ORIGINAL ARTICLE

Association of *Helicobacter Pylori* Infection with Anemia: A Retrospective Study

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Abstract

Background: *Helicobacter pylori* (*Hpylori*) infection affects around half of the worlds' population. Anemia is considered a complication of *Hpylori* infection. The present study aimed to determine the association of *Hpylori* infection with anemia in the Pakistani population.

Methods: This retrospective observational study was conducted in Ziauddin University Hospital after taking ethical approval from the ethics committee. Medical records were reviewed for all those patients who investigated for *helicobacter pylori* infection and hematological parameters during 2020. Patients' age, gender, residence, body mass index, presenting features, comorbidity, *Hpylori* status and other hematological parameters including hemoglobin (g/dL), packed cell volume (L/L), red blood cells (mcL), mean corpuscular volume (fL), mean corpuscular hemoglobin (pg) and mean corpuscular hemoglobin concentration (g/dL) were retrieved and analyzed.

Results: A total of 370 records were reviewed. The median age of patients was 39 (IQR=27–50.3) years and the majority of them were females (54.6%). Nearly half of the participants had a *helicobacter pylori* infection (48.1%). Patients' age (p=0.034), body mass index (p=0.048), gender (p=0.048) and symptom of heartburn (p=0.002) were significantly different among patients with and without *Hpylori* infection. 194 (52.4%) patients had anemia. The frequency of anemia among *Hpylori* positive and negative was 53.9% and 51% respectively. The risk of anemia was higher among *Hpylori* infected patients than non-infected patients but statistically, it was not significant (aOR=1.22, 95% CI: 0.79 - 1.86). The likelihood of microcytic hypochromic anemia was significantly higher in *Hpylori* infected patients than non-infected (aOR=1.78, 95% CI: 1.14 - 2.76).

Conclusion: The present study did not find the association of *Hpylori* infection with anemia among the Pakistani population.

Keywords: *Helicobacter pylori, anemia, hematological parameters, gastrointestinal diseases.*

INTRODUCTION

Helicobacter pylori (*Hpylori*) is a gram-negative bacteria spiral-shaped which is colonizing on the gastric mucosa to lead to upper gastrointestinal (GI) diseases and affecting around half of the population around the world and is highly prevalent in developing countries [1, 2]. Although *Hpylori* is a global public health issue its prevalence differs from country to country [3]. The prevalence of *Hpylori* infection ranges from 20%-40% in European countries while in the Eastern Mediterranean region, the reported prevalence ranges from 22% to 87.6% [4]. A high prevalence of 67.28% was also reported from Pakistan in patients with symptoms of heartburn, nausea, dyspepsia, epigastric pain, belching and vomiting [5].

The following are the states of patient presentation; abdominal pain, occasional fevers, gastric reflux, intestinal bleeding, and weight loss. Owing to these states, gastric ulceration and perforation can happen if not timely treated [6]. *Hpylori* is the leading basis for chronic or atrophic gastritis, gastric lymphoma, gastric carcinoma and peptic ulcer [7]. In the preceding three decades, hematological disorders have also been reported as the epigastric manifestation of *Hpylori* but still, the contribution of this infection on hematological system diseases is not deeply studied and more strong evidence is needed. The most frequent hematological disorder is anemia which increases with increasing age [8, 9].

It was demonstrated in a study that *Hpylori* was linked with iron deficiency anemia (IDA) even in patients of celiac disease, which was intensely evidence-based, however inadequately noted in practice [10]. There is much evidence from clinical and epidemiological studies that support a link between anemia and *Hpylori*. To the best of our familiarity, no local investigation has been conducted yet to determine the *Hpylori* impact on anemia. Therefore, we planned the current study to determine the association of *Hpylori* infection with anemia in the Pakistani population.

