

Investigation of risk factors predicting recurrence of colonic diverticular hemorrhage and development of a recurrence risk score

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Abstract

Aim : Colonic diverticular hemorrhage often recurs. Several studies have identified risk factors for recurrence, but to our knowledge, none have focused on risk factors in the clinical situation. The present study aimed to identify risk factors for the recurrence of hemorrhage and to create a recurrence risk score.

Method : Hospitalized patients diagnosed with diverticular bleeding from 2008 to 2013 (N = 151) were included in a retrospective cohort study. Risk factors predicting re-bleeding were identified using multivariate analysis, and a risk score was developed using receiver operator characteristic (ROC) analysis.

Results : Recurrence was identified in 52 patients (34.4%) at a median interval of 11.5 months. A history of hypertension and hyperlipidemia, a faster heart rate on admission, and longer hospitalization period were significant risk factors for re-bleeding. We developed a re-bleeding risk score by using these 4 factors ; the area under the curve of ROC curve was 0.8. With this risk score, if the cut-off point is 7, then the sensitivity is very high (94% ; specificity : 26%) ; if the cutoff point is 14, the specificity is very high (97% ; sensitivity : 40%). This enables the division of patients into 3 groups : high risk, intermediate risk, and low risk.

Conclusion : Colonic diverticular hemorrhage often recurs, and patients have high recurrence rates within short periods. Risk factors for re-bleeding include a history of hypertension and hyperlipidemia, faster heart rate, and longer hospitalization period, and the risk score may supply useful information for clinicians to aid management. (*Acta gastroenterol. belg.*, 2014, 77, 408-412).

Key words : colonic diverticular hemorrhage, recurrence, risk factor, risk score.

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Introduction

Colonic diverticulosis is pseudodiverticulum caused by rising pressure in the bowel. The prevalence is 33% at 50 years old, and 60% at 80 years old (1-4). Three to 15% of individuals with diverticular disease present with bleeding. Diverticular hemorrhage is very common and is the main cause of lower gastrointestinal bleeding (1-5). Patients with diverticular hemorrhage present with hematochezia without abdominal pain. It has been shown that a history of hypertension, diabetes mellitus, and ischemic heart disease (IHD), and use of anticoagulants and non-steroidal anti-inflammatory drugs (NSAIDs) are risk factors associated with diverticular hemorrhage (5,6).

While 90% of bleeding episodes resolve spontaneously and are relatively minor, 5% of patients have severe hemorrhage. The recurrence rate is known to be 25-50%, and this high recurrence rate is a major problem for patients (4-6). Several studies have focused on risk factors for recurrence ; they have shown that factors associated with arteriosclerosis (age > 70 years, a history of hypertension, creatinine > 1.5 mg/dl), and use of anticoagulants and NSAIDs were risk factors for recurrent bleeding in multivariate analyses (5,6). However, to our knowledge, no studies have focused on the use of these risk factors in the clinical situation.

The aim of this study was to identify risk factors associated with re-bleeding and to develop a risk score for recurrent bleeding.

Patients and methods

In this retrospective study, we collected the medical records of 151 hospitalized patients diagnosed with colonic diverticular bleeding in the Gastroenterology Department at Asahi General Hospital between January 2008 and January 2013. The incidence of re-bleeding up to December 2013 was determined. For patients who died, the date and cause of death were determined. Data from patients who died of causes other than bleeding or those who were lost to follow-up after discharge were considered censored. All patients underwent colonoscopy or abdominal computed tomography (CT) to exclude other diseases such as colonic cancer, other causes of inflammation, or infection of the colon. Those who underwent colonoscopy were diagnosed based on the criteria described by Jensen *et al.* (7) Recurrent bleeding was diagnosed similarly, and almost all patients underwent colonoscopy or CT again to rule out other causes of hemorrhage. In most of the patients, colonoscopy was performed after using polyethylene glycol-containing lavage solution for colon preparation.

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This study complied with all the provisions of the Declaration of Helsinki. Ethics approval was given by the Ethics Committee of Asahi General Hospital.

