# Upper gastrointestinal bleedings in patients with hereditary coagulation disorders in Northwest of Iran: prevalence of *Helicobacter pylori* infection

Roya Dolatkhah[a], Manouchehr Khoshbaten[d], Iraj Asvadi Kermani[b], Mohammad Reza Bonyadi[e], Morteza Ghojazadeh[f], Zohreh Sanaat[b], Touraj Asvadi Kermani[c] and Neda Dolatkhah[c]

***Objective*** **Upper gastrointestinal (UGI) bleeding is one of the most life-threatening complications, in up to 25% of persons with hemophilia (PWH). Recurrent bleeding is common and can be caused by the *Helicobacter pylori* infection. Our aim was to evaluate the role of *H. pylori* infection in UGI bleeding in PWH.**

***Material and methods*** **Ninety patients with hereditary bleeding disorders, 30 patients with (group A), and 60 patients without (group B) a history of UGI bleeding episodes were included. The prevalence of *H. pylori* infection was investigated by stool antigen test, and serum serologic tests including immunoglobulin G and anti-CagA.**

***Results*** **Among 90 patients (81 men, nine women, mean age 31.30 ± 10.72 years), 66 patients with hemophilia A, 10 patients with hemophilia B, six patients with Von Willebrand disease, five patients with platelet function disorders, and three patients with other factor deficiencies were evaluated. About 46.7% of patients in group A, and 23.3% of patients in group B were anti-CagA–positive ($P = 0.02$), whereas 76.7% of patients in group A and 51.7% of patients in group B had *H. pylori* immunoglobulin G antibodies ($P = 0.02$). *H. pylori* antigen in stool was positive in 76.7% in group A and 55% in group B ($P = 0.03$). No statistically significant difference was found between type and severity of diseases and risk of UGI.**

***Conclusion*** ***H. pylori*** **infection should be considered as an important cause of UGI bleeding in PWH. We would recommend stool antigen test as a new and noninvasive screening test for diagnosis of *H. pylori* infection in all patients with hereditary hemorrhagic disorders. *Eur J Gastroenterol Hepatol* 23:1172–1177 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

**European Journal of Gastroenterology & Hepatology** 2011, **23**:1172–1177

**Keywords:** ***Helicobacter pylori*****, hemophilia, hereditary coagulation disorders, upper gastrointestinal bleeding**

[a]Department of Hemophilia and Thalassemia, [b]Hematology and Medical Oncology, [c]Hematology and Oncology Research Center, [d]Gastrointestinal Disease, Liver and Gastrointestinal Disease Research Center, [e]Department of Immunology, Faculty of Medicine, Drug Applied Research Center and [f]Department of Physiology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz-Iran

Correspondence to Dr Zohreh Sanaat, MD, Imam Reza Educational and Treatment Center, Shahid Ghazi Tabatabai Hospital, Daneshgah Street, PO Box: 51665–158, Tabriz-Iran
Tel: +0098 (411)3343811 133; fax: +0098 (411)3361358;
e-mails: horc_tums@tbzmed.ac.ir; royadolatkhah@yahoo.com

**Received** 22 June 2011 **Accepted** 17 July 2011

## Introduction

Upper gastrointestinal (UGI) bleeding is one of the most life-threatening complications in patients with hereditary bleeding disorders. Ten to 25% of these patients experience gastrointestinal (GI) bleeding at least once in their lives, despite different replacement therapies. The mortality rate of GI bleeding in these patients is reported to be 30%, considering that surgical and endoscopic interventions to control bleeding become necessary in 20% of these patients [1].

The pathological effects of *Helicobacter pylori* on chronic gastritis, duodenal ulcers, and most gastric ulcers have been confirmed. UGI bleeding following erosive gastritis, duodenal, and gastric ulcers caused by *H. pylori* plays a major role in the mortality of patients with hereditary bleeding disorders [2].