METHODS

This retrospective observational study was conducted at Dr. Ziauddin Univesity Hospital, Keamari campus after taking approval from the hospital ethics committee (ERC# 3370221MVMED). Data were retrieved for the year 2020. Patients of both the gender of age 18 to 60

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years who were investigated for *Hpylori* infection and hematological parameters were included in the study. Patients with peptic ulcers, erosive hemorrhagic gastritis, gastric malignancy, varices, malabsorption features, intestinal worm infestation, concomitant other severe systemic diseases, regular users of non-steroidal anti-inflammatory drugs, diagnosed cases of hematological diseases, pregnant and lactating women were excluded. In a previously conducted study, the frequency of anemia in *Hpylori* positive and negative was 35.6% and 22.1% respectively [11]. At a 95% confidence interval and power of 80%, a sample of 354 patients is required with a 1:1 ratio of exposed and unexposed groups. Sample size calculation was performed on the online available calculator Open-Epi.

Patients' records were reviewed to retrieve their age, gender, body mass index, residence, presenting features, comorbidity, *Hpylori* status and other hematological parameters including hemoglobin (g/dL), packed cell volume (PCV, %), red blood cells (RBC, mcL), mean corpuscular volume (MCV, fL), mean corpuscular hemoglobin (MCH, pg) and mean corpuscular hemoglobin concentration (MCHC, g/dL).

Body mass index (BMI) was computed by dividing weight (kg) by a square of height (m). According to Asian thresholds, participants were labelled as underweight, normal, overweight and obese with BMI range of <18.5 kg/m^2, 18.5 – 22.9 kg/m^2, 23-24.9 kg/m^2 and ≥25 kg/m^2 respectively [12]. *Hpylori* status was determined either through a stool antigen test or gastric biopsy. Following samples were drawn for gastric biopsy according to hospital protocol; 1 sample from antrum and incisura, and 2 from the body. If there was a lesion, multiple samples were taken from edges also. The presence of comma or curved-shaped organisms on gastric biopsy was considered positive for *Hpylori* infection. On stool antigen test, if the white line above the C and T marks on the kit turned from white to red, it is labelled as *Hpylori* infection. World Health Organization (WHO) hemoglobin thresholds were used to define anemia. Males and females were labelled as anemic for hemoglobin levels <14 g/dL and <12 g/dL respectively. Based on the levels of hemoglobin, severity of anemia was assessed and labelled as normal (12-16.g/dL for women, 14.0 – 18.0 g/dL for men), mild (10g/dL to levels within normal limits), moderate (8.0 – <10.0 g/dL), severe (6.5 - <8g/dL) and life-threatening (<6g/dL) [13]. Morphological types of anemia were categorized as normocytic anemia (NA, 80 ≤ MCV ≤ 100 fL), macrocytic anemia (MA, MCV > 100 fL), and microcytic hypochromic anemia (MHA, MCV < 80 fL) [14].

Data were entered into SPSS version 21 for statistical analysis. Categorical variables were expressed as frequency and percentage. Continuous variables were presented as median with inter-quartile range (IQR) after assessing the assumption of normality with the Shapiro-Wilk test. Chi-square/Fisher exact test was applied to compare categorical variables among two groups of patients. Mann-Whitney U test was applied to compare non-normal numerical variables among two study groups. Binary logistic regression was applied to assess the association of *Hpylori* with anemia. Multinomial logistic regression was applied to determine the association of *Hpylori* infection with morphological types of anemia. Odds ratios were adjusted for socio-demographic variables such as age, gender, residence and effect of comorbidity was also studied in a regression model. Variables with p>0.25 were not entered to compute adjusted odds ratios. Statistical significance was considered when the two-tailed p-value was less than or equal to a 5% level of significance.

RESULTS

Total 370 records were reviewed in this study with median age of 39 (IQR=27–50.3) years. Majority of the study participants were females (n=202, 54.6%) and belonging to urban areas (n=294, 79.5%). Mostly participants were obese (n=150, 40.5%) whereas 128 (34.6%) had normal weight. Few participants were overweight (n=62, 16.8%) and underweight (n=30, 8.1%). The most prevalent symptom was epigastric pain (n=109, 29.5%) followed by heart burn (n=86, 23.2%), nausea (n=63, 17%), indigestion (n=47, 12.7%), loss of appetite (n=43, 11.6%), bloating (n=38, 10.3%), taste disturbances (n=37, 10%), early satiety (n=30, 8.1%), regurgitation (n=25, 6.8%), belching (n=15, 4.1%), postprandial symptoms (n=7, 1.9%) and diarrhea (n=2, 0.5%).

