Risk factors for adverse in-hospital outcomes in acute colonic diverticular hemorrhage

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Abstract

AIM: To investigate the factors associated with transfusion, further bleeding, and prolonged length of stay.

METHODS: In total, 153 patients emergently hospitalized for diverticular bleeding who were examined by colonoscopy were prospectively enrolled. Patients in whom the bleeding source was identified received endoscopic treatment such as clipping or endoscopic ligation. After spontaneous cessation of bleeding with
INTRODUCTION

Colonic diverticular bleeding (CDB) is the most common form of acute lower gastrointestinal bleeding (LGB)\(^1\) and is increasing in Japan\(^\text{[3]}\). A significant proportion of patients with colonic diverticular experience severe, continuous, or refractory bleeding, necessitating a blood transfusion and prolonged hospitalization\([6-8]\). Prevention of poor outcomes requires the identification of high-risk patients who may benefit from intensive inpatient monitoring and early intervention.

We previously reported the use of non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet drugs, and co-morbidities as risk factors for diverticular bleeding\([\text{6,10}]\). However, the impact of these factors on in-hospital outcomes remains unknown. The objective of this study was to elucidate the risk factors associated with in-hospital outcomes such as transfusion requirement, further rebleeding, and prolonged hospitalization.

MATERIALS AND METHODS

Study design, setting, and participants

Patients admitted to our hospital between September 2009 and December 2013 for examination of acute LGB at the endoscopy unit of the National Center for Global Health and Medicine (NCGM) were prospectively enrolled. The NCGM is a large emergency hospital, with 900 beds, located in metropolitan Tokyo, Japan. The Institutional Review Board at NCGM approved this study (approval No. 1579) and all clinical procedures conformed to Japanese and international ethical guidelines (Declaration of Helsinki). All patients gave informed written consent prior to enrolment. Patients from a previous study cohort\([\text{10}]\) and a newly diagnosed cohort were prospectively selected. Inclusion criteria were: (1) > 18 years old; (2) Japanese nationality; (3) overt LGB that was examined within 1 wk of onset; and (4) management as an in-patient. Exclusion criteria were: (1) no informed consent provided; (2) not independent in activities of daily living; (3) not undergoing colonoscopy; (4) LGB due to causes other than CDB; and (5) barium impaction therapy in the randomized controlled trial (ClinicalTrials.gov number
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000002832)\textsuperscript{[9]}. All inclusion criteria were fulfilled before patients were enrolled.

**Data sources and measurements**

The questionnaire survey form asked about the use of NSAIDs, low-dose aspirin, and other antplatelets, as well as warfarin, acetaminophen, and oral corticosteroids. The questionnaire included photographs of all of these oral drugs, as previously reported\textsuperscript{[9]}. Use of a medication was defined as oral administration starting at least 1 mo before the interview. While hospitalized, NSAIDs, low-dose aspirin, other antplatelet drugs, and warfarin were temporarily stopped whenever possible after consulting an cardiologist or neurologist. Hypertension, diabetes mellitus, dyslipidemia, cerebro-cardiovascular disease, chronic liver disease, and chronic kidney disease (CKD) were assessed. Cerebral infarction, cerebral hemorrhage, myocardial infarction, and angina pectoris were considered cerebro-cardiovascular disease. CKD was considered present in patients on hemodialysis or peritoneal dialysis, or in patients with a glomerular filtration rate < 60 mL/min per 1.73 m\textsuperscript{2} for 3 mo. Chronic liver disease included chronic viral hepatitis and alcoholic liver disease.

