

[ORIGINAL ARTICLE]

Clinical Characteristics and Risk Factors for Rebleeding in Patients with Obscure Gastrointestinal Bleeding

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Abstract:

Objective With the advent of capsule endoscopy (CE) and double-balloon endoscopy (DBE), the diagnosis and treatment of obscure gastrointestinal bleeding (OGIB) have markedly progressed. However, rebleeding sometimes occurs and is difficult to diagnose and treat. The aim of the present study was to investigate the clinical features of OGIB and risk factors for rebleeding in our hospital.

Methods A total of 195 patients who underwent CE and/or DBE for OGIB in our hospital from January 2009 to July 2016 were included in the present study. We analyzed 168 cases of small intestinal OGIB, after excluding 27 cases of extra small intestinal bleeding. The clinical characteristics and risk factors related to rebleeding were retrospectively studied.

Results Among the 168 patients who were included in the analysis, 95 patients (56.5%) were male. The mean age was 64.5 years (range, 8 to 87 years). Hypertension (31.0%) was the most frequent comorbidity, followed by chronic kidney disease (19.0%). The final diagnoses were ulcerative lesions (n=50, 29.8%), vascular lesions (n=30, 17.9%), tumors (n=7, 4.2%), and diverticula (n=2, 1.2%). The bleeding source was undetermined in the remaining 79 cases (47.0%). Rebleeding was confirmed in 29 cases (17.3%). In a univariate analysis, chronic kidney disease, vascular lesions, and overt previous bleeding were significantly associated with the risk of rebleeding. A multivariate analysis showed that chronic kidney disease, vascular lesion, and overt previous bleeding were significantly associated with the risk of rebleeding.

Conclusion Patients with OGIB with overt previous bleeding, vascular lesions, and/or chronic kidney disease had a higher risk of rebleeding.

Key words: obscure gastrointestinal bleeding, overt previous bleeding, vascular lesions, chronic kidney disease

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Introduction

Obscure gastrointestinal bleeding (OGIB) is a form of gastrointestinal bleeding whose source is unknown, despite the performance of upper and lower gastrointestinal endoscopy. It accounts for 5% of all cases of gastrointestinal bleeding (1). Many of these cases are caused by small intestinal lesions (2). OGIB is classified into two subtypes in the American Journal of Gastroenterology Clinical Guideline: i) overt bleeding, manifesting as melena or hematochezia; and

ii) occult bleeding, presenting as a positive fecal occult blood test with or without iron-deficiency anemia (3). Overt bleeding is further divided into two groups: i) overt ongoing bleeding (continuous bleeding); and ii) overt previous bleeding (previous bleeding). With the development of capsule endoscopy (CE) (4) and double-balloon endoscopy (DBE) (5), the diagnosis and treatment of OGIB have markedly progressed. However, rebleeding sometimes occurs, and most rebleeding cases are difficult to diagnose and treat. Thus, it is important to identify the characteristics of cases in which rebleeding occurs. The aim of the present study

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Table 1. Patient Characteristics.

Patient characteristics	n=168
Sex (male), n (%)	95 (56.5)
Mean age, years (range)	64.5 (8-87)
Comorbidity, n (%)	
Hypertension	52 (31.0)
Chronic kidney disease	32 (19.0)
Diabetes mellitus	30 (17.9)
Ischemic heart disease	29 (17.3)
Liver cirrhosis	27 (16.1)
Malignant tumors	13 (7.7)
Hematologic disease	10 (6.0)
Anti-thrombotic drugs, n (%)	60 (35.7)
Anti-platelet/Anticoagulant	42/31
NSAIDs, n (%)	57 (33.9)
aspirin/Non-aspirin	35/27
PPI, n (%)	90 (53.6)

NSAIDs: nonsteroidal anti-inflammatory drugs, PPI: proton-pump inhibitor

Table 3. The Final Diagnosis of Rebleeding Cases.

	Positive group (n=21)	Negative group (n=8)	Total (n=29)
Vascular lesions	12	2	14
Ulcerative lesions	8	1	9
Tumors	0	0	0
Diverticula	0	0	0
Unclassified	1	5	6

was to investigate the clinical features of OGIB and risk factors for rebleeding.