Nearly half of the study participants were positive for *Hpylori* infection (n=178, 48.1%). *Hpylori* infected patients were significantly younger than *Hpylori* negative patients (p=0.034). The median BMI of *Hpylori* infected patients was significantly lower than patients without *Hpylori* (p=0.048). Females were significantly more likely to be affected with *Hpylori* infection than males (p=0.040). The frequency of heartburn was higher in *Hpylori* infected group than the non-infected group (p=0.002) (**Table 1**). None of the hematological parameters was significantly different among patients with and without *Hpylori* infection (**Table 2**).

More than half of the participants had anemia (n=194, 52.4%). Out of 194 anemic patients, 164 (84.5%), 29(14.9%) and 1 (0.5%) had mild, moderate and severe anemia respectively. Only gender distribution was significantly different among patients with and without anemia (p<0.001) (**Table 1**). The frequency of anemia among *Hpylori* infected and non-infected is depicted in **Fig. (1)**.

Table **3** displays the association of anemia with *Hpylori* infection. The model was adjusted with age, gender body mass index, residence, presence of diabetes, hypertension, and coronary artery diseases. The risk of anemia was higher among *Hpylori* positive patients than patients who were negative for *Hpylori* but statistically, it was not significant (aOR=1.22, 95% CI: 0.79 - 1.86).

Table 1: Comparison of participants' characteristics among patients with and without *Helicobacter pylori* infection and anemia.

Study Variables	*Hpylori* Infection			Anemia		
	Positive n(%)	Negative n(%)	p-value	Yes n(%)	No n(%)	p-value
Age (in years)#	36(25 - 49)	41(29 - 52)	*0.034	36.5(28 - 50.25)	39.5(26 - 50.75)	0.431
Body mass index						
Underweight	18(60)	12(40)	0.205	13(43.3)	17(56.7)	0.781
Normal	67(52.3)	61(47.7)		68(53.1)	60(46.9)	
Overweight	25(40.3)	37(59.7)		29(46.8)	33(53.2)	
Obese	68(45.3)	82(54.7)		80(53.3)	70(46.7)	
Gender						
Male	71(42.3)	97(57.7)	*0.040	105(62.5)	63(37.5)	**<0.001
Female	107(53)	95(47)		89(44.1)	113(55.9)	
Residence						
Rural	30(39.5)	46(60.5)	0.091	53(56.6)	33(43.4)	0.417
Urban	148(50.3)	146(49.7)		151(51.4)	143(48.6)	
Comorbid						
Diabetes	9(37.5)	15(62.5)	0.282	11(45.8)	13(54.2)	0.503
Hypertension	12(38.7)	19(61.3)	0.274	17(54.8)	14(45.2)	0.779
Coronary artery disease	5(35.7)	9(64.3)	0.344	7(50)	7(50)	0.853
Presenting symptoms						
Epigastric pain	50(45.9)	59(54.1)	0.578	53(48.6)	56(51.4)	0.343
Heartburn	54(62.8)	32(37.2)	**0.002	46(53.5)	40(46.5)	0.823
Nausea	34(54)	29(46)	0.307	37(58.7)	26(41.3)	0.272
Bloating	17(44.7)	21(55.3)	0.661	21(55.3)	17(44.7)	0.712
Belching	5(33.3)	10(66.7)	0.242	8(53.3)	7(46.7)	0.943
Loss of appetite	23(53.5)	20(46.5)	0.453	21(48.8)	22(51.2)	0.616
Taste disturbances	17(45.9)	20(54.1)	0.781	18(48.6)	19(51.4)	0.627
Early satiety	15(50)	15(50)	0.829	20(66.7)	10(33.3)	0.103
Indigestion	25(53.2)	22(46.8)	0.455	28(59.6)	19(40.4)	0.294
Regurgitation	16(64)	9(36)	0.100	11(44)	14(56)	0.382
Diarrhea	1(50)	1(50)	1.00	1(50)	1(50)	ǂ1.00
Postprandial symptoms	2(28.6)	5(71.4)	0.451	2(28.6)	5(71.4)	ǂ0.264
Dry mouth	8(47.1)	9(52.9)	0.929	12(70.6)	5(29.4)	0.125