*H. pylori*, which affects almost half the world's population, is one of the most common infections. The route of transmission is human–human, oral–oral, and oral–fecal. The prevalence of *H. pylori* infection is directly related to the national socioeconomic status and is 80–96% among the disease-free population in developing countries and 20–40% in developed countries [3]. Different seroepidemiological studies carried out in different parts of Iran have shown prevalence of infection in 90% of adults over 35 years of age. A recent study in Ardabil confirmed prevalence in 90% of the normal population [4–6]. Somi *et al.* [7] in a study carried out in Tabriz, reported prevalence in 81.5% of patients with reflux-induced esophagitis and 87.10% in the control group.

Very few studies have been carried out on the prevalence of *H. pylori* in patients with hereditary bleeding disorders and its relation with UGI bleeding. In a study by Braden *et al.* [2], which was carried out on 70 patients with bleeding disorders in Germany, no difference could be

The research was conducted at Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz-Iran.

0954-691X © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MEG.0b013e32834b0e7a

found between these patients and the control group in the prevalence of *H. pylori* by urease breath test. In another study conducted on 37 patients in Greece, *H. pylori* antibodies were measured using the enzyme-linked immunosorbent assay (ELISA) method. Patients were divided into two groups, with and without a GI bleeding background. Finally, the anti-CagA antibody was positive in 83% of the patients having a GI bleeding background, whereas only 26.3% of the patients with no history of GI bleeding were positive ($P < 0.01$) [1].

Among various noninvasive techniques, serology and urea breath tests (UBTs) are considered as standard techniques and are most widely used. A novel noninvasive method for the measurement of stool antigens to evaluate *H. pylori* infection with high sensitivity and specificity (100 and 94.9%, respectively) is used in this study. This test has recently been approved by the USA Food and Drug Administration , with indication for use in primary diagnosis of *H. pylori*, and also in the monitoring of post-treatment outcome [8]. In a study carried out by Shimoyama *et al.* on 994 patients in Japan, the sensitivity of the two methods (serological and stool) was compared. The stool antigen test was positive in 22 cases despite negative serological tests. According to the results of this study, the sensitivity of stool antigen tests is higher than that of serology tests (94.9 vs. 80–90%, respectively), and the specificity of serodiagnosis is lower than that of other diagnostic tests (90 vs. 97% for stool test and 96% for UBT) [9,10].

Complications of UGI bleeding in patients with hereditary bleeding disorders, such as hemophilia A and B, and Von Willebrand disease become more important and, on the other hand, replacement therapies with blood products can lead to blood-transferred diseases and extra ongoing costs for providing blood factors to patients. In contrast, numerous studies have proven that *H. pylori* eradication treatment not only cures duodenal and gastric ulcers and improves the histological pattern, but also prevents recurrence and bleeding [2].

As very few studies have been conducted on the prevalence of *H. pylori* infection in patients with hereditary bleeding disorders, the aim of this study, which to our knowledge has not been carried out previously in Iran, was to evaluate the prevalence of *H. pylori* infection among patients with hereditary bleeding disorders and find out its relation with the prevalence of UGI bleeding in these patients.

## Materials and methods

A prospective study was conducted in the Hematology and Oncology Research Center of the Tabriz University of Medical Sciences, Iran from October 2009 to September 2010. Ninety patients with hereditary bleeding disorders, including hemophilia A and B and Von Willebrand disease, referred to the Hemophilia and Thalassemia clinic of Shahid Ghazi were selected. This study is based on a case–control method. Patients were selected randomly and divided into two groups; case (30 patients) and control (60 patients), depending on whether they had a previous or existing history of UGI bleeding. A questionnaire containing information on disease type and severity, patient's age, sex, history of GI bleeding, and other clinical data was filled out for all patients. Demographic data questionnaire included a history of dyspepsia signs, duodenal and gastric ulcers, and GI bleeding. Dyspepsia includes recurrent signs like pain in epigastrium, discomfort, fullness, belching, and reflux that last for more than 3 months. Patients with active UGI bleeding were referred to the gastroenterology subspecialist participating in this study; the specialist performed endoscopies. Serologic pylori and specific stool antigen ELISA tests were also performed on all patients to detect *H. pylori* infection. All patients gave informed consent and the study was approved by the Ethical Committee of Tabriz University of Medical Sciences.