**Diagnostic criteria and clinical outcome measures**

An electronic high-resolution video endoscope (model CFH260; Olympus Optical, Tokyo, Japan) was used after spontaneous cessation of bleeding. CDB was defined as either definite or presumptive on the basis of colonoscopy with multidetector computed tomography (MDCT)\textsuperscript{[11-13]}. Definitive diagnosis was based on colonoscopic visualization of colonic diverticulum with stigmata of recent hemorrhage (SRH) such as active bleeding, adherent clot, or visible vessel\textsuperscript{[11,12,14]}. A presumptive diagnosis was based on MDCT visualization of the extravasation of contrast medium in colonic diverticulum and colonoscopy showing: (1) a potential bleeding site in an area of positive MDCT findings\textsuperscript{[13]}; (2) fresh blood localized to colonic diverticulum in the presence of a potential bleeding source on complete colonoscopy; or (3) bright red blood in the rectum confirmed by objective color testing and colonoscopy demonstrating a single potential bleeding source in the colon, complemented by negative upper endoscopy or negative capsule endoscopy\textsuperscript{[11,12]}. Patients in whom the bleeding source was identified received endoscopic treatment such as clipping or endoscopic ligation\textsuperscript{[15]}. The clinical outcomes assessed were need for transfusion (≥ 2 units) within 24 h of admission or during hospitalization, further bleeding after spontaneous cessation of hemorrhage, and length of hospital stay. Cases requiring a transfusion ≥ 2 units were considered severe bleeding cases\textsuperscript{[16,17]}. During hospitalization, blood transfusion was indicated for patients when the hemoglobin level fell below 7.0 g/ dL, or 8.0 g/dL in those showing unstable vital signs. Further bleeding was defined as significant fresh bloody or maroon-colored stools (> 200 mL) along with unstable vital signs, a systolic blood pressure ≤ 90 mmHg or pulse ≥ 110 beats/min, and lack of response to 2 or more units of transfused blood during a 24-h period. In these cases, colonoscopy was performed to evaluate the bleeding source in addition to anoscopy or MDCT wherever possible. After spontaneous cessation of bleeding with conservative treatment or hemostasis with endoscopic treatment, all patients were started on a liquid food diet and gradually progressed to a solid diet over 3 d, and they were later discharged.

**Statistical analysis**

To determine the risk factors associated with inhospital outcome in patients with CDB, we conducted multiple logistic regression analysis, using the backward elimination method, of factors found to be significant (P < 0.05) on univariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The ORs for transfusion need within 24 h of admission or hospitalization, further bleeding, and prolonged length of hospital stay were estimated. Prolonged hospital stay was defined as ≥ 8 d, which was the median length in this study. A value of P < 0.05 was considered significant. All statistical analysis was performed using Stata version 10 software (StataCorp, College Station, Texas, United States). The statistical methods of this study were reviewed by Takuro Shimbo from the Department of Clinical Research and Informatics, National Center for Global Health and Medicine.

**RESULTS**

**Participants**

During the study period, 378 patients were admitted to our hospital for acute LGIB. After exclusion of ineligible patients, 153 patients with CDB were analyzed in this study. Of these patients, 18% (27/153) had colonoscopic evidence of a diverticulum with SRH: 63% (17/27) in the ascending colon, 19% (5/27) in the transverse colon, 3.7% (1/27) in the descending colon, and 15% (4/27) in the sigmoid colon. All patients with SRH in diverticula were treated by endoscopic procedures such as clipping (18/27) and ligation (9/27). No patients required angiographic embolization or surgical resection during hospitalization. Patient characteristics are shown in Table 1. Approximately half of the patients were elderly (> 70 years). Drugs commonly used by these patients were NSAIDs and low-dose aspirin. The most common comorbidities were hypertension (64%), diabetes mellitus (20%), dyslipidemia (21%), cerebro-cardiovascular disease (26%), chronic liver disease (3.9%), and CKD (8.5%).

**In-hospital outcomes**

Clinical outcomes of patients with diverticular bleeding
Table 1 Baseline characteristics (n = 153) a (%)  

