, where low cardiac output leads to inadequate perfusion of vital organs, including the liver (4).

H. pylori is a gram-negative bacterium colonising the human stomach, leading to gastrointestinal disorders such as gastritis, peptic ulcer disease, and gastric cancer. Recent studies have shown that H. pylori colonisation can also impact extra-gastrointestinal conditions, including cardiovascular diseases (5-7). While the exact mechanisms underlying ischemic hepatitis in heart failure patients are not fully understood, previous studies have suggested that H. pylori colonisation may be involved. And again, recent studies have indicated that H. pylori infection may play a role in developing ischemic hepatitis in these patients, possibly through inflammation and oxidative stress mechanisms (8).

The present study aimed to investigate the relationship between H. pylori colonisation in the stomach and the development of ischemic hepatitis in patients with heart failure. We hypothesised that H. pylori colonisation might facilitate the development of ischemic hepatitis in these patients. To test this hypothesis, we retrospectively analysed patient data from a tertiary care hospital in Turkey. Our study provides important insights into the complex interplay between H. pylori infection, HF, and liver dysfunction. It has implications for developing new therapeutic strategies to prevent and treat ischemic hepatitis in these patients.

Research Article

Received 20-06-2023

Accepted 01-07-2023

Available Online: 02-07-2023

Published 30-07-2023

MATERIAL and METHODs

The local ethics committee of Giresun Training and Research Hospital approved the study protocol. Informed patient consent was waived due to the retrospective design of the study. This study was conducted on the relevant ethical principles of the Declaration of Helsinki, revised in 2013. The study was conducted at Giresun Training and Research Hospital in Giresun province.

A total of 80 patients were included in the study. Between January 2020 and December 2022, the medical records of 40 patients who were treated with the diagnosis of ischemic hepatitis due to heart failure in the gastroenterology clinic and 40 patients who were treated only for heart failure in the cardiology clinic were retrospectively reviewed. Patients who developed ischemic hepatitis due to heart failure were determined as the study group. The control group consisted of patients with heart failure who did not establish ischemic hepatitis. The typical features of the two groups were that they were diagnosed with heart failure and described dyspeptic complaints such as bloating and indigestion during their treatment. Patients with a history of vascular intervention or surgery in the two weeks before admission, patients with acute systemic infection, patients with known malignancy, and a previous history of the severe renal or haematological disease, viral hepatitis, alcohol-related liver disease, and autoimmune liver disease were excluded from the study.

Patients' demographics such as age and gender, laboratory results such as white blood cell (WBC), haemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), platelet (PLT), monocytes, neutrophils, lymphocytes, eosinophils, basophils, creatinine, urea, glucose, alanine transaminase (ALT), aspartate transaminase (AST), protein, albumin, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), sodium (Na), potassium (K), calcium (Ca), C reactive protein (CRP), values were recorded through medical records. The diagnosis of ischemic hepatitis was based on the presence of elevated liver enzymes (ALT and AST) and a history of heart failure with evidence of reduced cardiac output, increased pulmonary artery pressure (PAP), and high NT-proBNP levels.

Detection of H.Pylori antibodies in the groups

The presence of H.pylori was investigated sutilising serological antibody concentrations. Accordingly, the enzyme-linked immunosorbent assay was based on quantitatively detecting H. Pylori (IgG, IgA) antibodies in the serum of the patients in the study group using a commercially available kit (Human-Germany) according to the manufacturer's instructions.

The principle of this test is based on binding specific antibodies (IgG, IgA) to H. Pylori, if present, to examine the antigens of this bacteria installed on the ELISA's inner surface test dish. Then, the dish is irrigated with a washing solution to remove the unbound substances. The plate is then incubated for 30 minutes after the completion of the washing process. The substrate (TMB) is added.

Statistical Analysis

Statistical analysis of the data obtained in this study was performed using the SPSS version 25.0 (SPSS for Windows, Statistical Package for the Social Sciences, IBM Corp., Armonk, NY). The normality of the variables was evaluated using the Shapiro-Wilk test. Continuous variables are expressed as mean ±standard, while categorical variables are given as frequency and percentage (n, %). To show the increase or decrease in the variables more clearly, the mean ± standard deviation values were used instead of the median (minimum: maximum) values. T-test was used for comparisons between two groups according to the normality test results, and the Mann-Whitney U test was used in cases where it did not show normal distribution. A comparison of categorical variables was sanalysed with the chi-square test and Fischer's exact test. In addition, ROC (Receiver Operating Characteristic) analysis, Logistic regression and Cohort analysis were also included. The data analysis's probability of error (significance level) was accepted as $p<0.05$.