### Serology test

*H. pylori* antigens anti-*H. Pylori* IgG and anti-Cag A antibody were analyzed using quantitative ELISA method [Padten and Diapro Kits (Dia.Pro-Diagnostic Bioprobes s.r.l Sede legale: Milano, Spain)] with five standards: 0, 15, 30, 60, and 100 unit (arbU/ml), with a specificity of 88% and sensitivity of 100%. The normal values determined by ELISA are as follows: IgG, neg $< 10$ U/ml, border-line $= 10-20$ Pos $> 30$; anti-CagA, neg $< 10$ arbU/ml, border line $= 10-20$ Pos $> 30$.

### *H. pylori* antigen enzyme immune assay test (stool antigen test)

*H. pylori*-specific antigens in stool samples were detected by an enzyme immunoassay (EIA) method. Antigen levels greater than 23 arbU/ml were considered positive.

Sensitivity and specificity: the *H. pylori* antigen EIA test kit has been compared with a leading commercial *H. pylori* antigen EIA test using clinical specimens. The results show that the clinical sensitivity of the *H. pylori* antigen EIA test kit is 98.6%, and the clinical specificity is 95.4% [according to ACON Laboratories Inc. (San Diego, California, USA); *http://www.aconlabs.com*]. According to some other studies, its sensitivity is 94.9–100% and specificity is 95.1–100% [11].

*H. pylori* antigen EIA versus other EIA

(1) Clinical sensitivity: 98.6% (92.4–100.0%; 95% confidence interval)
(2) Clinical specificity: 95.4% (90.3–98.3%; 95% confidence interval)
(3) Overall agreement: 96.5% (93.0–98.6%; 95% confidence interval)

This study was a case–control study and all data were analyzed statistically using the SPSS17 software (SPSS

Inc., Chicago, Illinois, USA). As no specific intervention was done during the treatment process, only one blood and stool sample were collected. In addition, patients infected by *H. pylori* were referred to a gastroenterologist and treated, which was not the aim of the study.

## Results

In this study, 90 patients with bleeding disorders referred to the Hemophilia clinic of Shahid Ghazi, were divided into two groups: 30 patients in group A, which was the case group (with a history of GI bleeding) and 60 patients in group B, which was the control group (without a history of GI bleeding). The mean age of the patients is 31.3 years with a range of 12–59. The results obtained from both groups are summarized in Table 1.

Figure 1 shows the frequency of blood disorders in both groups. Of the 30 patients in the case group, 12 had mild, 10 had moderate, and eight had severe diseases. In the control group, 38 patients had mild, 12 had moderate, and 10 had severe diseases. There was no significant statistical relation between the type of bleeding disorder, the severity, and the prevalence of GI bleeding ($P = 0.06$ and $P = 0.11$, respectively).

A statistically significant relation was found between the prevalence of GI bleeding and smoking in both the case and control groups ($P = 0.008$). It should be noted that most patients were smokers (90.5%); most of the patients smoked cigarettes with a mean rate of $3.46 \pm 5.66$ and $2.59 \pm 6.42$ cigarettes per day, in the case and control groups, respectively. There was no significant statistical relation between NSAID administration and the prevalence of GI bleeding in both groups ($P = 0.0411$), and most of the patients used ibuprofen (45.6%). There was no significant statistical relation between the administration of antiviral treatment and the prevalence of GI bleeding in both groups ($P = 0.229$).

History of dyspepsia for more than 3 months was found in 23 (79.3%) patients and for less than 3 months in six (20.7%) patients in the case group. Dyspepsia for more than 3 months was also reported in 25 (46.3%) patients and for less than 3 months in 11 (20.4%) patients of the control group. A statistically significant relation was found between the prevalence of GI signs including recurrent epigastrium pain ($P = 0.001$), discomfort ($P = 0.001$), fullness ($P = 0.001$), belching ($P = 0.001$), and reflux ($P = 0.001$) in both the case and control groups. The prevalence of GI complaints is shown in Table 2.

