IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 10 Ser.3 (October. 2022), PP 38-45
www.iosrjournals.org

"Prevalence of Helicobacter pylori infection in chronic alcoholic liver disease patients"

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Abstract
Background*:*
Helicobacter pylori (H. pylori) is a slow-growing, microaerophilic bacteria and gram-negative rod shaped bacteria which colonises the gastric mucosa and reported to be class I carcinogenic factor and also involved in various systemic i.e. vitamin B12 deficiency, iron deficiency anaemia (IDA), idiopathic thrombocytopenic purpura type ,II diabetes mellitus (DM) and Non-alcoholic fatty liver disease (NAFLD).About half of the world's population is estimated to be infected with H. pylori with greater prevalence in developing countries like India than in developed countries. H. pylori also affects the physiology of the liver and this is observed more in those who have cirrhosis. Alcohol interferes with the symbiotic complex between gut immunity and microbe complex, thus favours the growth of H. pylori in the gut. Ingestion of alcohol is found to have a positive relationship with gastric ulcers /Peptic Ulcer Disease, ultimately leading to chronic active gastritis and gastric adenocarcinoma.Hence, we conducted this study to estimate its prevalence and significance with chronic alcoholic liver disease patients.
Methods: *This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from August 2019 to September 2021.124 cases of chronic alcoholic liver disease patients above 18 years who attended Medicine /Gastroenterology OPD or admitted in the General Medicine wards were enrolled. Helicobacter Pylori was detected by either -H. pylori specific IgG antibody detection in serum /Rapid Urease Test positivity of biopsy specimen /Histopathological examination (Gram stain & Giemsa stain) of biopsy specimen. Liver function tests, viral markers, prothrombin time, complete hemogram, USG whole abdomen and other investigations as per clinical suspicion were done.*
Results: *A total of 124 diagnosed cases of chronic alcoholic liver disease were included in the study. The mean age of the study population was 55.29 ± 10.6 with the majority in age group 49-58 years (37.1%) and majority of them were males 85.5%. Dyspepsia (97.5%) was the most common presenting symptom. In the present study, the prevalence of H.pylori was found to be 63.7%*which was the same as *H. pyloriIgG positivity. But as per the Rapid urease test and histopathological examination results, the H. pylori prevalence rate in the study was 84.8%. Thus, Rapid urease test and histopathological examination reported a higher prevalence than H. pylori IgG positivity.*
Conclusion:*The prevalence of H. pylori was found to be 63.7% and had significant association with chronic alcoholic liver disease patients with more frequent consumption of large quantity of alcohol for longer duration and those belonging to Child Turcotte Pugh Class B, thereby suggesting specific anti H. pylori therapeutic interventions in CLD patients.*
Keyword: *alcohol, alcoholic liver disease, gastric ulcer, helicobacter pylori, rapid urease test*

Date of Submission: 26-09-2022 Date of Acceptance: 11-10-2022

I. Introduction

A symbiotic relationship exists between the human host and gastrointestinal microbiome, and both co-exist together as a complex ecosystem[1] About half of the world's population is estimated to be infected with H. pylori with greater prevalence in developing countries like India than in developed countries.[2-3]Helicobacter pylori (H. pylori) is a slow-growing, microaerophilic bacteria and gram-negative rod-shaped bacteria. H. pylori colonize in the gastric mucosawhich shields them against the acidic pH of the stomach. Adhesins like

