

Frequency of H-Pylori Infection in Immune Thrombocytopenic Purpura

Aqsa Javed Butt, Uzma Zaidi, Muhammad Shujat Ali, Rabeea Munawar Ali, Sidra Zafar, Tahir Shamsi

ABSTRACT

Objective: To determine the frequency of *Helicobacter pylori* infection in patients with Immune Thrombocytopenia (ITP) and the impact of eradication therapy on platelet counts.

Study design & Setting: It was a cross-sectional study conducted at National institute of blood disease and bone marrow transplant (NIBD) hospital, Karachi, Pakistan from January 2021 to September 2022.

Methodology: Adults between 18 to 70 years of either gender with thrombocytopenia (platelet count less than $100 \times 10^9/L$) with or without bleeding manifestation from last six months were recruited. The immunoassay was used for stool sample to detect *H. pylori* antigen, eradication therapy was administered and platelet counts were evaluated at 3rd and 6th month of treatment.

Results: Of 120 patients with ITP, the mean age was 36.67 ± 15.32 years, and 76.7% were female. 35.83% had *H. pylori* positive. The eradication treatment on platelet counts was statistically significant ($p=0.001$). Median platelet counts at baseline, 3 months and 6 months were 43.50(23.00- 77.00), 136.50 (57.00- 237.00), and 192.00 (130.50-275.50) patients respectively. Platelet counts were statistically different between baseline with three and six months ($p=0.007$ and $p=0.001$, respectively).

Conclusion: People with ITP frequently have *H. pylori* infections, and eradication treatment could contribute to the increase in platelet count.

Keywords: Bacteria, Eradication, *H. pylori*, ITP, Platelet count

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INTRODUCTION:

Immune thrombocytopenia (ITP), is characterised by isolated thrombocytopenia (platelet count $<100 \times 10^9/L$) without a known cause.¹ IgG autoantibodies that target structural platelet membrane glycoproteins IIb-IIIa are thought to be the cause of ITP.² This makes platelets vulnerable to being phagocytized by Kupffer cells in the liver and splenic macrophages. These autoantibodies are present in 40-60% of affected individuals. Other mechanism like impaired production of a stimulant of platelet production called thrombomodulin and triggers like exposure to viruses and pregnancy are also likely causes of ITP.² Usually in ITP studies, H-pylori antigen, Hepatitis C, a peripheral blood smear and HIV testing are essential investigations.² The timing and persistence of symptoms are used to further divide primary ITP into three stages i.e. newly diagnosed ITP (with less than 3 months of duration), Chronic ITP is the continuation of ITP beyond the initial diagnosis of 3 to 12 months, whereas persistent ITP is the referring to low platelet count for more than 3-12 months.³

A gram-negative bacterium called *Helicobacter pylori* (*H. pylori*) was initially discovered by Warren et al. in 1984.⁴ It occurs in the human stomach. Most of the individuals remain asymptomatic for a long time. As a result, long term

colonization will lead to damage of gastric mucosa causing peptic ulcers, chronic gastritis, atrophic gastritis gastric malignancies like mucosa-associated lymphoid tissue lymphoma, gastric cancer.⁵ Although the pathogenesis of H. pylori-associated ITP is still uncertain, several studies have suggested that H. pylori virulence factor, cytotoxin-associated gene A (CagA), stimulates the development of anti-CagA antibodies (Abs) that cross-react with platelet surface antigens (Ags), resulting in thrombocytopeni.^{3,7} Its prevalence is highest in African countries (79%), Caribbean and Latin America (63%), and Asia (55%).⁶ Pakistan has the greatest frequency of H. pylori among South Asian countries, followed by Nepal (70%) and India (64%), respectively.⁶ Food and hygiene, age, socio-economic status, ethnicity, number of siblings, household crowding, sanitary facilities, infection status of family members, and migration from high prevalence regions are known risk factors of H pylori.^{7,8}

Many research studies have revealed significant correlation between H pylori and extra-digestive diseases like iron deficiency anemia, vitamin B12 deficiency, and ITP.^{4,5,8,9} Autoantibodies against platelets cause the acquired bleeding illness known as ITP, which impact all ages.^{10,11} It may be a primary or secondary disease brought on by neoplasms, autoimmune disorders, viral or bacterial infections, or both.^{10,11}

Literature found that individuals with ITP had higher proportion of H. Pylori.^{4,5,11} Additionally, it has been seen that H. pylori significantly impact the pathophysiology due to the complete or partial recovery of thrombocytopenia following H. pylori eradication.^{4,5,11} So, one of the treatments for ITP is the eradication of H. pylori infection.^{4,11}

The purpose of the current study was to ascertain how frequently H. pylori is present in patients with immune thrombocytopenic (ITP) who report to a tertiary care hospital in Karachi, Pakistan, as well as the impact of eradication therapy on platelet count. The results of this study would enable the development of guidelines for the identification and eradication of H. pylori in ITP patients.

