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Original Article

Physiology Section

Comparison of Haematological Variables in *Helicobacter pylori*-Infected Patients with Ulcer and without Ulcer: A Cross-sectional Study

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ABSTRACT

Introduction: *Helicobacter pylori* (*H. pylori*) is predominantly responsible for acute and chronic progressive gastroduodenal inflammation. Symptoms of gastric diseases vary from dyspepsia to altered bowel movements, leading to ulcers and potential gastrointestinal bleeding. Consequently, *H. pylori* can have a variable effect on the gastrointestinal tract and other organs. Ongoing research has shown associations between *H. pylori* and haematological manifestations. Recent studies have reported a 90% incidence of duodenal ulcers and an 80% incidence of gastric ulcers in patients with *H. pylori* infection.

Aim: To investigate haematological manifestations in *H. pylori*-infected patients with and without ulcers, and to compare the haematological variables.

Materials and Methods: This cross-sectional study was conducted in the Department of Gastroenterology at King George's Medical University in Lucknow, India, from October 2021 to October 2022. One hundred patients diagnosed with *H. pylori*-positive biopsy through endoscopy were enrolled in the study. Among these patients, 51% had ulcers with *H. pylori* infection (enrolled as cases), while 49% were *H. pylori* infected but without ulcers (enrolled as controls). Samples were analysed for Haemoglobin (Hb) levels, Red Blood Cell (RBC) count, Reticulocyte Count (RetC), serum iron, serum ferritin, Total Iron Binding Capacity (TIBC), serum vitamin B12, and Homocysteine (HCy) levels. Statistical analysis involved independent sample t-tests to compare continuous data and chi-square tests to compare categorical data.

Results: The majority of patients included in the study, both with ulcers (70.6%) and without ulcers (59.2%), were males with mean±Standard Deviation (SD) ages of 32.39±7.25 years and 29.86±7.66 years, respectively. In the present study, low reticulocyte count, anaemia, deranged RBC count, low serum iron, high TIBC, and low ferritin were observed in 9%, 22%, 61%, 11%, 12%, and 8% of the patients, respectively. Vitamin B12 deficiency and hyperhomocysteinemia were observed in 6% and 1% of the cases, respectively. Among patients with ulcers, the strongest correlation was found between serum iron and serum ferritin (r-value=0.901), while the weakest correlation was found between vitamin B12 and RetC (r-value=0.206). Among patients without ulcers, the strongest correlation was found between serum iron and Hb (r-value=0.884), while the weakest correlation was found between TIBC and HCy (r-value=0.270).

Conclusion: The present study demonstrates a significant association between *H. pylori* infection-induced ulcers and decreased mean reticulocyte count, serum iron, and serum ferritin levels. Recognising these haematological derangements and including them as indications for *H. pylori* eradication may lead to a remarkable improvement in the management regime.

Keywords: Anaemia, Ferritin, Haemoglobin, Homocysteine

INTRODUCTION

Helicobacter pylori is a spiral-shaped bacterium found on the mucosa of the human gastrointestinal tract and is associated with a variety of gastric diseases [1]. The prevalence of *H. pylori* ranges from 8.7% to 85.5% in different parts of the world [2,3]. On average, almost half of the global population is affected by *H. pylori* [4]. *H. pylori* infection is common in developing countries. In India, 80% of adults are infected at some point but remain asymptomatic for longer periods. Sero-surveys show a prevalence of 22-57% in children under the age of five and 80%-90% up to the age of 20 [5]. *H. pylori* primarily affects the upper gastrointestinal tract and is responsible for both acute and chronic progressive gastroduodenal inflammations. These inflammatory changes often remain asymptomatic and undiagnosed for a considerable period of time [6]. The clinical manifestations of *H. pylori* include gastrointestinal conditions such as gastritis, gastric atrophy, gastric ulcers, early gastric cancer, and primary gastric B-cell lymphomas [7]. Recent studies have reported a 90% incidence of duodenal ulcers and an 80% incidence of gastric ulcers in patients with *H. pylori* infection [8-11].