Treatments

All treatments were conducted at the discretion of the treating physician in an open-label manner. When active bleeding, a non-bleeding visible vessel, or an adherent clot was not identified on colonoscopy, medical treatment alone was administered. Endoscopic clipping was performed when the bleeding source was identified on colonoscopy. When the bleeding source was not identified because of heavy bleeding, emergency surgical resection was performed after discussion with the surgeon. Blood transfusion was considered according to the transfusion criteria for upper gastrointestinal bleeding described by Villanueva *et al.* (8) because, to our knowledge, there are no guidelines or studies that describe a transfusion strategy for lower intestinal bleeding. In this study, in contrast to previous studies, we did not perform emergency angiography because it was not available. In a previous study, 8 patients from a group of 172 patients underwent angiography, and had no complications (5). All antithrombotic drugs were discontinued; they were resumed in all patients after discharge. IHD was defined as being equivalent to acute coronary syndrome or old myocardial infarction. Cerebral vascular disease was defined as cerebral infarction in this study.

Statistical analysis

The risk factors for re-bleeding were analyzed using Fisher's exact test for categorical outcomes and t-tests or Wilcoxon rank sum test for continuous variables, as appropriate, in the univariate analysis. In the multivariate analysis, logistic regression analysis was used for factors that were significant in the univariate analysis. Any quantitative data that were significant in the multivariate analysis were used for the cutoff point at the median value for developing the risk score. The risk score was determined from the odds ratio (OR) for each factor in the multivariate analysis and was then analyzed by Fisher's exact test for categorical outcomes, and t-tests or the Wilcoxon rank sum test for continuous variables, as appropriate.

Results

The baseline characteristics of all patients are shown in Table 1. The mean age was 70.5 years old (94 men, 57 women). A total of 52 patients (34.4%) experienced a recurrent hemorrhage. The mean length of the initial hospital stay and the mean length of the post-discharge observation period were 6.9 ± 4.1 days and 30.2 ± 17.7 months, respectively (Table 1). The cumulative rates of recurrent hemorrhage in all patients at 12, 18, and 24 months were 20%, 30%, 40%, respectively (Fig. 1).

Total colonoscopy was performed in all patients (N = 151). Of these, 50 patients had diverticular hemorrhage on the right side, 47 on the left side, and 54 patients bilaterally. Endoscopic clipping was performed in 37 patients. All patients were treated successfully and no complications were observed. The patients who were hemodynamically unstable due to the severe hemorrhage underwent surgery within 48 h after initial colonoscopy. No major complications were observed after surgery. Blood transfusion was performed in 47 patients. We compared the first bleeding incident between patients with recurrence (n = 52) and those with no recurrence (n = 99), and investigated the risk factors for recurrence. Then, we developed a risk score for recurrence using factors found to be significant in the multivariate analysis. In univariate analysis, a longer hospitalization period ($P = 0.003$), use of antiplatelet drugs ($P = 0.02$), history of cardiovascular disease ($P = 0.013$), hypertension ($P < 0.001$) and hyperlipidemia ($P < 0.001$), and faster heart rate on admission ($P = 0.02$) were found to be significant (Table 2). We performed multivariate analysis

Table 1. — Clinical characteristics of study patients (N = 151)

Category	Number or mean \pm SD
Age (years)	70.5 \pm 12.2
Sex (male/female)	94/57
Observation period (months)	30.24 \pm 17.7
Hospitalization (days)	6.9 \pm 4.1
Treatment method	
Medical	109
Endoscopic clipping	37
Surgical	3
Body mass index (kg/m ²)	24.3 \pm 4.4
Use of antiplatelet drugs (yes/no)	8/142
Use of anticoagulant drugs (yes/no)	48/103
Use of NSAIDs (yes/no)	18/133
History of hypertension (yes/no)	104/47
History of ischemic heart disease (yes/no)	37/114
History of cerebral vascular disease (yes/no)	23/128
History of diabetes mellitus (yes/no)	30/121
History of hyperlipidemia (yes/no)	49/102
History of smoking (yes/no)	33/60
History of drinking (yes/no)	37/55
Vital signs on admission	
Systolic blood pressure (mmHg)	136 \pm 2.28
Heart rate (bpm)	89.5 \pm 19.6
Laboratory data on admission	
Hemoglobin (g/dL)	11.3 \pm 2.56
Creatinine (mg/dL)	1.23 \pm 1.47
Recurrence of hemorrhage (yes/no)	52/99
Time until rehemorrhage (months)	11.5 \pm 10.4
Blood transfusion (yes/no)	47/104
Position of hemorrhage	
Right side	50
Left side	47
Bilateral	54