RESULTS

Eighty patients were included in the study, 40 in the study group and 40 in the control group. Of these patients, 47 (58.8%) were male, and 33 (41.3%) were female. All patients' mean age was 71.83±13.60 (range: 26-95) years. The rate of H.Pylori positivity was found as 58.8%.

No statistically significant difference was found between the two groups regarding age and gender. Considering the biochemical parameters, except for monocytes, eosinophils, basophils, glucose, GGT, ALP and sodium values, other parameters differed statistically between the groups. Of the 40 patients in the control group, 17 (42.5%) were H. pylori positive, 23 (57.5%) were H. pylori

nificant between the groups ($p<0.05$). The comparison of demographic features, biochemical parameters and H. pylori status between the groups is given in **Table 1.**

The values of H. pylori (+) and H. pylori (-) status of the patients in the study group were sanalysed in Table 2. It was observed that the GGT, Cl and amylase values of the patients in the study group had a statistically significant difference according to the H. pylori (+) and H. pylori (-) status ($p<0.05$). It was observed that GGT and Cl values increased in the H. pylori positive condition, while amylase value decreased in the H. pylori positive condition.

In order to compare the diagnostic performances of the significant laboratory tests in the study group, ROC analysis was performed, and the ROC graph below was obtained (**Figure 1**).

 http://dx.doi.org/10.36472/msd.v10i7.980

Table 1. Comparison of demographic features, biochemical parameters and H.pylori status between the study and control groups

Variables	Control Group (n=40)	Study Group (n=40)	T/U/χ^2	p*
Age (years)	66 (48:94)	75 (26:95)	1.022	**0.032**
WBC	6.99 (3.17:15)	9.31 (4.41:25.43)	1061	**0.012**
HGB	12.96±2.03	10.9±1.98	4.58	**<0.001**
HCT	38.91±5.76	31.85±5.96	5.39	**<0.001**
MCV	86.70±5.29	89.15±4.77	-2.177	**0.033**
PLT	247.5 (123:548)	219 (77:470)	594	**0.047**
Monocytes	0.69±0.34	0.66±0.34	0.381	0.704
Neutrophils	4 (1.66:12.62)	7.37 (2.49:23.33)	1207	**<0.001**
Lymphocytes	1.87 (0.5:3.42)	1.01 (0.25:2.87)	233	**<0.001**
Eosinophils	0.15 (0.02:0.79)	0.11 (0.01:0.94)	638	0.119
Basophils	0.03 (0.01:0.12)	0.03 (0.01:0.12)	736.5	0.535
Creatinine	0.79 (0.43:5.53)	1.59 (0.61:5.48)	1321	**<0.001**
Urea	26.5 (12:86)	56 (22:208)	1451.5	**<0.001**
Glucose	101.5 (75:518)	115.5 (70:313)	982	0.080
ALT	19 (8:332)	79.5 (8:1108)	1256	**<0.001**
AST	19 (12:273)	68 (20:1300)	1468.5	**<0.001**
Protein	73.82±3.41	58.77±10.34	8.754	**<0.001**
Albumin	44.02±4.36	31,32±5.60	11.32	**<0.001**
GGT	19 (8:183)	46 (25:98)	1422.5	**<0.001**
ALP	82.5 (44:137)	69.5 (21:221)	661	0.181
Na	138.03±4.59	137.13±5.62	0.784	0.435
K	3.99±0.44	4.32±0.76	-2.354	**0.022**
Ca	9.47±0.78	8.41±0.99	5.315	**<0.001**
CRP	14.27±29.51	75.22±73.86	-4.856	**<0.001**
	n (%)	**n (%)**		
Gender				
Male	24 (51.1)	23 (48.9)	0.052	0.820
Female	16 (48.5)	17 (51.5)		
H. pylori				
Positive	17 (36.2)	30 (63.8)	8.717	**0.003**
Negative	23 (69.7)	10 (30.3)		

Variables mean±standard deviation and median(min:max) are expressed ; T: Student's t-test; U: Mann-Whitney U test; χ^2: Chi-square test; *p<0.05