Among the various extragastric manifestations of *H. pylori* infection, iron deficiency anaemia is one of the most common clinical findings [12]. It occurs due to impaired iron absorption caused by chronic gastritis. A review study conducted by Lahner E et al., demonstrated that *H. pylori* infection is associated with decreased levels of serum vitamin B12 [13]. Hyperhomocysteinemia has also been found to be associated with neurodegeneration in *H. pylori*-infected cases [14]. Some researchers have explored the role of *H. pylori* infection in other extragastric manifestations such as respiratory illness, diabetes, glaucoma, coronary artery disease, dermatologic conditions, and Parkinson's disease [15-22]. Another study showed a positive association between *H. pylori* infection and the prevalence of hypertension [23]. All these studies suggest different pathways, primarily based on increased inflammatory activity due to *H. pylori* infection, as the possible mechanisms behind these relationships. These clinical findings indicate that *H. pylori* infection extends beyond the traditional view of gastrointestinal disease. It may cause systemic, immune, and inflammatory implications that need to be explored through comprehensive patient assessments to establish cause-effect

relationships and identify any correlations between *H. pylori* infection and its magnitude with various extragastric manifestations. Therefore, the present study was proposed to investigate haematological manifestations and compare haematological variables in *H. pylori*-infected patients with and without ulcers.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Gastroenterology, King George's Medical University, Lucknow, India, from October 2021 to October 2022. The study was carried out in accordance with the guidelines of good medical research as outlined in the Helsinki Declaration. Participants were enrolled voluntarily after obtaining informed consent and clearance from the Institutional Ethics Committee (IEC) (Registration No. ECR/262/Inst/UP/2013/RR-19). The study procedure was described in detail to the participants, including potential benefits and risks.

Inclusion criteria: Patients aged 18-45 years who were diagnosed with *H. pylori* infection at the gastroenterology outpatient clinic were included in the study.

Exclusion criteria: Patients with a history of metabolic syndrome, cardiovascular disease, previous stomach or intestinal surgery, treatment for anaemia, pregnancy, severe illness, piles, and dysmenorrhoea were excluded from the study.

Sample size calculation: The present study was conducted as an observational cross-sectional study using an exploratory design. The sample size was calculated using the following formula:

$$N=C^2\frac{p(1-p)}{d^2}$$

For an exploratory study, p was assumed to be 0.5, C was a constant at a certain confidence level (with a value of 1.96 at a 95% confidence limit and 80% power), and d was the error allowance (taken as 10% or 0.10). Placing these values into the equation, we obtained:

$$N=1.96^2\times0.5*(1-0.5)/0.1^2$$
$$=3.84\times0.25/0.01$$
$$=96$$

Thus, with a 95% confidence level, 80% power, and a 10% error allowance, the calculated sample size was 96. After accounting for contingency provisions, the final sample size was set at 100.

Study Procedure

All the patients were divided into two groups based on the presence of an ulcer: *H. pylori* infected patients with an ulcer in one group (cases) and *H. pylori* infected patients without an ulcer in another group (controls). After obtaining the patients' informed consent, demographic data such as age and sex were recorded. The endoscopic findings regarding the presence or absence of ulcers were retrieved from the patients' clinical records. Two 5 mL blood samples were collected from all patients under aseptic conditions. One sample was sent to the Department of Clinical Hematology for autoanalyser evaluation of Hb, RBC, reticulocyte count, serum iron, serum ferritin, and TIBC. The other blood sample was sent to the Department of Biochemistry for immunoassay autoanalyser determination of serum levels of vitamin B12 (Cobalamin) and homocysteine. The resulting clinical reports, including the parameters to be noted, were collected. The following normal ranges were used: reticulocyte count (25-100×103 cells/mm^3), haemoglobin (males: 13-18 g/dL and females: 11.5-16 g/dL), RBC count (5×106 cells/mm^3), TIBC (240-450 µg/dL), serum ferritin (20-250 ng/mL), serum iron (60-170 µg/dL), serum vitamin B12 (190-950 pg/mL), and serum homocysteine (5-15 µmol/L).