| Characteristic                          | n (%)     |
|----------------------------------------|-----------|
| Age (yr), median (IQR)                 | 72 (60-79) |
| Age > 70 yr                            | 82 (54)   |
| Sex, M/F                               | 102 (67)/51 (33) |
| Current smoker                         | 41 (27)   |
| Current drinker                        | 108 (71)  |
| NSAIDs                                 | 41 (27)   |
| > 1 mo administration                  | 27 (18)   |
| Low-dose aspirin (< 100 mg)            | 38 (25)   |
| > 1 mo administration                  | 38 (25)   |
| Non-aspirin antiplatelets              | 29 (19)   |
| > 1 mo administration                  | 28 (18)   |
| Sarpogrelate hydrochloride             | 2 (0.3)   |
| Ethyl isocapentate                     | 1 (0.7)   |
| Dilazeo                                | 1 (0.7)   |
| Ticlopidine                            | 6 (3.9)   |
| Clopidogrel                            | 10 (6.5)  |
| Clofazol                               | 10 (6.5)  |
| Limaprost alfadex                      | 2 (5.6)   |
| Dipiridamalone                         | 1 (0.7)   |
| Limaprost                              | 1 (0.7)   |
| Warfarin                               | 10 (7.0)  |
| > 1 mo administration                  | 8 (5.0)   |
| Acetaminophen                          | 2 (1.3)   |
| > 1 mo administration                  | 1 (0.7)   |
| Corticosteroids                        | 5 (3.3)   |
| > 1 mo administration                  | 5 (3.3)   |
| Hypertension                           | 98 (64)   |
| Diabetes mellitus                      | 31 (20)   |
| Dyslipidemia                           | 32 (21)   |
| Cerebro-cardiovascular disease         | 40 (26)   |
| Chronic liver disease                  | 6 (3.9)   |
| Chronic kidney disease                 | 13 (8.5)  |

IQR: Interquartile range; NSAIDs: Non-steroidal anti-inflammatory drugs.

are shown in Table 2. At least 2 units of packed red blood cells were required by 34 patients (22%) within 24 h of admission, of which 13 patients (38%) required 2 units, 10 patients (29%) required 4, 6 patients (18%) required 6, and 5 patients (15%) required > 8. Univariate analysis revealed that age > 70 years (P = 0.03), female sex (P = 0.02), low-dose aspirin use (P = 0.01), warfarin use (P < 0.01), cerebro-cardiovascular disease (P < 0.01), and CKD (P = 0.04) were significantly associated with transfusion need with 24 h of admission (Table 3). Multivariate analysis showed that female sex (OR = 2.7, 95%CI: 1.2-6.2, P = 0.02), warfarin use (OR = 7.2, 95%CI: 1.8-29, P < 0.01), and CKD (OR = 3.6, 95%CI: 1.0-12, P = 0.04) were independent risk factors for transfusion need within 24 h of hospitalization (Table 3).

During hospitalization, 40 patients (26%) received a median of 6 (interquartile range [IQR]: 4-8) units of packed red blood cells. Univariate analysis revealed that age > 70 years (P < 0.01), female sex (P = 0.03), low-dose aspirin use (P = 0.03), warfarin use (P < 0.01), cerebro-cardiovascular disease (P = 0.02), and CKD (P < 0.01) were significantly associated with transfusion need (Table 4). Multivariate analysis revealed that female sex (OR = 2.5, 95%CI: 1.1-5.6, P = 0.02), warfarin use (OR = 9.3, 95%CI: 2.2-40, P < 0.01), and CKD (OR = 5.9, 95%CI: 1.7-20, P < 0.01) were independent risk factors for transfusion (Table 4).

During hospitalization, 6 patients (3.9%) experienced further bleeding. Use of NSAIDs was significantly greater among these patients (9.8%, 4/41) than patients with no further bleeding (1.8%, 2/112) (OR = 5.9, 95%CI: 1.0-34, P = 0.04). Patients with colonoscopic evidence of SRH in diverticulum treated by endoscopic procedures also had a significantly higher rate of further bleeding (15%, 4/27) compared with patients with presumptive bleeding (1.6%, 2/126) (OR = 11, 95%CI: 1.9-62, P < 0.01).

Median (IQR) length of hospital stay was 8 (6-11) days. Univariate analysis indicated that age > 70 years (P = 0.02) and NSAID use (P = 0.02) were significantly associated with prolonged hospitalization (Table 5). Multivariate analysis revealed that age > 70 years (OR = 2.1, 95%CI: 1.0-4.2, P = 0.04) and NSAID use (OR = 2.7, 95%CI: 1.1-6.4, P = 0.03) were independent risk factors for prolonged hospitalization (Table 5).