liposaccharides and outer proteins enable H. pylori attachment to the mucosal surface. These organisms make their environment favourable by producing abundant urease enzyme that hydrolyses urea to ammonia and carbon dioxide, making environment alkaline for H. pylori.Hence, diagnostic investigations for H. pylori are also done by detecting urease either by breath analysis or Rapid Urease Test (RUT) of biopsy specimen from stomach. They also produce toxins like vacuolating toxins (VacA) which cause direct mucosal injury and highly virulent cytotoxin associated gene A (CagA), which causes actin remodelling, IL-8 induction, host cell growth and apoptosis. Few studies have reported that H. pylori bacteria can have an impact on many pathological process both in the stomach and systemically[4] H. pylori induces changes in the gut microbe or due to the release of various cytotoxic substances which activate inflammatory mediators and induce autoimmunity.[5-7] such as cytokines IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17 interferon-β, and TNF-α.[8]Hence, a positive association has been discovered between H. pylori and cardiac infarction[9] , rosacea[10]and bronchiectasis.[11] The CagA positive variants are capable of producing local and systemic, humoral and cellular inflammatory response.[12]and has a causative role in the development of chronic gastritis,[13] peptic ulcer disease,[14] gastric adenocarcinoma, low-grade B-cell lymphoma of gastric mucosa-associated lymphoid tissue (MALT-lymphoma)[15], and gastric cancer.[16] This sequalae of activation of inflammatory markers and autoimmunity can bring about inflammatory reactions which can cause atrophic gastritis, metaplasia, and dysplasia, leading to the development of gastric cancer. The World Health Organisation (WHO), has reported H. pylori as oncogenic. H. pylori has been identified as a Group I carcinogen by the International Agency for Research on Cancer and currently is considered a necessary but insufficient cause of gastric adenocarcinoma.[17-18]

H. pylori also affects the physiology of the liver and this is observed more in those who have cirrhosis.[19] It was also reported that *H.pylori* eradication therapy can increase the levels of high-density lipoprotein cholesterol in the infected patients with chronic gastritis.[20] The role of H. pylori bacteria in idiopathic thrombocytopenic purpura and iron deficiency anaemia (IDA) has been shown in all age groups.[21] Current research shows that *H. pylori* may also be associated with vitamin B12 deficiency, type II diabetes mellitus (DM) and Non-alcoholic fatty liver disease (NAFLD).

Alcohol interferes with the symbiotic complex between gut immunity and microbe complex, thus favours the growth of *H. pylori* in the gut. Ingestion of alcohol is found to have a positive relationship with gastric ulcers /Peptic Ulcer Disease. Ingestion of alcohol over a longer duration of time is also associated with chronic active gastritis. The gastric ulcers and their sequelae of inflammatory events have a crucial role in decreasing the protective function of the mucosal layer of the stomach. Alcohol is degraded in the hepatic cells majorly by an enzyme named alcohol dehydrogenase (ADH). Additionally, the microsomal ethanol oxidizing system (MEOS) and catalase are also involved in the metabolism of alcohol. Similar to alcohol dehydrogenase of the liver, the mucosal layer of the stomach also produces an isoenzyme which degrades about 10% of the consumed alcohol in the stomach itself. The *H. pylori* bacteria inhibits the alcohol dehydrogenase enzyme in the stomach ,thus enabling a higher concentration of alcohol to reach the hepatocytes.[22] Through this mechanism *H. pylori* supplements further damage to hepatocytes. *H. pylori* bacteria and alcohol together can react and produce inflammatory reaction in the stomach. In the small intestine and colon, alcohol can deplete the normal bacterial flora with its anti-inflammatory activity leading to a condition called "leaky gut" where intestines are damaged.

Since *H. pylori* is reported to be involved in various systemic diseases and is also considered as class I carcinogenic factor, a study on the prevalence of *H. pylori* infection in liver disease in this part of country is necessary for the commencement of preventive and therapeutic strategies thereby resulting in this study.

II. Materials and Methods

This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from August 2019 to September 2021.Chronic alcoholic liver disease patients who attended Medicine OPD/Liver clinic or admitted in the General Medicine wards were enrolled following the criteria.

Inclusion Criteria

Patients diagnosed as chronic alcoholic according to the working definition with evidence of underlying Chronic Liver Disease (CLD) of age more than or equal to 18 years were enrolled in the study.

Exclusion Criteria include patients with History of systemic helicobacter-pylori eradication therapy within past 6 weeks, terminally ill patients and those not giving consent.