STATISTICAL ANALYSIS

The data obtained was entered into the computer using Microsoft Excel 2013 software. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) software version 21.0. The data were presented as numbers (frequency), percentages (proportions), or mean±SD. Independent samples t-test was used to compare continuous data presented as mean±SD. The chi-square test was used to compare categorical data presented as numbers and percentages. The confidence level of the study was set at 95%, therefore, a p-value of 0.05 was considered as the cut-off for statistically significant associations.

RESULTS

One hundred patients with *H. pylori* infection were included in the study, with 51 patients having ulcers (cases) and 49 patients without ulcers (controls). The mean age±SD was 32.39±7.25 years for the cases and 29.86±7.66 years for the controls. The majority of patients with ulcers (70.6%) and without ulcers (59.2%) were males [Table/Fig-1]. Analysis of haematological parameters revealed abnormal reticulocyte counts, haemoglobin levels, and red blood cell counts in most patients. Serum iron levels and TIBC were outside the normal range in 11% and 12% of patients, respectively. Serum ferritin levels were within the normal range in 92% of patients, while 8% had below-normal levels [Table/Fig-2].

Patients without ulcers had higher mean reticulocyte counts, haemoglobin levels, RBC counts, serum iron levels, and serum ferritin levels, while those with ulcers had a higher mean TIBC. Statistically significant differences were found in reticulocyte counts, serum ferritin levels, and serum iron levels (p-value <0.05) [Table/Fig-3]. Additionally, there was a significant difference in RBC counts between the two groups (p-value=0.009) [Table/Fig-4]. Vitamin B12 deficiency and hyperhomocysteinemia were observed in 6% and 1% of cases, respectively [Table/Fig-5]. Although, the mean serum homocysteine level was considerably higher in ulcer patients (p-value=0.009), only one case in the ulcer group (2%) had elevated serum homocysteine levels [Table/Fig-6], compared to the group without ulcers [Table/Fig-7].

Characteristics		Cases (n=51)	Controls (n=49)	Statistical significance
Age (years) (Mean±SD)		32.39±7.25	29.86±7.66	t-value=1.700; p-value=0.092
Sex, n (%)	Male	36 (70.6)	29 (59.2)	χ^2=1.429; p-value=0.232
	Female	15 (29.4)	20 (40.8)	

[Table/Fig-1]: Demographic profile of patients enrolled in the study.
Student's t-test: Age; Chi-square test: Sex

Parameters	Normal range	Mean±SD	Below normal (n)	Normal (n)	Above normal (n)	Deranged (%)
Reticulocyte count	25-100×10^3 cells/mm^3	54.24±22.78	9	91	0	9
Hb	Males: 13-18 g/dL Females: 11.5-16 g/dL	13.86±2.43	22	78	0	22
RBC count	5×10^7 cell/mm^3	4.76±0.53	44	39	17	61
Serum iron	60-170 µg/dL	106.89±38.69	11	89	0	11
TIBC	240- 450 µg/dL	349.41±68.04	0	88	12	12
Serum ferritin	20-250 ng/mL	105.45±71.14	8	92	0	8

[Table/Fig-2]: Haematological profile of study population.

Parameters	Cases (n=51) Mean±SD	Controls (n=49) Mean±SD	Statistical significance t-value	p-value
Reticulocyte count (cells×10^3/mm^3)	48.31±21.20	60.41±22.93	-2.740	0.007
Hb (g/dL)	13.61±2.05	14.12±2.77	-1.041	0.301
RBC count (cells×10^6/mm^3)	4.71±0.46	4.81±0.60	-1.010	0.315
Serum iron (µg/dL)	96.96±35.45	117.22±39.55	-2.700	0.008
TIBC (µg/dL)	360.55±70.31	337.82±64.27	1.686	0.095
Serum ferritin (ng/mL)	82.94±61.65	128.88±73.36	-3.395	0.001

[Table/Fig-3]: Comparison of haematological parameters between *H. pylori* infection patients with and without ulcer.

