

Retrospective Study

Clinical characteristics of *Helicobacter pylori*-negative drug-negative peptic ulcer bleeding

Woo Chul Chung, Eun Jung Jeon, Dae Bum Kim, Hea Jung Sung, Yeon-Ji Kim, Eun Sun Lim, Min-ah Kim, Jung Hwan Oh

Woo Chul Chung, Eun Jung Jeon, Dae Bum Kim, Hea Jung Sung, Yeon-Ji Kim, Eun Sun Lim, Min-ah Kim, Jung Hwan Oh, Department of Internal Medicine, St. Paul's Hospital, College of Medicine, the Catholic University of Korea, Seoul 137-701, South Korea

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Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of the Catholic University of Korea (PC14RISI0012).

Informed consent statement: Informed consent was not obtained because this study is a retrospective analysis of the clinical data collected after treatment course was completed. And the data of peptic ulcer bleeding were collected through computerized data analysis to target medical history. Therefore, this study does not affect the future treatment of patients. This study give rise to minimal risk to the patients. In this study, the patient's clinical data collection and analysis, writing papers and papers from all over the research process, including the publication of a study were managed in secret for personal information (such as anonymized medical records). In addition, Institutional Review Board of the Catholic university of Korea, St. Paul's hospital approved that this study has exemption from the informed consent.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at jwchulgi@gmail.com. Informed consent was not obtained but the presented data are anonymized and risk of identification is low. No additional data are available.

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Correspondence to: Eun Jung Jeon, MD, Department of Internal Medicine, St. Paul's Hospital, College of Medicine, the Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, South Korea. jwchulgi@gmail.com
Telephone: +82-2-9582343
Fax: +82-2-9687250

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Abstract

AIM: To investigate the clinical characteristics and outcomes of idiopathic *Helicobacter pylori* (*H. pylori*)-negative and drug-negative] peptic ulcer bleeding (PUB).

METHODS: A consecutive series of patients who experienced PUB between 2006 and 2012 was retrospectively analyzed. A total of 232 patients were enrolled in this study. The patients were divided into four groups according to the etiologies of PUB: idiopathic, *H. pylori*-associated, drug-induced and combined (*H. pylori*-associated and drug-induced) types. We compared the clinical characteristics and outcomes between the groups. When the silver stain or rapid urease tests were *H. pylori*-negative, we

obtained an additional biopsy specimen by endoscopic re-examination and performed an *H. pylori* antibody test 6-8 wk after the initial endoscopic examination. For a diagnosis of idiopathic PUB, a negative result of an *H. pylori* antibody test was confirmed. In all cases, re-bleeding was confirmed by endoscopic examination. For the risk assessment, the Blatchford and the Rockall scores were calculated for all patients.

RESULTS: For PUB, the frequency of *H. pylori* infection was 59.5% (138/232), whereas the frequency of idiopathic cases was 8.6% (20/232). When idiopathic PUB was compared to *H. pylori*-associated PUB, the idiopathic PUB group showed a higher rate of re-bleeding after initial hemostasis during the hospital stay (30% *vs* 7.4%, $P = 0.02$). When idiopathic PUB was compared to drug-induced PUB, the patients in the idiopathic PUB group showed a higher rate of re-bleeding after initial hemostasis upon admission (30% *vs* 2.7%, $P < 0.01$). When drug-induced PUB was compared to *H. pylori*-associated PUB, the patients in the drug-induced PUB were older (68.49 ± 14.76 years *vs* 47.83 ± 15.15 years, $P < 0.01$) and showed a higher proportion of gastric ulcer (77% *vs* 49%, $P < 0.01$). However, the Blatchford and the Rockall scores were not significantly different between the two groups. Among the patients who experienced drug-induced PUB, no significant differences were found with respect to clinical characteristics, irrespective of *H. pylori* infection.

CONCLUSION: Idiopathic PUB has unique clinical characteristics such as re-bleeding after initial hemostasis upon admission. Therefore, these patients need to undergo close surveillance upon admission.