Study procedure Independent variables: Personal details including a detailed history of presenting symptoms (Dyspepsia, Fatigue, Anorexia, Malena, Hematemesis, Yellow Eyes, Abdominal Distension), past history and personal history were recorded in proper proforma along with age, sex, socio economic status, drinking pattern and smoking. A validated World Health Organization AUDIT (Alcohol Use Disorders Inventory Test) questionnaire was used to assess alcohol consumption.A complete physical examination with emphasis on the disease activity and duration of every subject was also done. Kidney function test, complete hemogram, liver

function tests, viral markers, prothrombin time and other investigations as per clinical suspicion were done.Child Turcotte Pugh Score was calculated.*Helicobacter Pylori*was detected by either -*H. pylori* specific IgG antibody detection in serum /Rapid Urease Test positivity of biopsy specimen /Histopathological examination (Gram stain & Giemsa stain) of biopsy specimen.
Chronic liver disease was defined as the presence of cirrhosis (due to chronic alcohol intake in the absence of any other etiology). Diagnosis of cirrhosis was based on clinical findings, biochemistry (low serum albumin, AST/ALT ratio >1), imaging (heterogeneous echo texture of liver with irregular outline, altered liver size depending on etiology, Portal vein > 13, Porto systemic collateral), Upper Gastrointestinal (GI) Endoscopy (showing esophageal varices) or documentation suggestive of prior decompensation. The severity of liver disease was classified as per Child–Turcotte-Pugh criteria.

Operational definitions:
Standard Alcoholic Drink: A standard alcoholic drink contains approximately 14gms of alcohol, which is equivalent to 12 ounces of beer (~5% alcohol), 8.5 ounces of malt liquor (~9% alcohol), 5 ounces of wine (~12% alcohol), 3.5 ounces of fortified wine (e.g., sherry or port), or 1.5 ounces of liquor (distilled spirits; ~40% alcohol).

Moderate Alcohol Consumption:
Men: No more than two standard alcoholic drinks/day
Women: No more than one standard alcoholic drink/day
Heavy alcohol consumption
Men: More than 14 standard alcoholic drinks/week or more than 4 standard alcoholic drinks in a day
Women: More than 7 standard alcoholic drinks/week or more than 3 standard alcoholic drinks in a day

Study tool: Hepatitis C serology was done by Flaviscreen method, Hepatitis B serology by Viruschek rapid test, HIV I & II serology done by Retrogine HIV kit and Sono Ace X S was used For Ultrasonography. Upper GI Endoscopy was done for every patient. H-Pylori specific IgG antibody detection in serum (ELISA) was done by using a commercial ELISA kit (GAP-IgG Test). Rapid Urease Test (CLO Test kit) was used for detection of *H. pylori* from Endoscopic Biopsy specimen from antrum. Histopathological examinationwere also done.

Statistical analysis: IBM SPSS Version 21.0 for Windows, Armonk NY: IBM Corp.were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.** Categorical variables were expressed in frequencies and proportion. Pie charts and bar graphs were used to depict the results. Chi square test and Fisher's exact test were used appropriately to test the significance between the *H. pylori* infection and clinico-demographic variables. A p-value of <0.05 was considered statistically significant.

Approval of Research Ethics Board and Informed consent: The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal.(Reference No- A/206/REB-Comm (SP)/RIMS/2015/555/33/2019).