Parameters	Cases (n=51) n (%)	Controls (n=49) n (%)	Statistical significance χ^2	p-value
Low reticulocyte count	3 (5.9)	6 (12.2)	1.235	0.266
Anaemia	13 (25.5)	9 (18.4)	0.739	0.390
RBC count				
Below normal	29 (56.9)	15 (30.6)	9.414	0.009
Normal	18 (35.3)	21 (42.9)		
Above normal	4 (7.8)	13 (26.5)		
Low serum iron	6 (11.8)	5 (10.2)	0.062	0.803
High TIBC	7 (13.7)	5 (10.2)	0.293	0.588
Low serum ferritin	3 (5.9)	5 (10.2)	0.634	0.426

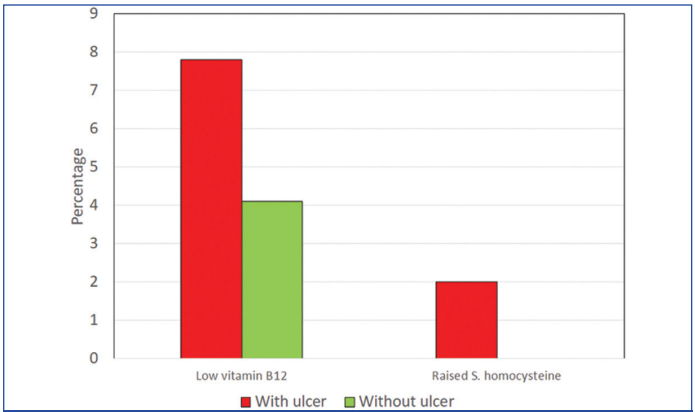
[Table/Fig-4]: Comparison of derangement in parameters between *H. pylori* infection patients with and without ulcer.

Parameters	Normal range	Mean±SD	Below normal (n)	Normal (n)	Above normal (n)	Deranged (%)
Serum vitamin B12	190-950 pg/mL	396.63±165.53	6	94	0	6
Serum homocysteine	5-15 µmol/L	10.60±3.36	0	99	1	1

[Table/Fig-5]: Biochemical profile of study population.

Parameters	Cases (n=51) Mean±SD	Controls (n=49) Mean±SD	Statistical significance t-value	p-value
Serum vitamin B12 (pg/mL)	354.22±148.96	440.78±171.75	-2.696	0.008
Serum homocysteine (µmol/L)	11.45±3.20	9.71±3.34	2.659	0.009

[Table/Fig-6]: Comparison of biochemical parameters between *H. pylori* infection patients with and without ulcer.



[Table/Fig-7]: Comparison of vitamin B12 and serum homocysteine status between *H. pylori* infection patients with and without ulcer.

With the exception of TIBC and HCy, there was a significant positive correlation between haematological parameters [Table/Fig-8]. All other correlations were significant, except for the correlations between RetC and serum ferritin, vitamin B12, and HCy. In the ulcer group, the strongest correlation was between serum iron and serum ferritin (r-value=0.901), while the correlation between vitamin B12 and RetC was the weakest (r-value=0.206) [Table/Fig-9]. The relationships in the group without ulcers followed the same patterns as the entire population. In the group without ulcers, the correlation iron and Hb was the strongest (r-value=0.884), while the correlation between TIBC and HCy was the weakest (r-value=0.270) [Table/Fig-10].