Key words: Peptic ulcer; Gastrointestinal bleeding; *Helicobacter pylori*; Non-steroidal anti-inflammatory drug

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Core tip: Recently, the number of *Helicobacter pylori* (*H. pylori*)-negative and drug-negative "idiopathic" peptic ulcers has increased. This study analyzed the clinical characteristics of idiopathic peptic ulcer bleeding (PUB) and compared different etiologies, including *H. pylori* infection and drug use. In conclusion, definite etiologic factors of PUB including drug and *H. pylori* infection seemed to play an insignificant role in the severity of PUB. Idiopathic PUB has unique clinical characteristics such as re-bleeding after initial hemostasis upon admission. Therefore, these patients need to undergo close surveillance upon admission.

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INTRODUCTION

Acute upper gastrointestinal bleeding is a common complication of peptic ulcer disease, often caused by *Helicobacter pylori* (*H. pylori*) and non-steroidal anti-inflammatory drug (NSAID)/aspirin use. Recently, with the declining prevalence of *H. pylori* infection, *H. pylori*-negative ulcers have been frequently reported. Epidemiological studies have been performed to investigate whether the number of *H. pylori*-negative and drug-negative ulcers, the so called "idiopathic ulcers", are increasing^[1-4]. For a diagnosis of an idiopathic ulcer, a negative result of an *H. pylori* tests performed during at least two different time points has to be confirmed, and the validity of the drug use history should be checked. Then, conditions associated with malignancy and stressful conditions such as trauma, burns and multi-organ failure should be excluded.

Previously, several studies have reported that idiopathic ulcer disease has a higher recurrence rate than *H. pylori*-associated peptic ulcers, and its long-term recurrence rate is significantly higher than that of drug-induced peptic ulcers as well as *H. pylori*-associated peptic ulcers^[3-6]. However, to date, the natural history of idiopathic PUB is unknown; the optimal management of these patients remains uncertain. In this study, we analyzed the clinical characteristics and outcomes of idiopathic peptic ulcer bleeding (PUB) and compared different etiologies, including *H. pylori* infection and drug use.

The Blatchford scores use pre-endoscopic clinical and laboratory variables to predict the need for clinical intervention (blood transfusion, endoscopy, surgery)^[7]. The Rockall scores have been developed from mathematical models to predict the risk of death or re-bleeding^[8]. Although the Blatchford and the Rockall scores lack subjective variables such as the severity of systemic diseases, these scoring systems have served as risk stratification tools and seem to perform well in predicting mortality^[9-11]. We also aimed to assess the severity of PUB among groups categorized by different etiologies using these scoring systems.

MATERIALS AND METHODS

Patients

The study was conducted at St. Vincent and St. Paul Hospital, the Catholic University of Korea. The medical records, charts and the digitalized picture archived images of consecutive patients who were admitted with PUB between January 2006 and January 2012 were collected. The patients presented with objective evidence of upper gastrointestinal bleeding

(hematemesis, melena or blood in nasogastric aspirates).

All of the patients underwent an emergency esophagogastroduodenoscopy within 24 h of initial presentation. No systemic sedative agent was given to any of the patients. The stigmata of bleeding were classified according to the Forrest classification^[12]. When the base of the ulcer was categorized as Forrest classification I or II a, endoscopic treatment was performed. All of the patients underwent second look endoscopy within 48 h of the initial endoscopic examination. During the second look endoscopy, two biopsy specimens were taken from the antrum (the greater curvature of the mid-antrum) and the corpus (the greater curvature of the mid-body) for histological assessment. The diagnosis of *H. pylori* infection was based on histological results, including a rapid urease test (CLO test®, Kimberly-Clark, Utah, United States) or a Warthin-Starry silver stain in any of the two specimens from the antrum and body. Alcohol use was defined as consumption of at least 20 g of alcohol/d for up to three times/week. Smoking was defined as current smoking.

A total of 465 patients had bleeding from a peptic ulcer as confirmed by endoscopy. Patients less than 17 years and more than 85 years of age were excluded from the study. We excluded patients with procedure related bleeding (e.g., after gastric polypectomy, endoscopic mucosal resection or endoscopic sub-mucosal dissection) and patients with medical comorbidities consisting of serious systemic diseases (heart failure, liver cirrhosis with a Child-Pugh score > 7, chronic obstructive pulmonary disorder, sepsis, hematologic disorder, etc.). Individuals with conditions that might have substantial effects on our study results (e.g., serum creatinine > 2.5 mg/dL and total bilirubin > 3.0 mg/dL) and bleeding associated with malignancy were excluded. We also excluded patients with a history of gastrectomy. However, patients with diabetes mellitus without any complications or well-controlled hypertension were included.