Materials and Methods

Study design and patients

This was a single-center, retrospective study. Among 195 patients who underwent CE and/or DBE for OGIB in our hospital from January 2009 to July 2016, 27 patients in whom the source of bleeding was proven to be outside the small intestine were excluded. We investigated the clinical characteristics of the remaining 168 patients. Among these, 148 underwent CE alone, 8 underwent DBE alone, and 39 underwent both CE and DBE. Total enteroscopy was performed in 153 cases. CE was performed with a video capsule endoscopy device (PillCam SB2, or SB3; Given Imaging, Yokneam, Israel). The images were analyzed with the RAPID Reader 6 software program (Given Imaging) on a RAPID 5 or 6.5 workstation (Given Imaging). DBE was performed with a DBE system (FUJIFILM, Saitama, Japan) employed with a FUJIFILM EN-450T5, EN-530T, or EN-580T endoscope. The clinical characteristics and factors related to rebleeding were retrospectively studied. This study was conducted in accordance with Declaration of Helsinki

Table 2. The Final Diagnosis of OGIB Cases.

	Positive group (n=104)	Negative group (n=64)	Total (n=168)
Classified (n=89)			
Vascular lesions	28	2	30
Ulcerative lesions	49	1	50
Tumors	7	0	7
Diverticulum	2	0	2
Unclassified (n=79)	18	61	79

OGIB: obscure gastrointestinal bleeding

and was approved by the Okayama University Hospital Ethics Committee in June 2018.

Variables

Medical records were retrospectively reviewed and evaluated for sex, age, comorbidities, oral medicine, clinical diagnosis, clinical course of the patient and outcome, and presence of rebleeding. Regarding deceased patients, the observation period was defined as the period until the day of death. Therapeutic intervention was defined as any of the various types of therapeutic intervention that were employed [e.g., endoscopic therapy, interventional radiology (IVR), medication, change of orally administered drugs, and surgery].

Types of OGIB bleeding and definition of rebleeding

As mentioned previously, OGIB was divided into three subtypes: overt ongoing bleeding, overt previous bleeding, and occult bleeding. In this study, rebleeding was defined as repeated visible bleeding or progressive anemia requiring repeated endoscopic examination. When the source of rebleeding was not confirmed in the small intestine, upper and lower gastrointestinal endoscopy were repeated in all cases.

Definition of the endoscopic findings and diagnoses

The endoscopic findings were classified as follows: no abnormality, ulcerative lesions (i.e., erosion or ulcer), vascular lesions (i.e., angiectasia, Dieulafoy lesions, or arteriovenous malformation), tumors, diverticula and others. The final diagnosis was made based on the endoscopic findings at not only the first bleeding episode but also rebleeding episodes. The endoscopic diagnosis was performed and discussed by two expert endoscopists (S.K and Y.B). Only definite findings of bleeding were regarded as positive findings.

Comorbidities and medications

Hypertension, chronic kidney disease (CKD), diabetes mellitus, ischemic heart disease, liver cirrhosis, malignant tumors, and hematologic disease were investigated as comorbidities. In this study, CKD was defined by a creatinine level that exceeded the standard laboratory value in our hospital. CKD was further divided into two groups as severe CKD (eGFR<30 mL/min/1.73 m²) or moderate CKD (eGFR 30 to <60 mL/min/1.73 m²). Anti-thrombotic drugs

Table 4. Rebleeding Rates after Therapeutic Intervention.

	OGIB cases		Vascular lesions	
	Total, n	Rebleeding, n (% incidence ratio)	Total, n	Rebleeding, n (% incidence ratio)
Therapeutic intervention	52	11 (21.1)	13	7 (53.8)
Hemostatic treatment	24	6 (25.0)	10	5 (50.0)
Endoscopic therapy	15	6 (40.0)	9	5 (55.6)
Surgery	8	0	0	0
IVR	1	0	1	0
Oral administration change/addition	28	5 (17.9)	3	2 (66.7)
Addition of other drugs	13	2 (15.4)	2	1 (50.0)
NSAIDs change	10	1 (10.0)	0	0
Antithrombotic drug change	5	2 (40.0)	1	1 (100)

IVR: interventional radiology, NSAIDs: nonsteroidal anti-inflammatory drugs, OGIB: obscure gastrointestinal bleeding

Table 5. Clinical Risk Factors for Rebleeding.