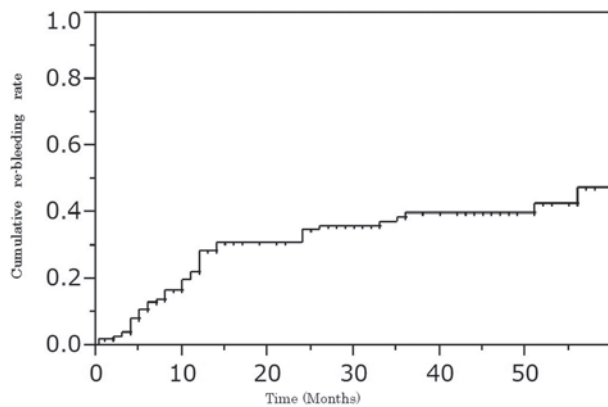


Fig. 1. — Cumulative re-hemorrhage rate in all patient (N = 151).

including these 6 categories. In multivariate analysis, a longer hospitalization period (OR : 1.19 [95% confidence interval 1.05-1.35], $P = 0.005$), history of hypertension (OR : 6.72 [95% confidence interval 2.33-23.5], $P < 0.001$), history of hyperlipidemia (OR : 3.55 [95% confidence interval 1.56-8.35], $P = 0.002$), and heart rate on admission (OR : 1.03 [95% confidence interval 1.01-1.06], $P = 0.01$) were found to be significant risk factors

for recurrent colonic diverticular bleeding. The OR and P values for these factors are shown in detail in Table 3. We then developed a risk score for recurrence using the 4 categories found to be significant in multivariate analysis. The cutoff points for heart rate and hospitalization period were at the median values.

We performed multivariate analysis with 4 categories using the cutoff point again, and determined the risk score for each category from their ORs (Table 4). Considering the data shown in Table 4, risk points were assigned as follows : 7 for history of hypertension, 4 for history of hyperlipidemia and heart rate > 100 bpm, and 3 for hospitalization period > 8 days. The risk score was the sum of the risk points for each category. The recurrence risk score was significantly greater in patients with recurrence (Table 5). We selected cutoff points using the ROC curve (Fig. 2, Table 6). Using this risk score with cutoff points of 7 or 4, the sensitivity is very high (94% and 98%, respectively). With a cutoff of 14 points, the specificity is 97%.

Discussion

Consistent with previous studies, we found that colonic diverticular bleeding often recurs, with 52 patients (33%) experiencing recurrent hemorrhage after initial

Table 2. — Univariate analysis of recurrent hemorrhage risk factors in patients (N = 151)

Category (recurred vs. nonrecurred)	Number or mean \pm SD	P value
Age (years)	72.0 \pm 11.0 vs. 69.8 \pm 12.8	0.29
Sex (male/female)	32/20 vs. 62/37	0.89
Hospitalization time (days)	8.31 \pm 0.55 vs. 6.22 \pm 0.40	0.003
Treatment method		
Medical	37 vs. 74	0.88
Endoscopic clipping	14 vs. 23	
Surgical	1 vs. 2	
Body mass index (kg/m ²)	24.0 \pm 3.70 vs. 24.5 \pm 4.81	0.6
Use of antiplatelet drugs (yes/no)	4/48 vs. 4/95	0.35
Use of anticoagulant drugs (yes/no)	23/29 vs. 25/74	0.02
Use of NSAIDs (yes/no)	8/44 vs. 10/89	0.34
History of hypertension (yes/no)	47/5 vs. 57/42	< 0.001
History of ischemic heart disease (yes/no)	19/33 vs. 18/81	0.013
History of cerebral vascular disease (yes/no)	11/41 vs. 12/87	0.14
History of diabetes mellitus (yes/no)	14/38 vs. 16/83	0.11
History of hyperlipidemia (yes/no)	29/23 vs. 20/79	< 0.001
History of smoking (yes/no)	8/22 vs. 25/38	0.22
History of alcohol consumption (yes/no)	10/18 vs. 27/37	0.56
Vital signs on admission		
Systolic blood pressure (mmHg)	138 \pm 30.2 vs. 136 \pm 26.3	0.57
Heart rate (bpm)	94.4 \pm 22.4 vs. 86.6 \pm 17.3	0.02
Laboratory data on admission		
Hemoglobin (g/dL)	11.1 \pm 2.62 vs. 11.4 \pm 2.53	0.41
Creatinine (mg/dL)	1.23 \pm 1.47	0.79
Blood transfusion (yes/no)	18/34 vs. 29/70	0.5
Position of hemorrhage		
Right side	19/31	0.78
Left side	16/31	
Bilateral	17/37	