#: Age is presented as median (quartile 1 - quartile 3), ǂ: Fisher-exact test was reported
*Significant at p<0.05, **Significant at p<0.01

Table 2: Comparison of hematological parameters among patients with and without *Helicobacter pylori* infection.

Hematological Parameters	With *Helicobacter pylori* Infection Median (IQR)	Without *Helicobacter pylori* Infection Median (IQR)	p-value
Hemoglobin	12 (10.6 - 13.5)	12.3 (10.53 - 13.7)	0.174
PCV	37 (33 - 40)	38 (34 - 41)	0.059
RBC	4.69 (4.36 - 5.09)	4.73 (4.36 - 5.20)	0.525
MCV	80 (74 - 85)	82 (74.3 - 86)	0.219
MCH	26 (23 - 28)	27 (24 - 29)	0.117
MCHC	32 (31 - 33)	32 (31 - 33)	0.073

IQR= interquartile range (first quartile – third quartile), PCV= Packed cell volume, RBC= Red blood cell, MCV= Mean corpuscular volume, MCH= Mean corpuscular hemoglobin, MCHC= Mean corpuscular hemoglobin concentration

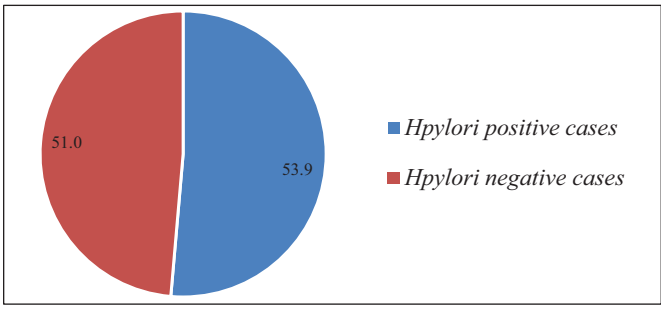

Fig. (1) : Frequency of anemia among *Helicobacter pylori* positive and negative cases.

Table **4** presents the association of *Hpylori* with morphological types of anemia. Multinomial logistic regression was built adjusting the effects for age, gender, body mass index, residence and comorbidities. The likelihood of MHA was nearly twice than NA in *Hpylori* infected patients than non-infected (aOR=1.78, 95% CI: 1.14 - 2.76).

DISCUSSION

The current study enrolled 48% *Hpylori* infected patients out of which *Hpylori* was significantly highly prevalent

Table 3: Association of *Helicobacter pylori* infection with anemia.

Study Variables	aOR (95% CI)	p-value
Age (in years)	1 (0.98 - 1.01)	0.683
Gender		
Male	2.27 (1.47 - 3.49)	**<0.001
Female	Ref	
Body mass index		
Underweight	Ref	
Normal	0.89 (0.38 - 2.07)	0.790
Overweight	0.66 (0.26 - 1.71)	0.390
Obese	0.97 (0.40 - 2.34)	0.940
Residence		
Rural	1.27 (0.75 - 2.14)	0.378
Urban	Ref	
Comorbid		
Diabetes	0.70 (0.27 - 1.83)	0.468
Hypertension	1.46 (0.55 – 3.90)	0.452
Coronary artery disease	0.72 (0.18 - 2.86)	0.641
***Helicobacter pylori* Infection**		
Positive	1.22 (0.79 - 1.86)	0.370
Negative	Ref	

aOR: Adjusted Odd ratio, CI: Confidence interval, Ref: Reference category, **Significant at p<0.01

in females (53%) than males (42.3%). Muhammad *et al.* also reported a higher frequency of *Hpylori* among females than males (54.1% *versus* 45.9%) [15]. Another Pakistani study did not report a gender-based prevalence of *Hpylori* [16]. The study conducted in China reported significantly higher *Hpylori* prevalence among males than females (39.8% *versus* 457%) [17]. The higher *Hpylori* prevalence among males in China could be due to differences in geographical regions.