III. Result

A total of 124 diagnosed cases of chronic alcoholic liver disease were included in the study. Baseline characteristics of the study subjects were given in table 1. The mean age of the study population was 55.29 ± 10.6 with the majority in age group 49-58 years (37.1%) and majority of them were males 85.5%.39.5% were current smokers. Dyspepsia (97.5%) was the most common presenting symptom. Majority of study participants belonged to Child Turcotte Pugh Class B (35.5%) testing positive for *H.pylori*infection than the others in this study (p=0.005) . Anemia was present in 50.8% and thrombocytopenia was detected in 75% of the study participants(p=0.002). In the present study, the prevalence of *H.pylori* was found to be 63.7%which was the same as *H. pylori* IgG positivity. But as per the Rapid urease test and histopathological examination results, the *H. pylori* prevalence rate in the study was 84.8%. Thus, Rapid urease test and histopathological examination reported a higher prevalence than *H. pylori* IgG positivity. Association of *H.pylori*infection with demographic variables were given in table 2 and with symptoms were given in table 3.Child Turcotte Pugh Score class association with *H.pylori* infection were given in table no 4. Consumption of large quantity of alcohol (10-20 drinks per week and more than 20 drinks per week), more frequently (4 or more times week), and for longer duration (16-20 years, more than 20 years) and those belonging to Child Turcotte Pugh Class B had significant association with *H.pylori* infection. However, there was no significant association between age, religion, education, occupation, marital status, socioeconomic status, place of residence, smoking status with the *H.pylori* infection.

Table1. Baseline characteristics of the study subjects.

Demographic Characteristics	Percent (%)
Age (in years)	
18-28	1.6
29-38	8.9
39-48	14.5
49-58	37.1
59-68	29.0
69-78	8.9
Gender	
Male	85.5
Female	14.5
Smoking pattern	
Current smoker	39.5
Former smoker	30.6
Non-smoker	29.8
Drinking pattern	
> 20 /week	43.5
10-20 drinks/week	35.5
<10 drinks/week	21
Duration of drinking alcohol (in years)	
5-10	
11-15	3.2
16-20	15.3
>20	18.5
	63
Types of alcohol	
Locally brewed	23.4
Beer	5.6
Hard liquor	11.2
Locally brewed + hard liquor	58
Wine	1.6
Clinical presentations	
Dyspepsia	94.4
Anorexia	68.5
Jaundice	61.3
Fatique	51.6
Abdominal distension	47.6
Hematemesis	30.6
Malena	48.4
Anemia	50.8
Thrombocytopenia	75

Table 2: Association between demographic variables and *H.pylori*infection (N=124)

Parameters	*H. pylori* Negative n (%)	*H. pylori* Positive n (%)	p-value
Age group (in years)			
18-28	2 (100%)	0 (0.0%)	
29-38	8 (72.7%)	3 (27.3%)	
39-48	5 (27.8%)	13 (72.2%)	0.099
49-58	11 (23.9%)	35 (76.1%)	
59-68	15 (41.7%)	21 (58.3%)	
69-78	4 (36.4%)	7 (63.6%)	
Gender			
Male	34 (32.1%)	72 (67.9%)	0.031
Female	11 (61.1%)	7 (38.9%)	
Smoking pattern			
Current smokers	16 (32.7%)	33 (67.3%)	
Former smokers	17 (44.7%)	21 (55.3%)	0.433
Non - smokers	12 (32.4%)	25 (67.6%)	
Drinking pattern			
2-4 times a month	11 (84.6%)	2 (15.4%)	
4 or more times /week	17 (27.9%)	44 (72.1%)	0.001
More than 20 years	23 (29.5%)	55 (70.5%)	0.003
Standard drinks/week of Alcohol			
<10 drinks/week	22 (84.6%)	4 (15.4%)	
10-20 drinks /week	8 (18.2%)	36 (81.8%)	<0.001

>20 drinks /week	15 (27.8%)	39 (72.2%)	

Table 3: Association between various symptoms and *H. pylori* infection(N=124)

Symptoms		***H. pylori* Negative n (%)**	***H. pylori* Positive n (%)**	**p-value**
Dyspepsia	Yes	40 (34.2%)	77 (65.8%)	0.033
	No	5 (71.4%)	2 (28.6%)	
Fatigue	Yes	15 (23.4%)	49 (76.6%)	0.002
	No	30 (50.0%)	30 (50.0%)	
Anorexia	Yes	25 (29.4%)	60 (70.6%)	0.019
	No	20 (51.3%)	19 (48.7%)	
Malena	Yes	19 (31.7%)	41 (68.3%)	0.300
	No	26 (40.6%)	38 (59.4%)	
Hematemesis	Yes	17 (44.7%)	21 (55.3%)	0.194
	No	28 (32.6%)	58 (67.4%)	
Yellow Eyes	Yes	25 (32.9%)	51 (67.1%)	0.322
	No	20 (41.7%)	28 (58.3%)	
Abdominal Distension	Yes	23 (39.0%)	36 (61.0%)	0.552
	No	22 (33.8%)	43 (66.2%)	
Anemia	Yes	23 (36.5%)	40 (63.5%)	0.959
	No	22 (36.1%)	39 (63.9%)	
Thrombocytopenia	Yes	37 (39.8%)	56 (60.2%)	0.161
	No	8 (25.8%)	23 (74.2%)	