Of the 30 patients in the case group with a positive bleeding history, 15 had a single episode of UGI bleeding and 15 had multiple episodes. UGI bleeding presented with hematochezia in one case (3.3%), hematemesis in 18 cases (60%), and melena in 24 cases (80%). UGI bleeding led to hospitalization in 12 cases (40%), 26 patients (86.7%) received medical treatment, and blood transfusion due to anemia was performed in 19 cases (63.3%).

Nineteen patients in the case group had acute GI bleeding throughout the study for which endoscopies were performed. The bleeding cause and site were duodenal ulcers in two patients (7.4%), gastric ulcers in two patients (7.4%), unknown in four patients (13.8%), and gastric erosions in the remaining cases. There were no reported cases of erosion, angiodysplasia, Mallory–Weiss syndrome, or esophagitis. Table 3 shows the results obtained in the serologic and stool *H. pylori* antigen tests. Levels of anti-CagA greater than 30 RU/ml, IgG greater than 30 RU/ml, and a stool Ag test result greater than 23 were considered positive.

The mean range of anti-CagA was 41.20 ( $\pm$ 10.52) and 23.33( $\pm$ 5.24) arbU/ml in the case and control groups, respectively. Anti-CagA was positive among 14 patients in both the case group (46.7%) and the control group (23.3%), and the difference between the two groups was statistically significant ($P = 0.02$).

The mean range of the IgG test was 56.03 ( $\pm$ 37.71) and 40.96 ( $\pm$ 33.88) U/ml in the case and control group, respectively. IgG was found positive among 23 patients of the case group (76.7%) and 31 patients of the control group (51.7%), and the difference between the two groups was statistically significant ($P = 0.01$).

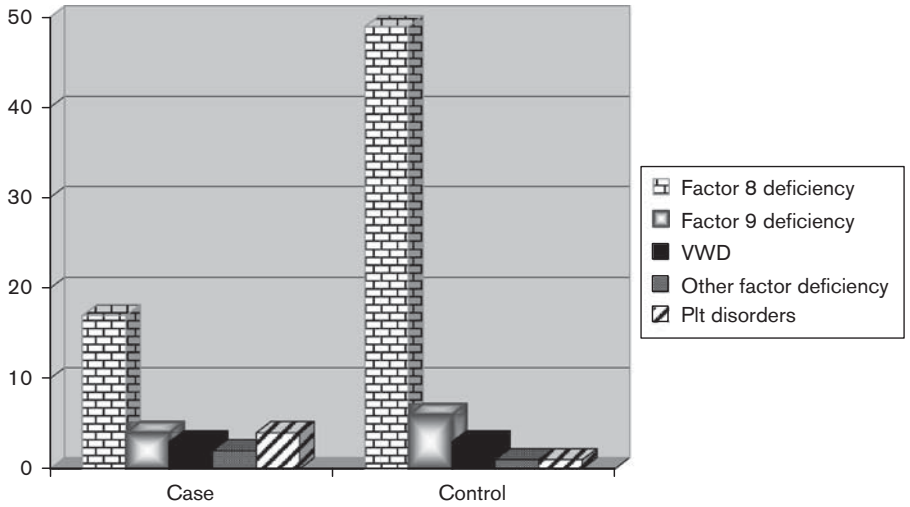
The mean range of stool Ag was 86.80 ( $\pm$ 15.91) and 59.11 ( $\pm$ 10.14) arbU/ml in the case and control groups, respectively. The stool Ag test was positive among 23