All of the patients with PUB were prescribed proton pump inhibitor (PPI) therapy for 4 wk or longer. If the silver stain and rapid urease test were *H. pylori*-negative, we obtained an additional biopsy specimen by performing endoscopy 6-8 wk after the initial examination. Patients did not take PPIs for at least 2 wk before the re-endoscopy. For the diagnosis of idiopathic ulcer bleeding, a negative result of an *H. pylori* antibody test was confirmed.

Methods

Variables including patient age, sex, smoking and alcohol history, initial hemoglobin level, duration of admission, ulcer size, need for transfusion, evidence of re-bleeding, use of anti-thrombotic agents, use of NSAIDs and the status of *H. pylori* infection were reviewed. Anti-thrombotic agents included low dose

aspirin and anti-platelet agents such as clopidogrel and ticlopidine. Re-bleeding was defined as objective evidence of bleeding with continuous melena, hematochezia, or the presence of fresh blood in vomit while in the hospital. When hemodynamic instability (systolic blood pressure < 90 mmHg or heart rate > 120 beats/min) developed or there was an abrupt drop of more than 2 g/dL in the hemoglobin level, these episodes were also defined as re-bleeding. In all cases, re-bleeding was confirmed by endoscopy. The Blatchford and the Rockall scores were calculated for all patients for the risk assessment.

Statistical analysis

For the quantitative variables, the mean \pm SD was calculated. One-way ANOVA along with a *post-hoc* test such as Dunnett test was used to compare continuous variables among subgroups of PUB. For the qualitative variables, the number of subjects in the subgroups was calculated. In addition, the χ^2 and/or Fisher's exact test were used to investigate the association with other variables. The binary logistic regression model was used for the univariate and the multivariate analysis. SPSS statistical package version 21.0 (SPSS Inc., Chicago, IL, United States) and R language ver. 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses. Statistical significance was defined as $P < 0.05$. The statistical methods of this study were reviewed by Jinho Yoo from Bio-Age Inc. in the Republic of Korea.

RESULTS

Characteristics and clinical outcomes

Of the 465 patients with PUB, 233 were excluded due to extreme age ($n = 12$), significant medical comorbidity ($n = 108$), procedure related bleeding ($n = 15$), a history of gastrectomy ($n = 34$), bleeding from gastric cancer ($n = 16$), and violation of protocol/loss of follow up ($n = 48$). Surgical intervention was performed in 7 patients (4 cases of gastric ulcer bleeding and 3 cases of duodenal ulcer bleeding), and these participants were excluded due to incomplete evaluation of *H. pylori* infection. Finally, a total of 232 patients (162 males and 70 females) were enrolled in this study. The mean age of the subjects was 57.13 ± 17.42 years.

For PUB, the frequency of *H. pylori* infection was 59.5% (138/232), whereas 20 patients who had negative results for *H. pylori* infection and no definite drug history were allocated into the idiopathic (*H. pylori*-negative and drug-negative) PUB group (Figure 1). The frequency of idiopathic PUB was 8.6% (20/232). The patients were divided into the following four groups according to the etiologies of PUB: idiopathic, *H. pylori*-associated, drug-induced and combined (*H. pylori*-associated and drug-induced) type. The *H. pylori*-associated PUB group included