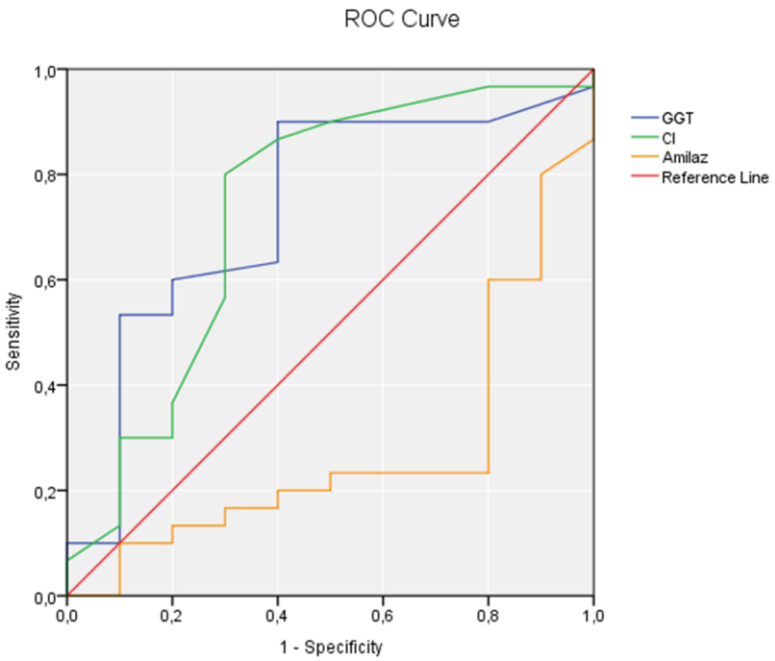

Figure 1. Parameters for which ROC analysis was performed in the study group

Table 2. Comparison of the parameters of the study group according to H.pylori positivity and negativity

Variables	*H.pylori (-)* (n=10)	*H.pylori (+)* (n=30)	T/U	p*
WBC	12.04 (5.55:25.43)	8.99 (4.41:21.79)	187.5	0.246
HGB	10.27±1.79	11.11±0.03	1.166	0.251
HCT	30±5.29	32.47±6.12	1.138	0.262
MCV	87.09±3.26	89.83±5.04	1.607	0.116
PLT	259.80±87.08	205.20±83.33	-1.775	0.084
Monocytes	0.61±0.40	0.68±0.32	0.544	0.590
Neutrophils	7.02 (4.36:23.33)	7.71 (2.49:20.22)	176.5	0.414
Lymphocytes	1.055 (0.55:2.87)	1.01 (0.25:2.28)	163.5	0.678
Eosinophils	0.07 (0.01:0.62)	0.11 (0.01:0.94)	126.5	0.469
Basophils	0.035 (0.01:0.07)	0.03 (0.01:0.12)	182	0,331
Creatinine	0.995 (0.61:5.48)	1.085 (0.67:3.86)	130	0.548
Urea	52 (27:168)	59 (22:208)	127.5	0.448
Glucose	119.5 (92:292)	113.5 (70:313)	175.5	0.432
ALT	76.5 (11:710)	79.5 (8:1108)	154.5	0.890
AST	59.5 (20:841)	70 (22:1300)	147	0.939
Protein	59.44±10.99	58.54±10.29	-0.233	0.817
Albumin	30.14±7.66	31.71±4.82	0.611	0.553
GGT	34.5 (27:88)	53 (25:98)	80	**0.028**
ALP	59 (21:199)	71 (36:221)	110	0.221
Na	134.80±4.80	137.90±5.73	1.538	0.132
K	4.33±0.95	4.31±0.69	-0.06	0.953
Ca	8.25±1.31	8.46±0.88	0.583	0.563
Cl	97±6.78	102.00±5.83	2.256	**0.030**
Total bil.	0.88 (0.52:25.38)	0.95 (0.28:13.55)	146	0.914
Direct bil.	0.47 (0.22:21.55)	0.46 (0.9:12.03)	145	0.890
CK	88 (23:1396)	71.5 (16:1480)	177.5	0.396
LDH	365 (107:1014)	298.5 (106:2843)	178	0.396
Amylase	103.5 (36:964)	53.5 (14:229)	218	**0.033**
Lipase	22.85 (17.9:47.7)	24.65 (11.6:38)	132	0.590
GFR	56.36±35.32	55.37±27.71	-0.091	0.928
CRP	28.26 (2.27:237.7)	56.09 (2.62:310)	121	0.379
Sedimentation	59±33.04	59.67±34.69	0.053	0.958
Procalcitonin	0.58 (0.0:6.25)	0.46 (0.01:8.93)	148.5	0.963
TSH	1.39 (0.13:4.57)	1.15 (0.12:6.51)	144	0.866
Free T4	1.09 (0.1:1.6)	1.16 (0.23:3.48)	121	0.379
Free T3	1.67±0.49	1.61±0.53	-0.284	0.778
Troponin	0.36 (0.01:5.08)	0.15 (0.01:1.65)	183	0.315
INR	1.33 (0.99:2.75)	1.12 (0.82:2.01)	211.5	0.054
APTT	28.65 (21.7:34.10)	27.95 (21.4:60.2)	134	0.634
Fibrinogen	497.5 (247:664)	381 (137:789)	192.5	0.187
D-dimer	6005 (1496:9926)	4764.5 (1494:9970)	173	0.488
HBsag	0.45±0.13	0.51±0.14	1.055	0.298
Anti HBs	165.29±283.92	254.43± 368.37	0.697	0.490
Anti HCV	0.05 (0.03:0.4)	0.04 (0.21:0.47)	172	0.508
Anti HIV	0.19 (0.15:0.26)	0.21 (0.15:0.51)	112.5	0.246
pH	7.39 (7.31:7.5)	7.36 (6.99:7.47)	186	0.272
Bicarbonate	26.23±5.54	24.92±5.00	-0.697	0.490
Lactate	2.05 (0.90:6.30)	1.7 (0.60:6.70)	163	0.701
NT-proBNP	4979.5 (1076:35000)	4898.5 (151:35000)	162	0.724
EF	52.5 (45:65)	50 (25:60)	163	0.701
PAP	35 (25:60)	35 (25:80)	138	0.724