**Table 1 The results obtained from both groups**

| | History of bleeding episodes ($n=30$) | No bleeding episodes ($n=60$) | | |
|---|---|---|---|---|
| | Count (% within group) | Count (% within group) | *P* value | OR (95% CI) |
| Sex | | | | |
| Men | 24 (80.0) | 57 (95.0) | 0.03 | 0.21 (0.04–0.91) |
| Women | 6 (20.0) | 3 (5.0) | | |
| Marriage | | | | |
| Married | 19 (67.9) | 24 (40.0) | 0.01 | 3.16 (1.22–8.15) |
| Single | 9 (32.1) | 36 (60.0) | | |
| Smoking | | | | |
| Yes | 15 (50.0) | 13 (22.0) | 0.00 | 3.53 (1.37–9.09) |
| No | 15 (50.0) | 46 (78.0) | | |
| NSAIDs | | | | |
| Yes | 20 (66.7) | 37 (61.7) | 0.41 | 1.24 (0.49–3.12) |
| No | 10 (33.3) | 23 (38.3) | | |
| HBV | | | | |
| Positive | 2 (6.9) | 5 (8.5) | 0.58 | 0.80 (0.14–4.39) |
| Negative | 27 (93.1) | 54 (91.5) | | |
| HCV | | | | |
| Positive | 13 (44.8) | 19 (31.7) | 0.16 | 1.75 (0.70–4.36) |
| Negative | 16 (55.2) | 41 (68.3) | | |
| Antiviral treatment | | | | |
| Yes | 11 (37.9) | 16 (27.6) | 0.22 | 1.60 (0.62–4.13) |
| No | 18 (62.1) | 42 (72.4) | | |

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio.

**Fig. 1**




Disease type frequency. VWD, Von Willebrand disease.

**Table 2 The prevalence of gastrointestinal complaints in both case and control groups**

| | History of bleeding episodes ($N=30$) | No bleeding episodes ($N=60$) | | |
|---|---|---|---|---|
| | Count (% within group) | Count (% within group) | *P* value | OR (95% CI) |
| Epigastrium pain | | | | |
| Yes | 25 (83.3) | 14 (23.3) | <0.001 | 16.42 (5.30–50.92) |
| No | 5 (16.7) | 46 (76.7) | | |
| Discomfort | | | | |
| Yes | 26 (86.7) | 18 (30.0) | <0.001 | 15.16 (5.62–49.78) |
| No | 4 (13.3) | 42 (70.0) | | |
| Fullness | | | | |
| Yes | 26 (86.7) | 12 (20.0) | <0.001 | 26.00 (7.61–88.78) |
| No | 4 (13.3) | 48 (80.0) | | |
| Belching | | | | |
| Yes | 19 (63.3) | 4 (6.7) | <0.001 | 24.18 (6.87–85.00) |
| No | 11 (36.7) | 56 (93.3) | | |
| Reflux | | | | |
| Yes | 18 (60.0) | 4 (6.7) | <0.001 | 21.00 (6.01–73.29) |
| No | 12 (40.0) | 56 (93.3) | | |

**Table 3 Results obtained from serologic and stool *Helicobacter pylori* antigen tests**

| | Total ($n=90$) | | | |
|---|---|---|---|---|
| *H. pylori* Tests | Case ($n=30$) | Control ($n=60$) | *P* value | OR (95% CI) |
| Hp(+) anti-Cag-A | 14 (46.7%) | 14 (23.3%) | 0.023 | 0.34 (0.13–0.88) |
| Hp(−) anti-Cag-A | 16 (53.3%) | 46 (76.7%) | | |
| Hp(+) IgG | 23 (76.7%) | 31 (51.7%) | 0.019 | 0.32 (0.12–0.87) |
| Hp(−) IgG | 7 (23.3%) | 29 (48.3%) | | |
| HpSA(+) | 23 (76.7%) | 33 (55.0%) | 0.037 | 0.37 (0.13–0.99) |
| HpSA(−) | 7 (23.3%) | 27 (45.0%) | | |

patients of the case group (76.7%) and 33 patients of the control group (55%), and the difference between the two groups was statistically significant ($P = 0.03$).

## Discussion

*H. pylori* infection is widespread throughout the world. Its prevalence rate is attributed to national socioeconomic status and is largely age related [3]. In the developing world, *H. pylori* is a challenging health problem as it is found at a prevalence of 20–40% among adolescents (20% in the USA) in comparison with infection rates exceeding 80–90% of the total population in developing countries [3,12]. One study in the northwest of Iran, a region with the highest mortality rate from gastric cancer in Iran, reported that *H. pylori* infection occurs among 89.2% of the residents [6]. Other surveys in different age groups from various regions of the country have reported that *H. pylori* infection occurs in 57–91% of the study subjects [5,13–15]. In another prospective study, *H. pylori* infection was reported in 67.1% of 1000 enrolled dyspeptic patients from the south of Iran [10]. In this study, we reported *H. pylori* infection in hereditary hemorrhagic disorder (HHD) patients from Tabriz, northwest of Iran.