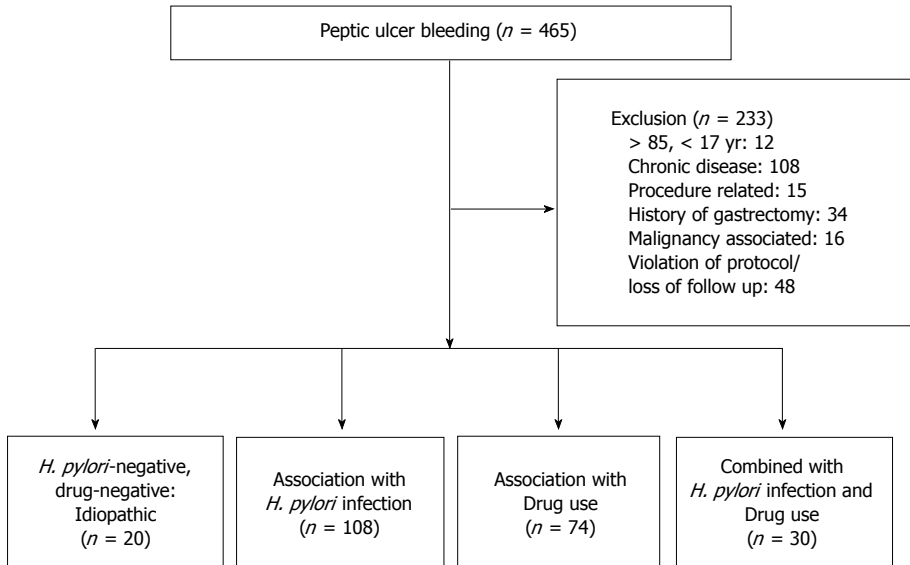


Figure 1 Study enrollment of the peptic ulcer bleeding. Drug: Non-steroidal anti-inflammatory drugs and/or antithrombotic agents; *H. pylori*: *Helicobacter pylori*.

Table 1 Clinical characteristics and outcomes of patients with peptic ulcer bleeding

| Etiology of PUB | Idiopathic (n = 20) | <i>H. pylori</i> -associated (n = 108) | Drug-induced (n = 74) | Combined (<i>H. pylori</i> , Drug) (n = 30) | <i>P</i> value | <i>P</i> value ¹ | <i>P</i> value ² | <i>P</i> value ³ |
|-------------------------------------|------------------------|---|--------------------------|---|---------------------|-----------------------------|-----------------------------|-----------------------------|
| Age | 55.15 ± 12.33 | 47.83 ± 15.15 | 68.49 ± 14.76 | 63.87 ± 14.79 | < 0.01 | 0.09 | < 0.01 | 0.09 |
| Sex (M:F) | 19:1 | 89:19 | 37:37 | 17:13 | < 0.01 | 0.2 ⁴ | < 0.01 | < 0.01 |
| Smoking (Yes:No) | 10:10 | 53:55 | 21:53 | 7:23 | < 0.01 | 1 | 0.12 | 0.10 |
| Alcohol (Yes:No) | 6:14 | 27:81 | 14:60 | 5:25 | 0.55 ⁴ | 0.85 | 0.36 ⁴ | 0.31 ⁴ |
| Gastric ulcer (GU) | 12 | 53 | 57 | 21 | < 0.01 | 0.64 ⁴ | 0.04 ⁴ | 0.08 ⁴ |
| Duodenal ulcer (DU) | 6 | 44 | 6 | 2 | | | | |
| GU + DU | 2 | 11 | 11 | 7 | | | | |
| Initial hemoglobin (g/dL) | 9.98 ± 3.15 | 9.36 ± 2.56 | 8.75 ± 2.73 | 8.84 ± 2.39 | 0.19 | 0.57 | 0.14 | 0.26 |
| Creatinine (mg/dL) | 1.040 ± 0.179 | 1.018 ± 0.435 | 1.255 ± 0.845 | 1.03 ± 0.356 | 0.05 | 0.99 | 0.27 | 1.00 |
| Duration of admission (d) | 6.15 ± 2.277 | 5.602 ± 2.411 | 8.473 ± 8.919 | 5.5 ± 2.556 | < 0.01 | 0.93 | 0.18 | 0.93 |
| Ulcer size (cm) | 1.21 ± 0.65 | 0.86 ± 0.51 | 1.25 ± 0.92 | 1.07 ± 0.80 | < 0.01 | 0.12 | 0.99 | 0.80 |
| Needs for transfusion (PRC no.) | 2.35 ± 2.46 | 2.21 ± 1.98 | 3.53 ± 4.94 | 2.53 ± 1.74 | 0.06 | 0.99 | 0.29 | 0.99 |
| Re-bleeding case upon admission: | 6 | 8 | 2 | 2 | < 0.01 ⁴ | < 0.01 ⁴ | < 0.01 ⁴ | < 0.05 ⁴ |
| Re-admission | 2 | 3 | 4 | 2 | 0.30 ⁴ | 0.17 ⁴ | 0.60 ⁴ | 1 ⁴ |
| Past history of ulcer | 6 | 25 | 2 | 8 | < 0.01 ⁴ | 0.57 ⁴ | < 0.01 ⁴ | 1 |
| Blatchford score | 8.85 ± 4.06 | 8.56 ± 3.71 | 9.78 ± 3.77 | 10.40 ± 3.94 | 0.05 | 0.97 | 0.56 | 0.29 |
| Rockall score | 3.50 ± 1.05 | 3.05 ± 1.54 | 4.73 ± 2.21 | 4.73 ± 1.87 | < 0.01 | 0.52 | 0.02 | 0.04 |