	No rebleeding n=139	Rebleeding n=29	p value
Sex (male)	80	15	0.57
Over 70 years	59	13	0.81
Liver cirrhosis	20	7	0.21
Chronic kidney disease	21	11	<0.01
Hemodialysis	6	3	0.23
Antithrombotic drugs	49	11	0.79
NSAIDs	24	3	0.33
Vascular lesions	16	14	<0.01
Overt previous bleeding	65	22	<0.01
Therapeutic intervention	41	11	0.38

NSAIDs: nonsteroidal anti-inflammatory drugs

Results

Patient characteristics

Table 1 shows the clinical characteristics of patients in this study. Among 168 patients, 95 (56.5%) were male, and the mean age was 64.5 years (range, 8-87 years). One-hundred fourteen patients (67.9%) had one or more comorbidities: hypertension was the most common (31.0%), followed by CKD (19.0%), diabetes mellitus (17.9%), ischemic heart disease (17.3%), and liver cirrhosis (16.1%). Sixty patients (35.7%) were taking oral antithrombotic drugs. Forty-two patients were using antiplatelet drugs and 31 were using anticoagulant drugs (including combined use). Fifty-seven patients (33.9%) were using NSAIDs, including aspirin (aspirin, n=35; NSAIDs other than aspirin, n=27). Ninety patients (53.6%) were using PPIs. The median period of observation was 31.5 months. 20 patients died during the observation period. The primary cause of death was progression of comorbidities (n=15). The other causes included sepsis, multiple organ failure, and unknown origin.

Endoscopic findings at the first procedure and final diagnosis

We investigated the endoscopic findings of 168 patients at the first bleeding episode. Endoscopic findings were positive in 104 patients (positive group), while no abnormalities were detected in 64 patients (negative group). The 104 patients in the positive group had ulcerative lesions (erosion and/or ulcer, n=49), vascular lesions (angiectasia, Dieulafoy lesions, and/or arteriovenous malformation, n=28), tumors (n=7), diverticulum (n=2), and unclassified lesions (n=18). In contrast, among the 64 patients in the negative group, vascular lesions (n=2) and ulcerative lesions (n=1) were detected at the second or subsequent bleeding event. Thus, the final diagnoses of 89 patients were as follows: ulcerative lesions (n=50), vascular lesions (n=30), tumors (n=7), and diverticulum (n=2) (Table 2). Seventy-nine patients were unclassified or impossible to diagnose.

were classified into antiplatelet drugs (e.g., aspirin and thienopyridine) and anticoagulants (e.g., warfarin and direct oral anticoagulants). Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, cyclooxygenase (COX) inhibitors (e.g., loxoprofen and diclofenac), and selective COX2 inhibitors (e.g., celecoxib, etodolac, and meloxicam). Proton-pump inhibitors (PPIs) included omeprazole, esomeprazole, lansoprazole, and rabeprazole. The potassium-competitive acid blocker (P-CAB) vonoprazan was not included because it was not administered to any of the patients.

Statistical analysis

Sequential data were expressed as the mean and median. Categorical data were compared using the chi-squared test or Fisher's exact test. Variables with p values of <0.05 in the univariate analysis were included in the multivariate logistic regression models. All statistical analyses were performed using the JMP Pro for Windows software program (version 13). P values of <0.05 were considered to indicate statistical significance.

Table 6. Antithrombotic Drugs Administered to Patients with Rebleeding.

	No rebleeding n=49	Rebleeding n=11	p value
Number of antithrombotic drugs			
Single	30	8	0.47
Multiple	19	3	0.47
Antiplatelet+Anticoagulant	10	3	0.62
DAPT	11	3	0.74
Type of antithrombotic drugs			
Aspirin	29	6	0.77
Ticlopidine	11	4	0.35
Cilostazol	6	0	0.11
Warfarin	20	5	0.77
DOAC	4	2	0.35

DAPT: dual antiplatelet therapy, DOAC: direct oral anticoagulants

Table 7. The Multivariate Analysis of Risk Factors for Rebleeding.