Table 4: Child Turcotte Pugh Score class and *H.pylori* infection (N=124)

Child Turcotte Pugh Score	***H. pylori* Negative n (%)**	***H. pylori* Positive n (%)**	**p-value**
Class A	17 (41.5%)	24 (58.5%)	0.005
Class B	8 (18.2%)	36 (81.8%)	
Class C	20 (51.3%)	19 (48.7%)	

IV. Discussion

Excessive alcohol consumption is a global healthcare problem with enormous social, economic, clinical consequences and damages nearly every organ in the body. However, the liver sustains the earliest and the greatest degree of tissue injury from excessive drinking because it is the primary site of ethanol metabolism.[23]

In the present study, the prevalence of *H.pylori* was found to be 63.7%, which was almost similar to the finding of Kim DJ et al[24](62.4%) ,Kirchner GI et al[25](61%)and Barbuti RC et al[26](60-70%). Most of the other studies reported a lower prevalence of *H. pylori* than the present study.Feng H et al[27]conducted the study on liver cirrhosis patients and reported a *H.pylori* prevalence of 52.26% and Gopinath JM et al[28]53.6%. Among our patients with gastroduodenal erosions, the prevalence of *H.pylori* was lower at around 47% in accordance with the study conducted by Kirchner GI et al[25]. Other studies conducted by Brenner H, et al[29] also showed that the prevalence of *H. pylori* infection was 39.2%. But Manes G et al[30]reported 38% *H.pylori*prevalence among patients with chronic pancreatitis and 28% among asymptomatic patients. Zhang L et al[31]reported *H.pylori*prevalence 27.3% in those with functional dyspepsia and Kim DJ et al[24]73.7% among patients with peptic ulcer disease. The wide variation in prevalence rates between the present study and the abovementioned studies maybe because, patient profiles chosen for each of these studies were suffering from different diseases.

As per the seropositivity, the *H.pylori* prevalence rate in the present study was 63.7%, same as that of overall prevalence. But Schulz C et al[32]and Pogorzelska J et al[33]reported a prevalence of *H.pylori* of only 21 % and 46.9%, respectively by serological tests. As per the Rapid Urease Test results, the *H.pylori* prevalence rate in the present study was 84.8% , which was higher than that by the antibody detection methodand was similar to study done by Saikumar C[34] (82.6%).In the study by Nardone G et al[35]*H. pylori* infection was diagnosed by a positive concordance of both quick urease test and histology, and it was seen that the prevalence was 41.85%.Schmulson MJ et al[36] reported that 50% of alcoholics and 42.9% of non-alcoholic cirrhotics were *H. pylori* positive by the Rapid Urease Test method.

As per the Histopathological examination results, the *H.pylori* prevalence rate in the present study was 84.8%, identical to that of Rapid Urease Test which were similarly shown by Saikumar C[34](82.6%). But Farinati F et al[37]stated that hypertensive gastropathy might not represent a favourable environment for growth of *Helicobacter pylori*, thus making the biopsy's diagnostic sensitivity lower than expected. In accordance with other studies that used the Histopathological examination method for *H.pylori*prevalence conducted by Elsebaey MA et al[38] and Auroux J et al[39]reported much lower values of 59.2% and 58% respectively. Saikumar C[34]registered a much lower *H. pylori* prevalence of 23.9% on culture.