P value by 1-way ANOVA. ¹*P* value by *post-hoc* test (Dunnett test between Idiopathic and *H. pylori*-associated); ²*P* value by *post-hoc* test (Dunnett test between Idiopathic and Drug-induced); ³*P* value by *post-hoc* test (Dunnett test between Idiopathic and Combined); ⁴*P* value by Fisher's exact test values shown as mean ± SD. PUB: Peptic ulcer bleeding; PRC: Packed red cell; *H. pylori*: *Helicobacter pylori*.

108 patients, whereas the drug induced PUB group included 74 patients who used aspirin ($n = 35$), anti-platelet agents ($n = 17$) and NSAIDs ($n = 43$). Twenty-one patients (28.4%) took two or more drugs. The combined type PUB group included 30 patients who used aspirin ($n = 13$), anti-platelet agents ($n = 5$) and NSAIDs ($n = 18$). Six patients (20.0%) took two or more drugs. Significant differences were found for age, sex, location of the ulcer, duration of admission, rate of re-bleeding after initial hemostasis, and the Blatchford and the Rockall scores among the four groups (Table 1).

Idiopathic (*H. pylori*-negative and drug-negative) peptic ulcer bleeding

The patient group consisted of 19 men (95%) and 1 woman (5%), and the mean age was 55.15 ± 12.33 years. The frequencies of gastric ulcer and duodenal ulcer were 60% (12/20) and 30% (6/20), respectively. The frequency of combined gastric and duodenal ulcers was 10% (2/20). When idiopathic PUB was compared to *H. pylori*-associated PUB, the idiopathic PUB group showed a higher rate of re-bleeding after initial hemostasis during the hospital stay (30% vs 7.4%, *P*

Table 2 Univariate and multivariate analysis between idiopathic and *Helicobacter pylori*-associated peptic ulcer bleeding

| | Idiopathic PUB (<i>n</i> = 20) | <i>Helicobacter pylori</i> -associated PUB (<i>n</i> = 108) | <i>P</i> value ¹ | OR (95%CI) ¹ | <i>P</i> value ² | OR (95%CI) ² |
|---------------------------------|------------------------------------|---|-----------------------------|-------------------------|-----------------------------|-------------------------|
| Age | | | 0.71 | 1.224 (0.43-3.49) | 0.94 | 1.04 (0.34-3.18) |
| ≥ 60 yr | 6 | 28 | | | | |
| < 60 yr | 14 | 80 | | | | |
| Ulcer size | | | 0.06 | 2.55 (0.96-6.77) | 0.15 | 2.13 (0.76-5.95) |
| ≥ 1.0 cm | 12 | 40 | | | | |
| < 1.0 cm | 8 | 68 | | | | |
| Re-bleeding case upon admission | | | | | | |
| Yes | 6 | 8 | < 0.01 | 5.36 (1.62-17.74) | 0.02 | 4.56 (1.34-15.54) |
| No | 14 | 100 | | | | |

¹*P* value and OR (95%CI) by univariate logistic regression analysis; ²*P* value and OR (95%CI) by multivariate logistic regression analysis. PUB: Peptic ulcer bleeding.

Table 3 Univariate and multivariate analysis between idiopathic and drug-induced peptic ulcer bleeding

| | Idiopathic PUB (<i>n</i> = 20) | Drug-induced PUB (<i>n</i> = 74) | <i>P</i> value ¹ | OR (95%CI) ¹ | <i>P</i> value ² | OR (95%CI) ² |
|---------------------------------|------------------------------------|--------------------------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
| Age | | | < 0.01 | 0.16 (0.05-0.47) | < 0.01 | 0.12 (0.03-0.55) |
| ≥ 60 yr | 6 | 54 | | | | |
| < 60 yr | 14 | 20 | | | | |
| Sex | | | < 0.01 | 19.00 (2.42-149.36) | 0.06 | 8.59 (0.94-83.82) |
| Male | 19 | 37 | | | | |
| Female | 1 | 37 | | | | |
| Ulcer type | | | 0.02 | 4.86 (1.37-17.29) | 0.08 | 3.86 (0.85-17.55) |
| Duodenal ulcer | 6 | 6 | | | | |
| Others | 14 | 68 | | | | |
| Ulcer size | | | 0.60 | 1.31 (0.48-3.58) | 0.16 | 2.65 (0.68-10.29) |
| ≥ 1.0 cm | 12 | 39 | | | | |
| < 1.0 cm | 8 | 35 | | | | |
| Re-bleeding case upon admission | | | | | | |
| Yes | 6 | 2 | < 0.01 | 15.43 (2.82-84.43) | < 0.01 | 19.76 (2.39-162.91) |
| No | 14 | 72 | | | | |