	Odds ratio	Confidence interval	p value
Chronic kidney disease	2.83	(1.06-7.58)	0.04
Vascular lesions	6.45	(2.48-16.72)	<0.01
Overt previous bleeding	3.68	(1.37-9.92)	0.01

Details of rebleeding cases

Rebleeding was confirmed in 29 patients (17.3%). In the positive group, rebleeding was observed in 21 patients (20.2%), with vascular lesion (n=12) being the most frequent diagnosis in cases of rebleeding. There was only one case in which a final diagnosis could not be obtained. In contrast, among the 64 patients in the negative group, rebleeding occurred in 8 patients (12.5%). In three cases, vascular lesions (n=2) and ulcerative lesions (n=1) were identified at the second or subsequent bleeding episode. However, a final diagnosis could not be obtained in 5 cases (62.5%). In the total population of 168 patients, rebleeding occurred in 29 patients (17.3%): vascular lesions (n=14), ulcerative lesions (n=9), and unclassified lesions (n=6). In this study, vascular lesions were the most frequent cause of rebleeding (Table 3). The median observation period from the first bleeding episode to rebleeding was 4 months.

Detail of rebleeding cases after therapeutic intervention

Among 168 patients with OGIB, 52 underwent therapeutic intervention such as endoscopic treatment, surgery, and oral administration change at the first event. Rebleeding occurred in 11 patients (21.1%). Vascular lesions were the most frequent cause of rebleeding (7 patients). In the 11 patients, 5 patients (55.6%) occurred rebleeding after endoscopic treatment. On the other hand, no rebleeding occurred after surgery or IVR (Table 4). In the patients who underwent a therapeutic intervention, rebleeding rate was higher

in those with overt previous bleeding (n=9, 81.8%) than in those with occult bleeding (n=2, 18.2%).

Risk factors for rebleeding

We investigated risk factors for rebleeding. In the univariate analysis, CKD, vascular lesions, and overt previous bleeding were significantly associated with higher risk of rebleeding (Table 5). Intake of any antiplatelet, anticoagulant, or combination use was not a risk factor of rebleeding (Table 6). In the multivariate analysis, CKD, vascular lesions, and overt previous bleeding were independent risk factors of rebleeding (Table 7).

With respect to the relationship between CKD and rebleeding, the rebleeding rate of patients with normal kidney function was 13.2%. In contrast, the rebleeding rate in moderate CKD was 33.3%, and that in severe CKD was 35.2% (Figure). The rebleeding rate in overt bleeding and occult bleeding cases were 22.5% (23 of 102 patients) and 9.1% (6 of 66 patients), respectively. The rebleeding rate in overt bleeding was significantly higher than that in occult bleeding (p=0.02). Additionally, the rebleeding rate in overt previous bleeding and others were 25.6% (22 of 86 patients) and 8.6% (7 of 81 patients), respectively (p<0.01). The rate of overt previous bleeding was significantly higher than that in other bleeding types.

Discussion

We investigated clinical features of patients with OGIB. In this study, we diagnosed OGIB according to the diagnos-

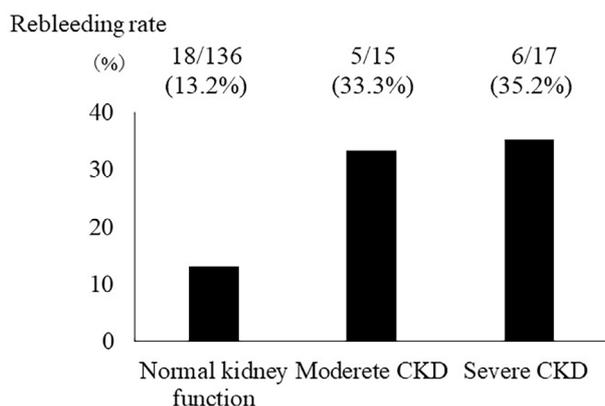


Figure. The rebleeding rates according to the renal function. CKD: chronic kidney disease

tic algorithm of the Japan Gastroenterological Endoscopy Society (6). This algorithm recommends that balloon endoscopy precede CE in cases when abnormalities are identified on enhanced CT and cases with massive bleeding. Thus, we included cases in which only DBE was performed and in which total enteroscopy was not performed.