Parameters	RetC	Hb	RBC	Serum iron	TIBC	Serum ferritin	Vitamin B12	HCy
RetC	1	0.612*	0.658*	0.460*	-0.511*	0.396*	0.344*	-0.299*
Hb		1	0.781*	0.860*	-0.635*	0.764*	0.652*	-0.567*
RBC			1	0.679*	-0.605*	0.618*	0.580*	-0.497*
Serum iron				1	-0.664*	0.882*	0.795*	-0.720*
TIBC					1	-0.583*	-0.494*	0.415*
Serum ferritin						1	0.792*	-0.719*
Vitamin B12							1	-0.833*
HCy								1

[Table/Fig-8]: Correlation of different biochemical and haematological parameters in the entire study population (N=100).
*This sign stands for/denotes Significant (statistically)

Parameters	RetC	Hb	RBC	Serum iron	TIBC	Serum ferritin	Vitamin B12	HCy
RetC	1	0.551*	0.552*	0.336*	-0.391*	0.265^{NS}	0.206^{NS}	-0.254^{NS}
Hb		1	0.672*	0.852*	-0.589*	0.750*	0.664*	-0.676*
RBC			1	0.647*	-0.504*	0.543*	0.564*	-0.582*
Serum iron				1	-0.681*	0.901*	0.916*	-0.805*
TIBC					1	-0.590*	-0.488*	0.502*
Serum ferritin						1	0.714*	-0.739*
Vitamin B12							1	-0.920*
HCy								1

[Table/Fig-9]: Correlation of different biochemical and haematological parameters in *H. pylori* infection patients with ulcer (n=51).
NS: Non Significant (statistically)

Parameters	RetC	Hb	RBC	Serum iron	TIBC	Serum ferritin	Vitamin B12	HCy
RetC	1	0.676*	0.749*	0.613*	-0.684*	0.584^{NS}	0.511*	-0.410*
Hb		1	0.843*	0.884*	-0.687*	0.796*	0.645*	-0.486*
RBC			1	0.706*	-0.700*	0.676*	0.586*	-0.425*
Serum iron				1	-0.628*	0.851*	0.750*	-0.425*
TIBC					1	-0.553 *	-0.464*	0.270*
Serum ferritin						1	0.820*	-0.663*
Vitamin B12							1	-0.837*
HCy								1

[Table/Fig-10]: Correlation of different biochemical and haematological parameters in *H. pylori* infection patients without ulcer (n=49).

DISCUSSION

Although, *Helicobacter pylori* is primarily associated with gastrointestinal diseases, its haematological manifestations are being explored. However, there is a lack of studies specifically focusing on the context of ulcers caused by *H. pylori* [24-27]. Therefore, the present study aimed to evaluate the haematological manifestations of *H. pylori* infection in patients with ulcers. A total of 100 patients with confirmed *H. pylori* infection were included in the study, with ages ranging from 18 to 45 years and a mean age of 31.15±7.52 years. The age distribution

in the present study was similar to that reported by Mwafy SN and Afana WM, who conducted their study on patients aged 18-50 years [26]. However, their study was a case-control study and did not include ulcer status for comparison.

Among the 100 patients in the present study, 51 had *H. pylori* infection with ulcers. The study found low reticulocyte counts, anaemia, abnormal RBC counts, low serum iron levels, high TIBC, and low ferritin levels in 9%, 22%, 61%, 11%, 12%, and 8% of the patients, respectively. It is hypothesised that the urease released by *H. pylori* disrupts the balance of haematological parameters through various mechanisms. The presence of ureolytic activity from *H. pylori*'s urease may lead to dehydration and volume reduction in reticulocytes. The prevalence of anaemia in *H. pylori* patients has been well-documented in various studies and is reported to be one of the most common extragastric manifestations of *H. pylori* [8,12]. In the present study, the prevalence of anaemia was only 22%. However, other contemporary studies have reported the prevalence to range from 5.3% to 37.5% in *H. pylori*-infected patients [8,28,29].

In the present study, 61% of patients showed RBC derangement. Among them, 44% had low RBC counts. While previous studies did not specifically report RBC status in terms of derangement, they did find significantly lower RBC counts in *H. pylori*-infected cases compared to controls [24,25].