¹*P* value and OR (95%CI) by univariate logistic regression analysis; ²*P* value and OR (95%CI) by multivariate logistic regression analysis. PUB: Peptic ulcer bleeding.

< 0.01) (Table 2). When idiopathic PUB was compared to drug-induced PUB, the patients in the drug-induced PUB group were older (55.15 ± 12.33 years vs 68.49 ± 14.76 years, $P < 0.01$). In addition, the idiopathic PUB group showed a higher rate of re-bleeding after initial hemostasis upon admission (30% vs 2.7%, $P < 0.01$) (Table 3).

Drug-induced peptic ulcer bleeding

When drug-induced PUB was compared to *H. pylori*-associated PUB, significant differences in age, sex, proportion of gastric ulcers, ulcer size, duration of admission, and Blatchford and Rockall scores were found. A multivariate analysis of the covariates that showed statistical significance in the univariate analysis was performed; the results showed that drug-induced PUB was more common in older patients (68.49 ± 14.76 years vs 47.83 ± 15.15 years, $P < 0.01$). The drug-induced PUB group had equal numbers of men and women, whereas the *H. pylori*-associated PUB group had a predominantly male pattern (50% vs 82%, $P = 0.03$). In the drug-induced PUB group, ulcers were more likely to occur in the stomach (77%

vs 49%, $P < 0.01$), and the duration of admission was longer (8.47 ± 8.92 d vs 5.60 ± 2.41 d, $P = 0.04$). However, the Blatchford and the Rockall scores were not significantly different between the two groups (Table 4).

Combined type (*H. pylori* associated and drug induced) peptic ulcer bleeding

When the combined type PUB was compared to *H. pylori*-associated PUB, the patients in the combined type PUB group were older (63.87 ± 14.79 years vs 47.83 ± 15.15 years, $P < 0.01$) and had a dominant pattern of gastric ulcers (70% vs 49%, $P < 0.01$). Additionally, the Blatchford and the Rockall scores were higher ($P < 0.01$). When the combined type PUB was compared to drug-induced PUB, no significant differences in the characteristics and clinical outcomes were found. The pattern of combined type of PUB was similar to that of drug-induced PUB.

DISCUSSION

The progressive decline of *H. pylori* infection and the

Table 4 Univariate and multivariate analysis between drug-induced and *Helicobacter pylori*-associated peptic ulcer bleeding

| | Drug-induced PUB (n = 74) | <i>Helicobacter pylori</i> -associated PUB (n = 108) | P value ¹ | OR (95%CI) ¹ | P value ² | OR (95%CI) ² |
|-----------------------|------------------------------|---|----------------------|-------------------------|----------------------|-------------------------|
| Age | | | < 0.01 | 7.71 (3.95-15.07) | < 0.01 | 4.51 (1.83-11.11) |
| ≥ 60 yr | 54 | 28 | | | | |
| < 60 yr | 20 | 80 | | | | |
| Sex | | | < 0.01 | 0.21 (0.11-0.42) | 0.03 | 0.39 (0.17-0.91) |
| Male | 37 | 89 | | | | |
| Female | 37 | 19 | | | | |
| Ulcer type | | | < 0.01 | 3.48 (1.80-6.73) | < 0.01 | 4.09 (1.73-9.64) |
| Gastric ulcer | 57 | 53 | | | | |
| Others | 17 | 55 | | | | |
| Ulcer size | | | 0.03 | 1.95 (1.07-3.57) | 0.62 | 0.82 (0.37-1.81) |
| ≥ 1.0 cm | 39 | 40 | | | | |
| < 1.0 cm | 35 | 68 | | | | |
| Creatinine | | | 0.61 | 0.85 (0.47-1.55) | 0.11 | 0.52 (0.23-1.16) |
| ≥ 1.0 mg/dL | 41 | 64 | | | | |
| < 1.0 mg/dL | 33 | 44 | | | | |
| Duration of admission | | | < 0.01 | 2.71 (1.45-5.07) | 0.04 | 2.28 (1.04-5.00) |
| ≥ 7 d | 36 | 28 | | | | |
| < 7 d | 38 | 80 | | | | |
| Needs for transfusion | | | 0.43 | 1.28 (0.70-2.34) | 0.62 | 1.23 (0.55-2.76) |
| ≥ 3 PRCs | 31 | 39 | | | | |
| < 3 PRCs | 43 | 69 | | | | |
| Blatchford score | | | 0.02 | 2.15 (1.16-3.96) | 0.2 | 1.70 (0.76-3.82) |
| ≥ 10 points | 48 | 51 | | | | |
| < 10 points | 26 | 57 | | | | |
| Rockall score | | | < 0.01 | 3.94 (2.09-7.43) | 0.49 | 1.35 (0.58-3.13) |
| ≥ 4 points | 51 | 40 | | | | |
| < 4 points | 23 | 68 | | | | |