Table 3. — Multivariate analysis of recurrent hemorrhage risk factors in patients (N = 151)

Category (recurred vs. nonrecurred)	Odds ratio (95% CI)	P value
History of hypertension (yes/no)	6.72 (2.33-23.5)	< 0.001
History of hyperlipidemia (yes/no)	3.55 (1.56-8.35)	0.002
Heart rate on admission	1.03 (1.01-1.06) ^a	0.01
Hospitalization	1.19 (1.05-1.35) ^a	0.005
Use of anticoagulant drugs (yes/no)	NS	0.522
History of ischemic heart disease (yes/no)	NS	0.7

^aUnit hazard ratio.

Table 4. — Multivariate analysis for developing a risk score for recurrence (N = 151)

Category (recurred vs. nonrecurred)	Odds ratio (95% CI)	P value
History of hypertension (yes/no)	7.41 (2.52-26.6)	< 0.001
History of hyperlipidemia (yes/no)	4.20 (1.83-10.0)	< 0.001
Heart rate >100 bpm (yes/no)	4.31 (1.74-11.4)	0.01
Hospitalization period >8 days (yes/no)	2.94 (1.23-7.29)	0.001

Table 5. — Univariate analysis of the risk score for recurrence

Risk score	Mean ± SD	Odds ratio (95% CI)	P value
Recurred	11.4 ± 0.55	1.43 (1.27-1.63) ^a	< 0.001
Nonrecurred	6.30 ± 0.40	1.00	

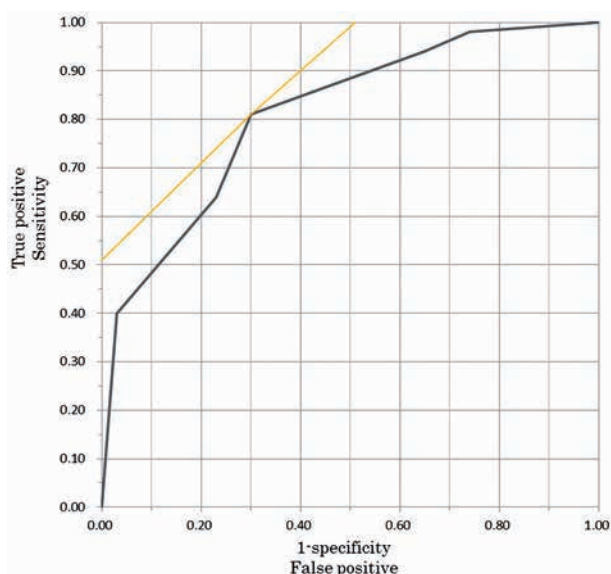
^aUnit hazard ratio.

Fig. 2. — ROC curve of bleeding recurrence score (area under the curve : 0.814).

improvement. The recurrence rate and length of time until re-bleeding were consistent with the results of previous studies (5,6,9). In univariate analysis, longer hospitalization period, use of antiplatelet drugs, history of cardiovascular disease, hypertension, and hyperlipidemia, and heart rate on admission were found to be significant risk factors for recurrent colonic diverticular

bleeding. Others have reported that the risk of colonic diverticular re-bleeding increases with age, obesity (body mass index > 25 kg/m²), history of smoking, use of anti-coagulants, and high creatinine level (5,6,10,11), and that these are linked to the pathophysiology of diverticular hemorrhage, resulting in rupture of an arteriosclerotic altered diverticular vessel (12-14). Niikura *et al.* reported that patients with colonic diverticular bleeding show high recurrence rates within a short period after treatment, and those risk factors for recurrence included the use of NSAIDs or antiplatelet drugs and hypertension (6). Our data were not consistent with this study on the use of NSAIDs, but other factors were comparable. The length of hospitalization period and heart rate are discussed later.