**DISCUSSION**

This study focused on drugs and diseases associated with poor clinical outcome of diverticular bleeding during hospitalization. Female sex, warfarin use, and CKD were associated with significantly greater risk of transfusion need, while NSAID use was associated with significantly greater risk of further bleeding during hospitalization and subsequently prolonged stay.

In this study, patients using NSAIDs had a 5.9-fold greater risk of further bleeding. Refractory bleeding during hospitalization is likely to prolong hospital stay, and several studies have shown a positive association between NSAIDs and the occurrence of diverticular bleeding. A prospective, large cohort study found that NSAID users had a 1.7-fold higher risk of CDB[19], and other case-control studies have reported increased bleeding risks of 4-15 fold[20-21] and re-bleeding risks of 3-6 fold[22,23]. Wilcox et al.[24] compared 105 patients with LGIB and 1895 non-bleeding controls and found that NSAID users had a 3.4-fold higher risk of CDB. Although the range of risk increases was wide, likely due to differences in study design or sample size, it is clear that NSAID use is an unequivocal risk factor for CDB.

Warfarin use was an independent risk factor for...
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Table 3  Risk factors for transfusion need within 24 h of admission (n = 153)

| None/transfusion within 24 h (n = 119/34) | Crude OR (95%CI) | P value | Adjusted OR (95%CI) | P value |
|-----------------------------------------|------------------|--------|---------------------|--------|
| Age > 70 yr                              | 58 (49)/24 (71)  | 2.5 (1.1-5.7) | 0.03               |        |
| Female                                  | 34 (29)/17 (50)  | 2.5 (1.1-5.5) | 0.02               | 2.7 (1.2-6.2) | 0.02 |
| Current smoker                          | 28 (24)/13 (38)  | 2.0 (0.89-4.5) | 0.09               |        |
| Current drinker                         | 80 (67)/28 (82)  | 2.3 (0.87-5.9) | 0.09               |        |
| NSAIDs                                  | 32 (27)/9 (26)   | 0.98 (0.41-2.3) | 0.96               |        |
| Low-dose aspirin                        | 24 (20)/14 (41)  | 2.8 (1.2-6.3) | 0.01               |        |
| Non-aspirin antiplatelets               | 20 (17)/9 (26)   | 1.8 (0.72-4.4) | 0.21               |        |
| Warfarin                                | 4 (3.4)/6 (18)   | 0.32 (1.6-23) | < 0.01             |        |
| Acetaminophen                           | 2 (1.7)/0        | 1.5 (0-19) | 1.0                |        |
| Corticosteroids                         | 5 (4.2)/0        | 0.51 (0.3-8.3) | 0.56               |        |
| Hypertension                            | 73 (61)/25 (74)  | 1.8 (0.75-4.1) | 0.20               |        |
| Diabetes mellitus                       | 25 (21)/6 (18)   | 0.81 (0.30-2.2) | 0.67               |        |
| Dyslipidemia                            | 25 (21)/7 (21)   | 0.97 (0.36-2.5) | 0.96               |        |
| Cerebro-cardiovascular disease          | 25 (21)/13 (44)  | 3.0 (1.3-6.7) | < 0.01             |        |
| Chronic liver disease                   | 6 (5.0)/0        | 0.41 (0.3-0.3) | 0.43               |        |
| Chronic kidney disease                  | 7 (5.9)/6 (18)   | 3.4 (1.1-11) | 0.04               | 3.6 (1.0-12) | 0.04 |

1Multiple logistic regression analysis, using the backward elimination method, of factors found to be significant (P < 0.05) on univariate analysis; 2Analysis by exact logistic regression. NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 4  Risk factors for transfusion need during hospital stay (n = 153)