Additionally, the present study found low serum iron levels in 11% of patients, high TIBC in 12% of patients, and low ferritin levels in 8% of patients. Iron deficiency is a commonly reported impact of *H. pylori* infection. This deficiency is related to gastric hypochlorhydria, which impairs iron absorption and metabolism from ferric to ferrous state [30]. *H. pylori* colonisation may also affect molecules involved in iron transport, and blood loss due to ulcers or gastritis may further contribute to iron deficiency. Additionally, inflammation caused by *H. pylori* can increase the production of interleukin-6 and other cytokines and chemokines, leading to increased production of hepcidin, which prevents iron release from enterocytes. Furthermore, the body may utilise stored iron during states of iron deficiency. In response, there is an increased production of transferrin to enhance iron transport. Consequently, with low levels of serum iron, low RBC counts, low Hb, and low reticulocyte counts, TIBC levels are found to be elevated. Eyoum Bille BB and Kouitcheu Mabeku LB reported iron deficiency in 31.5% of patients in their study [27]. In another study, Lee JY et al., reported a prevalence of iron deficiency based on serum ferritin levels of 25.1% in *H. pylori*-infected patients [30].

In the present study, vitamin B12 deficiency and hyperhomocysteinemia were observed in 6% and 1% of cases, respectively. However, other studies have reported higher prevalence rates for vitamin B12 deficiency and hyperhomocysteinemia in *H. pylori*-infected patients. For example, Rasool S et al., reported vitamin B12 deficiency and hyperhomocysteinemia rates of 23.8% and 46.2%, respectively, in *H. pylori*-infected patients with functional dyspepsia [31]. Several other studies have also found significantly lower vitamin B12 levels in *H. pylori* infection cases compared to controls [32,33]. The lower prevalence of vitamin B12 deficiency and hyperhomocysteinemia in the present study may be attributed to differences in dietary profiles, lifestyle factors, and environment among the study population. The mechanisms underlying vitamin B12 and homocysteine levels in *H. pylori* infection are not fully understood. Vitamin B12 is an essential cofactor in homocysteine metabolism, and decreased levels of vitamin B12 are associated with increased levels of serum homocysteine.

Significant correlations were found between different haematological and biochemical parameters, indicating a mutual relationship between these parameters and micronutrient levels. This partially explains the lower prevalence of biochemical and micronutrient abnormalities in the present study, which may be attributed to the relatively lower prevalence of haematological abnormalities like anaemia. Therefore, it is suggested that extensive studies on *H. pylori*-infected cases should be conducted, including the analysis of additional inflammatory markers like interleukin-6, to better understand other extragastric manifestations caused by *H. pylori* infection.

Furthermore, it is recommended that routine screening for vitamin B12, serum iron, haemoglobin levels, TIBC, RBC counts, and serum ferritin levels be conducted in confirmed *H. pylori*-infected patients, particularly in Outpatient Departments (OPDs) of tertiary care centers. Additionally, early-stage screening for *H. pylori* infection in school-going children through health check-up camps may help prevent anaemia and benefit society on a larger scale.

Limitation(s)

Longitudinal and detailed studies with larger sample sizes are needed to establish the impact of *H. pylori* infection treatment on changes in haematological and biochemical parameters. Furthermore, the investigation of other extragastric manifestations of early-diagnosed *H. pylori* infection requires longer follow-up durations.

CONCLUSION(S)

The present study demonstrated a significant association between *H. pylori* infection-induced ulcers and decreased mean reticulocyte count, serum iron, and serum ferritin levels. Recognising these haematological abnormalities and considering them as indications for the eradication of *H. pylori* infection could lead to a significant improvement in the management approach. Furthermore, the eradication of *H. pylori* infection can bring additional benefits, particularly in relation to peptic ulcer disease, haematological manifestations, and gastric cancer.

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