METHODOLOGY:

This was a cross-sectional study carried out at the department of Haematology NIBD, Karachi, Pakistan from January 2021 to September 2022. Sample size of 115-120 patients with ITP was estimated using Open epi sample size calculator, by taking prevalence of H pylori as 40.9%, bond on error as 9% and 95% confidence level. The study comprised patients with a platelet count <100x10⁹/L who had thrombocytopenia with or without bleeding and were between the ages of 18 and 70. The research excluded patients having a history of malignancy, disseminated intravascular coagulation, bone marrow failure, hypersplenism, or who were receiving drug therapy that was known to cause thrombocytopenia. The approach of non-probability consecutive sampling was used.

The NIBD ethical review committee approved this study (NIBD/IRB-254/26-2021). A written informed consent was taken from all the eligible participants. On a pre-made proforma, information on patient's age, gender, diseases, and comorbid conditions including diabetes and hypertension were collected. On a stool sample, the immunoassay technique was used, and the H. pylori antigen was detected. For haematological assessment (haemoglobin, TLC, and platelet counts), blood was drawn from the patients in EDTA tube, and the CBC was done. In H. pylori positive cases, eradication therapy was given (Cap Omeprazole 20mg twice daily, Tablet Clarithromycin 500mg twice daily and Tab Amoxil 1gm twice daily for 14 days) and platelet counts were evaluated at 3rd and 6th month of treatment.

Statistical analysis was carried out using SPSS version 23. Mean and SD/Median and IQR were reported for numeric variables like age, Hb, TLC and platelet counts. For categorical characteristics including gender, illness type, comorbid, and H. pylori, frequency and percentage were provided. H. pylori were stratified with age, gender, disease nature, comorbid, Hb, TLC and platelet counts. Post-stratification Chi-square test, Independent t-test or Mann-Whitney U test/ were applied. Effect of eradication therapy was assessed by comparing platelet counts at baseline, three months and six months using Friedman test and post hoc pair-wise comparison was done. Level of significance for this study was set at 5%.

RESULTS:

Baseline characteristics of ITP patients are displayed in table 1. Of 120 patients, 76.7% were females, with mean age as 36.67±15.32 years. At baseline, the mean hemoglobin was 12.09±2.22, median TLC was 8.81 and median platelet was 40x 10⁹. Most frequent comorbid was hypertension.

Insignificant statistical difference was found with a p-value higher than 0.05 when comparing the ITP patients with and without H. pylori in terms of age, gender, comorbid, or hematological parameters (Table 2).

Out of 120 patients, 35.83% (43/120) tested positive for H. pylori while 64.17% (77/120) were negative for H. pylori. The significant effect of eradication therapy of H. pylori positive cases (p=0.001) had been observed on platelet counts. In H pylori positive cases, median platelet counts at baseline, 3 months and 6 months were 43.50 (23.00-77.00), 136.50 (57.00-237.00), and 192.00 (130.50-275.50), respectively. There was a statistically significant difference observed in platelet counts at baseline versus 3 months (p=0.007) and baseline versus 6 months (p=0.001). However, the difference was insignificant when platelet counts at 3 months versus 6 months (p=0.055) were compared. In H pylori negative cases, median platelet counts at baseline, 3 months and 6 months were 36.0 (18.0-60.0), 94.0 (36.5-221.5), and 83.0 (33.0-197.0), respectively. Statistically significant difference was observed in platelet counts at

baseline versus 3 months ($p=0.026$). However, there was insignificant difference observed in platelet counts at baseline versus 6 months ($p=0.068$) and at 3 months versus 6 months ($p=0.999$).

Table 1: Descriptive analysis of enrolled ITP patients (n=120)

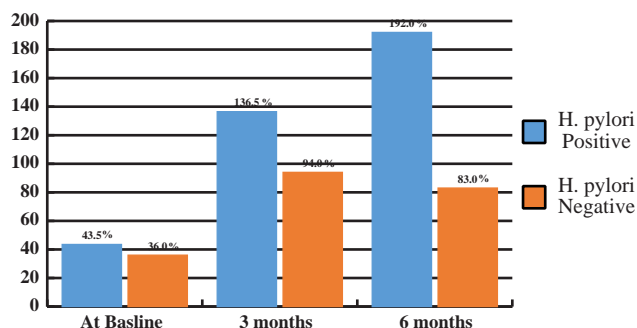
Variables	
Age (years)	36.67±15.32
Hemoglobin at baseline (g/dL)	12.09±2.22
TLC at baseline ($\times 10^9/L$)	8.81 (6.66-11.73)
Platelet at baseline ($\times 10^9/L$)	40 (17.5-75)
Gender	
Female	92 (76.7)
Male	28 (23.3)
Hypertension	
Yes	23 (19.2)
No	97 (80.8)
Diabetes	
Yes	20 (16.7)
No	100 (83.3)

Data showed in the form of Mean±SD or Median (IQR) or n (%)

Table 2: Comparison of baseline characteristics between H. pylori positive and negative in ITP (n=120)