In the present study, the overall prevalence of anemia was 52.4% whereas anemia prevalence was surprisingly higher in males (62.5%) than females (44.1%). A similar finding was also noted in another Pakistani study that reported 71% anemia prevalence in hospitalized patients with higher anemia prevalence in males (67%) than females (62.5%) [18]. This is also noticeable that anemia frequency in the current study is lower than previously Pakistani study and the most likely reason for this difference is obvious that the previous study was conducted on hospitalized patients while the current study also included samples of outpatients. In contrast to the gender-based prevalence of anemia in the present study, a higher prevalence of anemia among females and lower among males is documented by WHO. According to WHO estimates, globally anemia prevalence is lowest in adult males (12.7%) while highest in pregnant (41.8%) and non-pregnant women (30.2%) [19].

On the other hand, anemia prevalence was 53.9% and 51% among *Hpylori* infected and non-infected cases respectively in the present study. A similar study conducted in China exhibited a difference of about 3% in the prevalence of anemia among *Hplyori* positive (5.3%) and negative cases (2.2%). However, statistically, this difference was significant but clinically not a meaningful difference [20]. Another similar study from China also reported significantly higher anemia prevalence in *Hpylori* infected cohort (5.5%) than the non-infected group (5.2%) but the difference between the two prevalence estimates was not meaningful [17].

Furthermore, it is noticeable that anemia prevalence in both Chinese studies is quite low as compared to our study. The most likely explanation for this difference is that China is economically more stable than our country. Thereby anemia prevalence was low in their study as compared to our study as anemia is linked to socioeconomic status [21]. Hou and coworkers also

Table 4: Association of *helicobacter pylori* infection with morphological types of anemia.

Variables	Microcytic Hypochromic Anemia *Versus* Normocytic Anemia		Macrocytic Anemia *Versus* Normocytic Anemia	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Age (in years)	0.99 (0.97 - 1)	0.278	0.97 (0.93 - 1.01)	0.096
Gender				
Male	0.69 (0.45 - 1.08)	0.104	1 (0.41 - 2.45)	1.000
Female	Ref		Ref	
Body mass index				
Underweight	0.73 (0.30 - 1.83)	0.511	0.65 (0.11 – 3.97)	0.643
Normal	0.75 (0.44 - 1.27)	0.282	0.99 (0.34 – 2.89)	0.978
Overweight	0.92 (0.49 - 1.74)	0.805	0.66 (0.16 - 2.72)	0.569
Obese	Ref		Ref	
Residence				
Rural	1.21 (0.71 - 2.07)	0.478	0.15 (0.02 - 1.16)	0.069
Urban	Ref		Ref	
Comorbid				
Diabetes	0.59 (0.20 - 1.72)	0.335	1.30 (0.20 - 8.41)	0.782
Hypertension	0.90 (0.34 - 2.36)	0.832	2.29 (0.43 – 12.26)	0.332
Helicobacter pylori Infection				
Positive	1.78 (1.14 - 2.76)	*0.011	0.48 (0.18 - 1.24)	0.129
Negative	Ref		Ref	

aOR: Adjusted Odd ratio, CI: Confidence interval, Ref: Reference category, *Significant at p<0.05

did stratification and observed that patients who had a higher comorbidity index, had a higher prevalence of anemia in *Hpylori* positive cases than *Hpylori* negative cases (10.3% *versus* 1.4%) [20]. However, none of the comorbidity in the present study was found to be associated with anemia. In contrast to our findings, a significantly higher prevalence of anemia among *Hpylori* infected patients (30.9%) as compared to *Hpylori* negative cases (22.5%) was reported in a study conducted in Ethiopia [22].