The multivariate analysis revealed that vascular lesions, overt previous bleeding, and CKD were independent risk factors for rebleeding. At first, vascular lesions often present as multiple lesions and develop synchronously and/or metachronously. Thus, metachronous bleeding can occur naturally. In addition, when the bleeding had stopped at the time of endoscopic observation, it was difficult to distinguish the source of bleeding from multiple vascular lesions. Rebleeding is likely to occur without appropriate hemostasis for bleeding sources. Furthermore, small vascular lesions may be overlooked during an endoscopic examination. For example, in the Yano-Yamamoto classification, punctate erythema (<1 mm) without oozing (i.e., type 1a lesions) and punctate lesions (<1 mm) with pulsatile bleeding (i.e., type 2a lesions) (7) are difficult to detect owing to the small size and subtle appearance. Careful observation is required to detect vascular lesions. Consequently, vascular lesions have been reported in several previous studies as a predictive factor for rebleeding in patients with OGIB (8-10). The results of the present study are consistent with those of previous reports.

In patients with overt previous bleeding, it is often difficult to identify the source of bleeding, because it often spontaneously stops during the endoscopic examination. In contrast, in patients with overt ongoing bleeding, the bleeding source is likely to be recognized during endoscopy (11). To the best of our knowledge, this is the first report to reveal that overt previous bleeding is a risk factor for rebleeding. In this context, patients should be alerted that it is necessary to promptly visit a hospital once they see bloody bowel discharge or tarry stool. It is also important for gastroenterologists to perform enteroscopic examinations immediately (12, 13).

Finally, in this study, CKD was a risk factor for rebleeding of small intestinal OGIB. The moderate and severe CKD

groups showed similar rates of rebleeding, and these were higher the rate in the normal kidney function group. This result indicates that CKD is a risk factor for rebleeding from the small intestine, not only in patients with end-stage kidney disease but also in patients with moderate kidney dysfunction. Ishigami et al. (14) reported that patients with moderate kidney dysfunction (eGFR, 30-59 mL/min/1.73 m²) are more susceptible to gastrointestinal bleeding in comparison to patients with a normal kidney function. Moreover, severe kidney dysfunction (eGFR<30 mL/min/1.73 m²) is associated with a greater risk of rebleeding than moderate kidney dysfunction. It has been hypothesized that the accumulation of uremic toxin in end-stage CKD attenuates platelet aggregation and normal platelet-vascular interaction, resulting in an increased risk of bleeding (15, 16). Another possible reason for the risk of rebleeding in patients with CKD is that although contrast-enhanced CT is described as a useful initial evaluation in the OGIB guideline (6), contrast media are not easily applicable in these cases. Because of the inability to perform contrast-enhanced CT, the bleeding source might be overlooked in some patients.

On the other hand, we could not demonstrate that therapeutic intervention contributed to reducing the risk of rebleeding. One reason for this is that various interventions such as surgery, endoscopic therapy, and oral administered agents or a change of medication were included as treatment interventions. Another reason is that rebleeding could occur from another lesion because in most cases multiple vascular lesions were found in the small bowel.

The present study was associated with some limitations. First, it was a single-center, retrospective study with a relatively small study population, and the effects of selection bias and confounding factors must be considered. Second, in this study, we defined rebleeding as repeated visible bleeding or progressive anemia requiring repeated endoscopic examination. However, since the attending physician decided whether they should perform repeated enteroscopy, some patients might have not undergone enteroscopic examinations even though they had repeated visible bleeding or progressive anemia. As a result, the incidence of rebleeding may have been underestimated.

In conclusion, we investigated the clinical features of OGIB in our hospital and the risk factors for rebleeding. Among patients with vascular lesions, overt previous bleeding, and CKD, there were significant many cases of rebleeding.

The authors state that they have no Conflict of Interest (COI).

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