Of all the patients, 66 had hemophilia A, 10 had hemophilia B, six had Von Willebrand disease, five had inherited platelet function disoders, and three had other factor deficiencies. There is no doubt that GI bleeding is more frequent in VWD than other hemophiliacs. But according to our data there was no difference between bleeders and nonbleeders in terms of type of disease and their degree of severity, maybe because of small numbers of cases in this study. ($P = 0.06$).

Of the 30 patients in the case group, 15 patients had GI bleeding once and 15 patients more than once. In addition, 19 patients from this group had endoscopies because of acute bleeding for which gastritis was reported to be the most common cause.

Very few studies have been carried out on the relation between *H. pylori* infection and GI bleeding in patients with bleeding disorders. Eleftheriadis *et al.* [1] studied 37 patients with bleeding disorders. In their study, ELISA tests, which included the detection of anti-CagA and IgG, were conducted to determine the *H. pylori* infection. The prevalence of anti-CagA in patients with bleeding disorders was significantly different in the two groups, with and without a history of GI bleeding (83 and 26.3%, respectively, $P < 0.01$). However, no statistically significant difference in IgG antibody could be found between case and control groups (72 and 58%, respectively, $P =$ NS). However, the data obtained in this study revealed a statistically significant difference between the case and control groups regarding both serologic and stool tests. According to these data, the most common causes of bleeding were gastritis and gastric erosion [1], which were in accordance with the endoscopic findings in our patients.

Among the noninvasive diagnostic tests of *H. pylori* infection, the 13C-UBT is recognized as the most accurate; however, this test is most recommended for monitoring *H. pylori* eradication. The test is currently not sued in the primary assessment of infection in many countries [16]. Braden *et al.* [2], in a study carried out on 70 patients with bleeding disorders, performed the urease breath test to identify *H. pylori* infection. Although this test possesses a high sensitivity of 88% and a specificity of 98%, no statistically significant difference in *H. pylori* infection was observed between case and control groups ($P = 0.97$). This test was not conducted in children and the elderly because it is expensive and difficult to perform, and the price of the 13C-UBT is still high compared with other tests in many countries, as well as our center.

In 2005, Szczepanik *et al.* conducted a vast amount of research on 146 patients with bleeding disorders that included 129 patients with hemophilia A and 17 patients with hemophilia B. Serologic tests were used in this study to identify *H. pylori* infection. *H. pylori* infection was identified in 33 patients with hemophilia and a history of GI bleeding (71.7%), whereas it was identified in 39 patients with hemophilia and no history of GI bleeding (39%). The prevalence of *H. pylori* infection was significantly different in the two groups ($P = 0.0002$) [6].

According to some studies, both the *H. pylori* infection rate and the history of dyspeptic symptoms in patients with severe bleeding diathesis are similar to the prevalence in the normal population [1–3,15,17], but according to statistical analyses, the frequency of *H. pylori* infection in hemophilic patients with a positive history of UGI bleeding is statistically more significant than in *H. pylori* negative patients. In this study, when we compared the prevalence of infection between the two subgroups of HHD patients (those with and those without a history of UGI bleeding), the prevalence was found to be significantly higher in the patients with a history of UGI bleeding (46.7 vs. 23.3%; $P < 0.01$ for Cag-A, 76.7 vs. 51.7%; $P = 0.01$ for IgG and 76.7 vs. 55.0%; $P = 0.01$ for stool Ag tests). This strengthens our contention that UGI bleeding complications are mainly caused by *H. pylori* infection [2], and that the bleeding may result from small mucosal injuries because of *H. pylori* pathogenic factors, which do not manifest themselves clinically in patients with normal hemostasis [3,18,19]. Choe *et al.* [20] found that the relationship between the severity of hemophilia and the amount of GI bleeding in children with *H. pylori* infection in Korea was unexpected, probably because of the small number of patients in their study, but our data also showed that there was no statistically significant relation between the severity, the type of bleeding disorder, and the prevalence of UGI bleeding.