The present study did not show any association between age and *H.pylori* infection which is in accordance withZhang L et al[31] and Schmulson MJ et al[36]studies.A significantly higher proportion of the males tested positive for *H.pylori* infection than the females in the present study (p=0.031), similar to study by Saikumar C[34]. This difference might have been due to the difference in demographic profile and alcohol

consumption patterns in the study population. Gender disparity in *H. pylori* infection is an intriguing topic, as gastric adenocarcinoma (the most serious complication of *H. pylori* infection) shows significant male predominance.

There was no association between education or occupation ,socioeconomic status and marital status with the *H.pylori*infection in the present study which is consistent with study bySyam AF et al[40]. But Lawlor DA et al[41]found that*H. pylori* infection is associated with childhood poverty. Similarly, Mitchell H et al[42]also found that higher prevalence was observed in people of lower socioeconomic status. The difference could be due to the study setting and various cultural practices followed in different geographical areas.

Regarding the clinical presentation, majority reported dyspepsia followed by thrombocytopenia, anorexia, fatigue and anaemia.But in the report of Tongtawee T et al[43]abdominal pain, followed by iron deficiency anemia, was the most common clinical presentation. Ortiz M et al[21]also showed thatthere was a significant association between *H. pylori* infection and anaemia. The present study showed that, among *H.pylori* positive patients, significantly higher proportion presented with dyspepsia (p=0.033), fatigue (p=0.002), anorexia (p=0.019) and moderate thrombocytopenia (p=0.002).

In the present study, a significantly higher proportion of the patients who consumed alcohol frequently for a duration of 4 or more times a week (p<0.001) , larger quantities i.e 10-20 standard drinks per week (p<0.001) ,more alcohol content (locally brewed alcohol and a combination of locally brewed & hard liquor) (p=0.005 & p 0.016 respectively) and those with drinking pattern of 2-3 times per week (p=0.001) and those who used for more than 20 years (p=0.002) had a higher prevalence of *H.pylori* infection, which is consistent with studies conducted byZhang L et al**[31]**,Lieber CS et al[44]and Ogihara A et al[45].These finding strengthen the hypothesis that alcohol exerts damaging effect on gastric mucosal barrier and decrease the local immunity which favours the growth of H.pylori , thus making those individuals at risk for infection. But in contrast to the findings of the present study Brenner H et al[29]andSaikumar C[34]showed findings to support the hypothesis that moderate alcohol consumption may facilitate the spontaneous elimination of *H. pylori* infection and the prevalence of *H. pylori* infection was higher in the non-alcoholics. There was no association between smoking and the *H.pylori* infection in the present study which is similar to Zhang L et al[31]study.But OgiharaA et al[45]in his study found thatsmoking was negatively associated with *H. pylori* infection and that the risk of *H. pylori* seropositivity decreased linearly with cigarette consumption per day. This was attributed to the increased acidity in the stomach through smoking.

In the present study,majority belonged toclass B of Child-Turcotte Pugh score, followed by class A and class C which were statistically significant (p = 0.005). Though in the study by Schmulson MJ et al[36] majority had class A,Kim DJ et al[24]had class C, they weresignificantly associated with *H. pylori* infection.

In the present study a statistically significant association for *H.pylori*infection was found with gender, frequency, duration, quantity and type of alcohol consumption.

V. Conclusion

The study concluded that the overall *H.pylori* prevalence rate in the study population was 63.7%. as compared to 84.8% by rapid urease test and histopathological examination. *H.pylori* had significant association with chronic alcoholic liver diseasewith more frequent consumption of large quantity of alcohol for longer duration and those belonging to Child Turcotte Pugh Class B.These findings necessitate preventive and therapeutic strategies *for H. pylori* eradication in CLD patients.

Declarations:
Funding: None
Conflict of Interest: None declared
Approval of research ethics board**:** Taken

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Dr Ningthoukhongjam Reema, et. al. "Prevalence of Helicobacter pylori infection in chronic alcoholic liver disease patients." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(10), 2022, pp. 38-45.