In the multivariate analysis, the length of hospitalization period (OR : 1.19 [95% confidence interval 1.05-1.35], $P = 0.005$, history of hypertension (OR : 6.72 [95% confidence interval 2.33-23.5], $P < 0.001$), history of hyperlipidemia (OR : 3.55 [95% confidence interval 1.56-8.35], $P = 0.002$), and heart rate on admission (OR : 1.03 [95% confidence interval 1.008-1.06], $P = 0.01$) were found to be significant risk factors for re-bleeding. This is consistent with prior studies that have found that risk factors associated with arteriosclerosis are also associated with the risk of recurrent hemorrhage. Our study showed that a longer hospitalization period and faster heart rate were significant risk factors for recurrent bleeding. Thus, patients whose heart rate is fast because of massive bleeding, and whose hospitalization period is

Table 6. — Cutoff points for risk score for recurrence (univariate analysis)

Cutoff point	Sensitivity	Specificity	Odds ratio (95% CI)	P value
4	98.1 (51/52)	26.3 (26/99)	18.2 (2.38-138)	< 0.001
7	94.2 (49/52)	35.4 (35/99)	8.93 (2.59-30.8)	< 0.001
10	80.8 (42/52)	69.7 (99/69)	9.66 (4.29-21.8)	< 0.001
11	63.5 (19/52)	76.8 (99/76)	5.74 (2.76-11.9)	< 0.001
14	40.4 (21/52)	97.0 (96/99)	21.7 (6.05-77.6)	< 0.001

Table 7. — Definition of recurrence risk group based on risk score

Recurrence risk	Risk Score	Sensitivity	Specificity	Recommendation
High	< 14	NS ^a	97	Follow up
Mid	7~14	NS ^a	NS ^a	Follow up
Low	< 7	94.2	NS ^a	No follow up

^a not significant clinically.

long because of an unstable systemic condition, are at high risk of recurrence. In addition, patients in whom it is difficult to control the first bleed are at significantly higher risk of recurrent bleeding.

Although studies have shown that patients with a high risk of recurrence should be followed up carefully (5,6), no previous study has quantified the risk, to our knowledge. We developed a risk score for recurrent bleeding using 4 categories found to be significant in multivariate analysis. As a result, with a cutoff point at 7, the sensitivity is very high (94%). Thus, for patients without hypertension, the recurrence rate is very low. With the cutoff point at 4, the sensitivity is 98%. Therefore, if there is no history of hypertension and none or only 1 other risk factor is present, then the risk of recurrence is almost 0. Clinicians might then not need to follow-up these low-risk patients. With a cutoff at 14 points, the specificity is 97% : that means almost every patient will have recurrence, so they should be followed up carefully for 18 to 24 months due to the cumulative re-bleeding rate (Fig. 1). However, we were not able to assign patients whose scores were between 7 and 13 because these scores have poor sensitivity and specificity. Therefore, according to this risk score, clinicians should follow-up mid- and high-risk patients (Table 7).

There are several limitations of the present study. The study was a retrospective chart review performed in a single center, and the post-discharge observation period was relatively short compared with previous studies. However prior studies that investigated risk factors for recurrent bleeding were performed with a similar length of observation and number of patients, and had similar patient characteristics and results ; therefore, we assert the validity of this study.

In conclusion, we confirmed, for the first time, that besides arteriosclerosis risk factors (hypertension, hyperlipidemia), the difficulty of controlling bleeding at first hospitalization was a risk factor for recurrent bleeding. Furthermore, we developed a useful risk score for recurrent bleeding, and succeeded in assigning patients into 1 of 3 risk categories. This score will provide physicians

with information on which patients should be followed up closely and which patients would benefit most from education regarding risk factors. A prospective multicenter study should be carried out to confirm the findings.

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