Variables mean±standard deviation and median(min:max) are expressed; T:Student's t-test; U: Mann-Whitney U test; *p<0.05; bil.: bilirubine; CK: Creatinine kinase; LDH: Lactat dehydrogenase; GFR: Glomerular filtration rate; TSH:Thyroid stimulating hormone; INR: International normalized ratio; APTT: Active partial thromboplastin time test; EF: Ejection fraction

When the ROC analysis results based on H. pylori positivity were examined, GGT, Cl and amylase values in the study group were statistically significant (p<0.05). Accordingly, the test shows that GGT and Cl values successfully separated H. pylori positive patients from H. pylori negative patients. However, the amylase value was significant but had low sensitivity and specificity. It remained below the ROC curve (AUC<0.5), so it can be said that it is not determinative in differentiating the cases (**Table 3**).

The effects of NT-proBNP, EF and PAP values on H. pylori status were investigated. Accordingly, it was determined that NT-proBNP, EF and PAP values did not affect the detection of H. pylori (p>0.05). On the other hand, it can be said that when the EF value increases by 1 unit, the risk of H. pylori will increase by 14.5%, and when the PAP value increases by 1 unit, the risk of H. pylori will increase by 1.7% (Table 4).

Considering the ROC analysis results NT-proBNP, EF and PAP values were not found to be statistically significant (p>0.05). Based on NT-proBNP, EF and PAP values, it was determined that the test was unsuccessful in distinguishing patients from H. pylori (+) or H. pylori (-). Figure 2 shows the ROC analysis results of the study group's NT-proBNP, EF and PAP values.

Table 3. ROC analysis results

Risk factors	AUC (95%)	Cut off	Sensitivity	Specificity	p*
GGT	0.733 (0.546;0.920)	44.5	0.633	0.60	0.029
Cl	0.732 (0.527;0.936)	99.0	0.667	0.70	0.030
Amilase	0.273 (0.092;0.455)	82.5	0.233	0.20	0.034

Table 4. Examination of the risk status of NT-proBNP, EF and PAP on H. pylori

Factors	ORs (Cls %95)	p*
NT-proBNP	0.95 (0.854;1.023)	0.174
EF	1.145 (0.935;1.401)	0.189
PAP	1.017 (0.939;1.102)	0.683