¹P value and OR (95%CI) by univariate logistic regression analysis; ²P value and OR (95%CI) by multivariate logistic regression analysis. PUB: Peptic ulcer bleeding; PRC: Packed red cell.

increasing use of NSAIDs and aspirin have changed the etiologic distribution of PUB in the last two decades. In this study, the prevalence of *H. pylori* infection was 59.5%. This finding is consistent with other studies that have found a prevalence of *H. pylori* infection ranging from 61%-68%^[13,14]. In the diagnosis of an idiopathic ulcer, the exclusion of an *H. pylori* infection is crucial, and the validity of the drug use history should be checked. Recently, Yoon *et al*^[6] reported that idiopathic peptic ulcer disease was an independent risk factor for ulcer recurrence. However, in this study, 14.3% of idiopathic ulcer patients were determined only by rapid urease test without histologic evaluation, it may be difficult to completely exclude the possibility that *H-pylori* positive patients might be included in the idiopathic peptic ulcer group^[6]. In the present study, to avoid an inaccurate diagnosis of *H. pylori* infection, we determined the *H. pylori* status twice by delayed diagnostic methods including histology. Furthermore, we performed the different types of diagnostic methods, such as *H. pylori* antibody tests, and confirmed the negative results. Then, we excluded malignancy, and other stressful conditions such as trauma, burns and multi-organ failure. Previously, several studies have reported that idiopathic ulcer disease has a higher recurrence rate than *H. pylori*-associated peptic ulcers, and its long-term recurrence rate is significantly higher than that of drug-induced

peptic ulcers as well as *H. pylori*-associated peptic ulcers^[3-6]. However, our results revealed no significant difference in long term recurrence rates. Further studies that assess the long term results are needed to determine the recurrence of idiopathic PUB compared to *H. pylori*-associated PUB. We also showed that patients with idiopathic PUB had a higher proportion of patients experienced re-bleeding during the hospital stay. Similar results were previously observed, suggesting that patients with idiopathic PUB have a substantial risk of recurrent bleeding^[3,4]. Although we did not evaluate the mortality of PUB directly, recurrent bleeding is known as an independent risk factor that potentially leads to mortality. In particular, in-hospital bleeders were hemodynamically more unstable and had significantly more deaths due to bleeding-related cause^[15,16]. Therefore, patients with idiopathic PUB have a potentially high risk of bleeding related mortality and need to undergo close surveillance upon admission.

Herein, we hypothesized the possible presence of an unidentified pathway that participates in the formation of idiopathic ulcers. Few data regarding the pathogenesis of idiopathic peptic ulcers exist in the literature. Recent studies have suggested that gastroduodenal ulcerations are related to sex hormone secretion. In this study, a predominantly male pattern was typically observed in the idiopathic PUB group,