The major finding in this study is the application of a novel laboratory approach to measure *H. pylori* antigen in stool using an ELISA method, which has the advantage of being noninvasive, simple, and convenient. The detection of *H. pylori* antigen in stool is highly sensitive and specific [7]. In a study carried out by Shimoyama *et al.*, a specificity of 100% and a sensitivity of 94.6% were reached. However, a sensitivity and specificity of 80 and 90%, respectively, were achieved for IgG antibody [7]. Overall, sensitivity and specificity of 88 and 100% are well-accepted values for the identification of *H. pylori* antibodies by ELISA serologic tests pylori [1].

According to a massive study by Nocon *et al.*, compared with the stool antigen test, the sensitivity of the 13C-UBT is higher in nine studies, lower in three studies, and one study reports no difference. The specificity is higher in nine studies, lower in two studies, and either higher or lower in two studies[16]. In another study from Spain performed by Calvet *et al.*, the comparison of stool antigen test and 13C-UBT revealed that the UBT had a sensitivity of 99.2% but a specificity of only 60.5%, with 32 false positive results. This was 90% sensitivity and 98% specificity for the stool antigen test, with only two false positive results [21]. In contrast, the stool Ag test is noninvasive and its cost is one-tenth of the cost of endoscopies and a third of the urease breath test in Iran. The simplicity of the procedure for children and those not willing to undergo endoscopic procedures is another advantage. In addition, this method allowed us to identify the primary infection before the production of antibodies. Another advantage of stool antigen test is that in contrast to serology tests, it becomes negative after previous *H. pylori* eradication.

In addition, in developing countries such as Iran there are only a few hemophilia clinics in the big cities. Patients from small cities have to travel a long distance to reach hemophilia centers, which is one of the severe stresses for them. Because of chronic joint disease, the hemophiliac is often unable to work, go to school, do their daily activities

and these make socioeconomic problems for them. The high percentage of psychiatric disorders that had been confirmed with standard interviewing indicated that hemophiliacs are exposed to very severe and different stresses, and for these reasons we need some easy and cost-effective methods for them [22]. Although the 13 C-UBT is the most accurate method in patients irrespective of age, the stool antigen test is a promising method because of its diagnostic performance in HHD patients, which is easy to perform in any laboratory.

*H. pylori* antigen was detected in stool samples from 23 patients in the case group (76.7%) and 33 patients in the control group (55%) that was statistically significant ($P = 0.037$). According to our data, *H. pylori* infection was detected more frequently in patients without a history of GI bleeding (55%) that could indicate the existence of a primary infection and shows the necessity of performing this test in routine screening of *H. pylori* infection.

*H. pylori* infection is considered the main etiologic cause of UGI bleeding and also life threatening bleedings in patients with bleeding disorders. According to the data obtained from this study, there are considerable differences regarding the prevalence of GI bleeding in *H. pylori*-positive patients. In view of the high prevalence rate of UGI bleeding associated with *H. pylori* infection in HHD patients and high treatment costs, performing noninvasive screening tests, and initiating eradication treatments in any recognized case of *H. pylori* infection, are strongly recommended. As the stool Ag test revealed a primary infection before the emergence of antibodies, and is also a convenient and noninvasive method, it would be advisable to use this method routinely to identify the disease and start the treatment before the emergence of GI symptoms.

## Acknowledgements

Authorship contributions: Roya Dolatkhah, MD, performed research, collected data, wrote the manuscript; Manouchehr Khoshbaten, MD, designed research, performed patients' gastrointestinal consultants; Iraj Asvadi Kermani, MD, performed research; Mohammad Reza Bonyadi, PhD, performed research, performed specialized lab tests; Morteza Ghojazadeh, PhD, performed research, analyzed and interpreted data, performed statistical analysis; Zohreh Sanaat, MD, performed research; Touraj Asvadi Kermani, MD, helped in writing of article; Neda Dolatkhah, MD, helped in Editing of article.

This study was supported by the Hematology and Oncology Research Center of Tabriz University of Medical Sciences, as an approved Research Project. The authors also would like to thank all the patients who participated in this study.

### Conflicts of interest

There are no conflicts of interest.

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