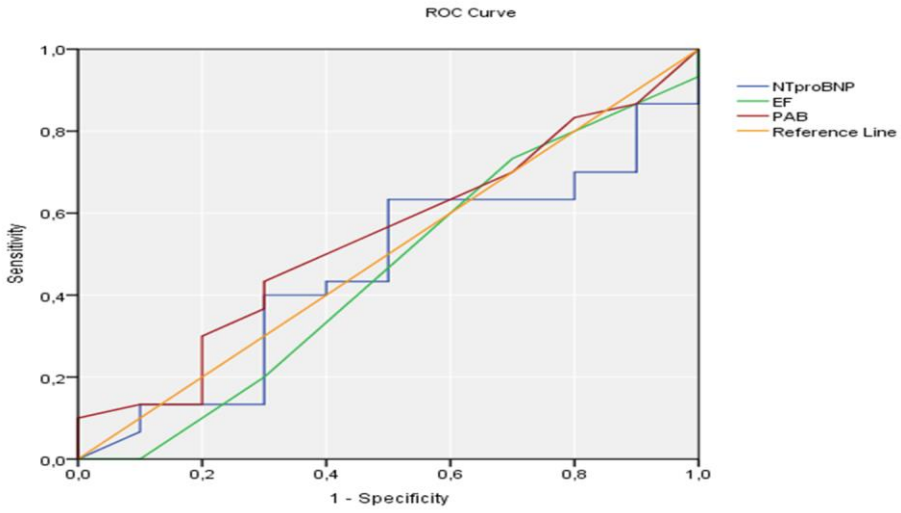

Figure 2. Parameters for which ROC analysis was performed in the study group

DISCUSSION

Our study found that H. pylori scolonisation in the stomach is more prevalent in patients with heart failure-related ischemic hepatitis and may be an independent risk factor for developing this condition. Patients with H. pylori scolonisation also had a higher prevalence of gastritis and peptic ulcer disease (9, 10). These findings have important implications for medicine, suggesting a potential link between H. pylori infection and heart failure-related ischemic hepatitis.

Our possible explanation for the association between H. pylori scolonisation and heart failure-related ischemic hepatitis is that the bacterium may contribute to the development of gastritis and peptic ulcer disease, which in turn may lead to ischemic hepatitis (11-15). Previous studies have shown that H. pylori infection can cause chronic inflammation of the gastric mucosa, leading to the development of peptic ulcers and gastritis (16). This chronic inflammation may also lead to oxidative stress and endothelial dysfunction, known risk factors for developing ischemic hepatitis (17-21). Another possible explanation is that H. pylori scolonisation may directly contribute to the development of ischemic hepatitis by causing microvascular dysfunction in the liver. This dysfunction could lead to decreased blood flow to the liver, resulting in ischemia and subsequent liver damage (22). This hypothesis is supported by previous studies showing that H. pylori infection can cause microvascular dysfunction in other organs, such as the heart and kidneys (23-28).

Study Limitations

One area for improvement of our study is its retrospective design, which may have introduced bias and limited our ability to control for potential confounding factors. Additionally, our study was conducted at a single centre and included a relatively small sample size, which may limit the generalizability of our findings. Future studies with larger sample sizes and more rigorous study designs must confirm our findings and explore the mechanisms underlying the association between H. pylori scolonisation and heart failure-related ischemic hepatitis.

CONCLUSION

In conclusion, our study found that patients with heart failure-induced ischemic hepatitis were more likely to have facilitated scolonisation of H. pylori in their stomachs compared to heart failure patients without ischemic hepatitis. This finding suggests a possible link between H. pylori and the development of ischemic hepatitis in heart failure patients.

This study highlights the importance of considering H. pylori scolonisation status in heart failure patients with liver dysfunction. Healthcare professionals may need to consider testing for H. pylori and providing appropriate treatment to prevent further complications. Further research is required to understand the underlying mechanisms behind the observed relationship between H. pylori and ischemic hepatitis in heart failure patients. Nevertheless, for the first time in the literature, our study adds to the existing knowledge base and provides a starting point for future investigations.

Our findings suggest that considering H. pylori scolonisation status may be a critical aspect of managing heart failure patients with liver dysfunction.

Acknowledgements: none

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions: Concept, Supervision, Resources Materials: Ahmet Cumhur Dülger, **Design**, **Data Collection and/or Processing, Analysis And/Or Interpretation**: Furkan Ali Uygur, **Literature Search** Selahattin Vural, **Writing Manuscript, Critical Review**: Ali Muhtaroğlu

Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Giresun Education And Research Hospital Non-Interventional Clinical Research Ethics Committee. Protocol Code: Kaek-38

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