	H. pylori		p-value
	Positive	Negative	
Age (years)	36.51±16.06	36.75±15	0.934
Hb g/dl at baseline	11.77±2.11	12.26±2.26	0.259
TLC $\times 10^9/l$ at baseline	9.30 (7.74-12.12)	8.65 (6.40-11.62)	0.336
PLT $\times 10^9/l$ at baseline	43.50(23.00-77.00)	36.0(18.0-60.0)	
Gender			
Male	13 (46.4)	15 (53.6)	0.182
Female	30 (32.6)	62 (67.4)	
Hypertension			
Yes	8 (34.8)	15 (65.2)	0.907
No	35 (36.1)	62 (63.9)	
Diabetes mellitus			
Yes	6 (30)	14 (70)	0.551
No	37 (37)	63 (63)	

Figure 1: Comparison of platelet counts at baseline, 3 months and 6 months in patients with and without H. pylori



DISCUSSION:

Since many years, H Pylori has been considered as the one of the reason of peptic ulcers, mucosa-related lymphoma, gastritis and gastric cancer.^{14,16-17} Recent research has revealed a link between h-pylori and autoimmune conditions such ITP^{14,16-17}. According to studies, H pylori is a frequent cause of ITP and that treatment for the infection typically results in a rise in platelet count in most cases.^{11-14,18}

The frequency of H. pylori among cases of ITP varied greatly between different countries. It is reported as 73% in Japan, 51% in Italy, 54.3% in Korea, 22% in Malaysia and in Northern America.^{5,11,12,14-15} Twenty-seven studies from across the world were merged and analysed, and the results showed that 1144 out of 1740 individuals with ITP had H. pylori infection, or 65.7% of the total.¹⁴ In addition, Ando et al. discovered that 83% of patients with ITP had a higher proportion of H pylori infection.¹⁹ In our study, we found 42.3% of the ITP patients had H pylori.¹⁵ Kakar et al. discovered that the proportion of H pylori was 40.5% in cases of ITP in a comparable Pakistani investigation. While in another Pakistani study by Shaikh et al. its prevalence is 63.3% in ITP.¹⁴ The frequent occurrence of H. pylori infection in underdeveloped countries can be due to socio-economic background and living conditions of the patients.

Several studies have found insignificant relationship with demographic and clinical factors in patients with ITP.²⁰ In our study, we also found no significant association of age, gender, haematological parameters, duration of disease and comorbid with H. pylori infection in patients with ITP. We found the frequency of H. pylori was high in females as compared to males, which may be due to high prevalence of ITP in females. Furthermore, average age of H. pylori positive and negative cases was similar. Similar results have been presented for Pakistani Population in the study by Kakar et. i.e. there was no difference in H. pylori frequency with respect to gender and age. Whereas, some international studies showed that the mean age of H. pylori patients having ITP was greater than uninfected patients.¹⁹⁻²¹

In the study by Gasbarrini et al. found that platelet counts remained unchanged in three H. pylori patients who were not treated for eradication, whereas, in eight H. pylori patients, platelet counts increased post ITP treatment.²² In another nation-wide study conducted in Japan including 207 patients with H. pylori infection showed that 63% of the patients achieved some platelet recovery and in this group 23% of the patients achieved complete remission after 1 year of eradication therapy.²¹ In our study, we found that median platelet count was low in patients without infection as compared to patients with infection. We also found significant effect of eradication therapy on platelet counts

in *H. pylori* patients with ITP after 3 months. Similarly, Kakar et al. also stated that mean platelet count was high in infected patients as compared to uninfected patients.¹⁵ In a recent research by Sheema et al., positive *H. pylori* patients had slightly lower platelet counts than controls.²³ Gan CC et al. found that patients with *H. pylori* had higher platelet counts than baseline controls in the Malaysian population²⁴. Although Hwang JJ et al. noted a statistically negligible difference in platelet count between patients with ITP who had *H. pylori* positivity and those who did not prior to eradication treatment.²⁵

There are few limitations of current study. This is a cross-sectional study, in which we are unable to assess the cause effect relation between *H. pylori* and ITP. We were unable to identify the consequence of haematological parameters, socio-demographic factors, and comorbid on *H. pylori* due to small size. In future, long-term studies should be conducted as well as effect of eradication therapy and bacterial strains should be explored.

CONCLUSION:

People with ITP frequently have *H. pylori* infections, and eradication treatment has a considerable impact on platelet count in ITP patients. Therefore, in patients with ITP at diagnosis, screening for *H. pylori* infection and attempt to eradicate the bacteria in positive cases appears to be a good approach.

Authors Contribution:

Aqsa Javed Butt: reviewed all the cases for inclusion, data collection, statistical analysis, drafted this article

Uzma Zaidi: conceptualized and supervised the study, reviewed all the cases for inclusion, critically reviewed the manuscript

Muhammad Shujat Ali: Data Collection

Rabea Munawar Ali: Data Collection

Sidra Zafar: Data Collection

Tahir Shamsi: Conceptualized and supervised that study.

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