| None/Transfusion in hospital (n = 119/34) | Crude OR (95%CI) | P value | Adjusted OR (95%CI) | P value |
|-----------------------------------------|------------------|--------|---------------------|--------|
| Age > 70 yr                              | 53 (47)/29 (73)  | 3.0 (1.4-6.6) | < 0.01             |        |
| Female                                  | 32 (28)/19 (48)  | 2.3 (1.1-4.8) | 0.03               | 2.5 (1.1-5.6) | 0.02 |
| Current smoker                          | 27 (24)/14 (35)  | 1.7 (0.79-3.7) | 0.38               |        |
| Current drinker                         | 76 (67)/32 (80)  | 1.9 (0.82-4.6) | 0.13               |        |
| NSAIDs                                  | 29 (26)/12 (30)  | 1.2 (0.56-2.8) | 0.6                |        |
| Low-dose aspirin                        | 23 (20)/15 (38)  | 2.3 (1.1-5.2) | 0.03               |        |
| Non-aspirin antiplatelets               | 18 (16)/11 (28)  | 2.0 (0.85-4.7) | 0.11               |        |
| Warfarin                                | 3 (2.7)/7 (19)   | 1.8 (0.3-32) | < 0.01             |        |
| Acetaminophen                           | 2 (1.8)/0        | 1.2 (0.1-15) | 1.0                |        |
| Corticosteroids                         | 3 (2.7)/2 (5.0)  | 1.9 (0.31-12) | 0.48               |        |
| Hypertension                            | 68 (60)/30 (75)  | 2.0 (0.88-4.5) | 0.10               |        |
| Diabetes mellitus                       | 24 (21)/7 (18)   | 0.79 (0.31-2.0) | 0.61               |        |
| Dyslipidemia                            | 23 (20)/9 (23)   | 1.1 (0.47-2.7) | 0.77               |        |
| Cerebro-cardiovascular disease          | 24 (21)/16 (40)  | 2.5 (1.1-5.4) | 0.02               |        |
| Chronic liver disease                   | 5 (4.4)/1 (2.5)  | 0.55 (0.06-4.9) | 0.6                |        |
| Chronic kidney disease                  | 5 (4.4)/8 (20)   | 5.4 (1.7-18) | < 0.01             | 5.9 (1.7-20) | < 0.01 |

1Multiple logistic regression analysis, using the backward elimination method, of factors found to be significant (P < 0.05) on univariate analysis; 2Analysis by exact logistic regression. NSAIDs: Non-steroidal anti-inflammatory drugs.

transfusion need within 24 h of admission and for prolonged hospitalization. Approximately 80% of CDB cases spontaneously resolve[6,22], but our findings indicate that patients on warfarin are more likely to experience severe rebleeding[25]. Toyoda et al.[26] recorded bleeding events in 4099 patients with stroke and cardiovascular disease and found that both life-threatening and major gastrointestinal bleeding and major intracranial bleeding were higher in patients on warfarin than those on antiplatelets. We suggest that warfarin may be more effective against clot formation than NSAIDs or antiplatelets.

In addition to drugs, CKD was associated with greater risk of transfusion need. Intermittent use of heparin for dialysis treatment and the presence of uremia-induced platelet dysfunction are associated with GI bleeding[27,28]. Patients with CDK also demonstrate abnormalities in blood coagulation and a bleeding predisposition, resulting in consistent anemia in upper gastrointestinal bleeding (UGIB) cases[28,29]. Thus, CKD patients with UGIB or LGIB should be managed carefully. Furthermore, such cases may become more common, as CKD and the concomitant need for dialysis are on the rise[28].

The strength of the present study is that all subjects underwent colonoscopy with other modalities, which enabled us to apply the strictest definition of diverticular bleeding. Moreover, data on comorbidities, smoking, alcohol consumption, and medication were collected prospectively. Nonetheless, there are several limitations of this study. First, while serious LGIB is lower in patients on selective cyclooxygenase (COX)-2
inhibitors compared with non-selective NSAIDs[30], only 3 patients in this cohort were taking COX-2 inhibitors, precluding an evaluation of their association with CDB outcome. Second, hemodynamic instability[16,17,31], hematocrit ≤ 35%[16], or abnormal white blood cell counts[30] contribute to poor outcome in LGIB, but data for these factors were not collected.

In conclusion, patients hospitalized for diverticular bleeding could be treated endoscopically and conservatively. Re-bleeding rate during hospitalization was low, but there was a substantial need for transfusion and prolonged hospitalization. Advanced age, female sex, NSAIDs, warfarin, and CKD increase the risk of an adverse clinical outcome in hospitalized patients with colonic diverticular bleeding.

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