although this is not statistically significant. Previous studies in different animal species and humans have suggested that sex hormones influence gastric acid secretion and contribute to the integrity of the oral and gastroduodenal mucosa^[17,18]. Another possibility is that the genetic and epigenetic changes in the mucin molecule may be responsible for idiopathic peptic ulcer disease^[19,20]. Iijima *et al.*^[21] proposed several factors including age, systemic complications such as hepatocirrhosis and psychological stress were related to the idiopathic ulcers. However, Kanno *et al.*^[22] reported that older age itself is not a risk factor for idiopathic peptic ulcers. Instead, this study revealed that the presence of multiple underlying comorbidities (such as hypertension, hyperlipidemia and diabetes mellitus) is an important risk factor for idiopathic peptic ulcers compared with simple *H. pylori*-positive ulcers^[22]. In the present study, we excluded hepatocirrhosis patients with moderate to severe portal hypertension, because this condition could affect the severity of PUB. In addition, we did not analyze that underlying comorbid disease between the four PUB subgroups that could be a cause of idiopathic peptic ulcers at least partially through local ischemia of the GI mucosa^[22]. Further research using a prospective design is needed in this area.

One potential limitation of our study was its retrospective design; therefore, possible inherent biases existed. Second, *H. pylori* duodenal colonization or infection with *Helicobacter heilmannii* was not ruled out^[23,24]. Third, a higher drop-out rate was observed in this study, which could be considered a limiting factor. However, we applied strict inclusion criteria for the enrolled patients and eliminated the other confounding factors. Generally, factors that affected the severity of PUB included the presence of conditions related to cardiac or multi-organ failure, particularly in older and comorbid patients, rather than the bleeding itself. In this study, it was noteworthy that we solely compared the severity of the bleeding from the peptic ulcer after excluding underlying diseases such as ischemic heart disease and chronic liver, lung and renal disease.

The high number of emergency admissions for upper gastrointestinal bleeding is due to drug use, especially in older patients^[25,26]. Furthermore, patients with PUB receiving aspirin or NSAIDs therapy are exposed to a greater risk of severe bleeding, which requires a transfusion^[27-29]. In this study, we examined whether the etiologic factors of peptic ulcer disease may be related to more severe clinical outcomes of PUB and whether *H. pylori* infection may influence the severity of PUB. To date, the characteristics and clinical outcomes of PUB according its etiology have not been clearly defined. Our results revealed that no significant difference in the severity of PUB in terms of the Blatchford and the Rockall scores between the drug-induced and *H. pylori*-associated group. Additionally, among the patients who experienced drug-induced PUB, no significant differences in clinical characteristics

and clinical outcomes were observed, irrespective of *H. pylori* infection. Altogether, *H. pylori* infection does not play an important role in the severity of PUB.

In conclusion, definite etiologic factors of PUB including drug and *H. pylori* infection seemed to play an insignificant role in the severity of PUB. Idiopathic PUB had unique and distinct clinical characteristics and outcomes compared to other etiologies of PUB. Clinically, it had a tendency for re-bleeding after initial hemostasis during the hospital stay. Therefore, the patients with idiopathic PUB should be under close surveillance.

COMMENTS

Background

Currently, the number of *Helicobacter pylori* (*H. pylori*)-negative and drug-negative ulcers, the so called "idiopathic" peptic ulcers, is increasing. However, the natural history and the optimal management of idiopathic peptic ulcer bleeding (PUB) remain uncertain.

Research frontiers

Previously, several studies have reported that idiopathic ulcer disease has a higher recurrence rate than *H. pylori*-associated peptic ulcers, and its long-term recurrence rate is significantly higher than that of drug-induced peptic ulcers as well as *H. pylori*-associated peptic ulcers.

Innovations and breakthroughs

In this study, the authors analyzed the clinical characteristics and outcomes of idiopathic PUB and compared different etiologies, including *H. pylori* infection and drug use. We also aimed to assess the severity of PUB among the groups categorized by the different etiologies using the Blatchford and the Rockall scoring systems.

Applications

Idiopathic PUB has unique and distinct clinical characteristics and outcomes compared to other etiologies of PUB. Clinically, it has a tendency for re-bleeding after initial hemostasis during the hospital stay. Therefore, the patients with idiopathic PUB should be under close surveillance.

Terminology

The Blatchford score uses pre-endoscopic clinical and laboratory variables to predict the need for clinical intervention (blood transfusion, endoscopy, surgery). The Rockall score has been developed from mathematical models to predict the risk of death or re-bleeding. Although the Blatchford and the Rockall scores lack subjective variables such as the severity of systemic diseases, these scoring systems have served as risk stratification tools and seem to perform well for predicting mortality.

Peer-review

The study is well written and organized. The issue is very interesting.

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