In 1991, Blecker *et al.* presented a case of hemorrhagic gastritis of *Hpylori* infection and a relationship of iron deficiency anemia and *Hpylori* infection was shown [23]. We have found no significant association between *Hpylori* and anemia in our study. Our findings are contradictory to other studies that reported a significant association of *Hpylori* and anemia [11, 22]. The most likely reason for this conflicting finding may be participants' characteristics as these studies recruited dyspeptic patients only whereas in our study, regardless of any specific conditions, all patients who underwent *Hpylori* testing were included. Antacids are usually used to treat dyspepsia and may inhibit iron absorption which may lead to anemia [24, 25]. Moreover, *Hpylori* infection is also responsible for impaired iron absorption due to gastritis hypochlorhydria which further leads to impaired reduction of the dietary iron from the ferric to ferrous form due to which anemia and iron deficiency anemia has been found to be associated with *Hpylori* in studies recruited only dyspeptic patients. The finding of our study was consistent with a Brazilian study that was a community-based study and concluded that there was no association between *Hpylori* and anemia among adults who attended primary healthcare units [26]. Another similar study conducted in Bangladesh recruited all patients who underwent Hypylori irrespective of whether they had dyspepsia or not and no association was observed between *Hpylori* and anemia [27].

In the present study, the association of *Hpylori* was observed with morphological types of anemia with a significantly higher risk of MHA as compared to NA anemia among *Hpylori* infected patients than patients found to be negative for *Hpylori*. The association of *Hpylori* and morphological anemia types was also concluded by Xu *et al.* However, Xu *et al.* fitted the regression model by treating morphological types as a predictor of *Hpylori* and we did oppositely [17]. A study conducted in India also reported that *Hpylori* is related to a moderate degree of anemia, mainly NA type. We believe the evidence of association of *Hpylori* with anemia and its types is weak in this Indian study as the author only enrolled participants having *Hpylori* infection and a conclusion was drawn based on the frequency of anemia and its type [28].

The current study is retrospective in nature with a limited sample size. We were not able to collect complete records for serum iron and ferrous and hence did not analyze iron deficiency anemia. Secondly, to the best of our knowledge, the association of *Hpylori* with a morphological type of anemia has not been widely studied. Therefore, a future study can be conducted in our region while addressing these limitations.

CONCLUSION

The present study did not find the association of *Hpylori* infection with anemia among the Pakistani population.

LIST OF ABBREVIATIONS

aOR : Adjusted odd ratio
BMI : Body mass index
CI : Confidence interval
Hpylori : *Helicobacter pylori*
IDA : Iron deficiency anemia
IQR : Inter-quartile range
MA : Macrocytic anemia
MCHC : Mean corpuscular hemoglobin concentration
MHA : Microcytic hypochromic anemia
NA : normocytic anemia
OR : Odd ratio
WHO : World Health Organization

ETHICS APPROVAL

The present study was conducted after taking ethical approval from Ziauddin Hospital Ethics Committee (IRB# 3370221MVMED).

CONSENT FOR PUBLICATION

The study is retrospective in nature and data was retrieved from medical records. Thus patient consent was not taken.

AVAILABILITY OF DATA

The data is confidential and is only available for reviewers and journal's editorial panel upon their request.

FUNDING

None

CONFLICT OF INTEREST

Authors declare none of the conflict of interest

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Declared none.

AUTHORS' CONTRIBUTION

MVP conceptualized the study. FS and MVP prepared the protocol for data collection. DJ and AAK were involved in data collection. FB entered and analyzed the data. MVP and FB wrote the results. AJK and FS wrote the initial draft of the manuscript. MVP and DJ critically revised the study initial draft and finalized the manuscript. All authors read and approved the manuscript.

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