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ORIGINAL ARTICLE—ALIMENTARY TRACT

Nationwide cohort study identifies clinical outcomes of angioectasia in patients with acute hematochezia

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Abstract

Background While angioectasia is an important cause of acute hematochezia, relevant clinical features remain unclear. This study aims to reveal risk factors, clinical

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outcomes, and the effectiveness of therapeutic endoscopy for patients with acute hematochezia due to angioectasia.
Methods This retrospective cohort study was conducted at 49 Japanese hospitals between January 2010 and December 2019, enrolling patients hospitalized for acute hematochezia (CODE BLUE-J study). Baseline factors and clinical outcomes for angioectasia were analyzed.
Results Among 10,342 patients with acute hematochezia, 129 patients (1.2%) were diagnosed with angioectasia by colonoscopy. The following factors were significantly associated with angioectasia: chronic kidney disease, liver disease, female, body mass index < 25, and anticoagulant use. Patients with angioectasia were at a significant increased risk of blood transfusions compared to those without angioectasia (odds ratio [OR] 2.61; 95% confidence interval [CI] 1.69–4.02). Among patients with angioectasia, 36 patients (28%) experienced rebleeding during 1-year follow-up. The 1-year cumulative rebleeding rates were 37.0% in the endoscopic clipping group, 14.3% in the coagulation group, and 32.8% in the conservative management group. Compared to conservative management, coagulation therapy significantly reduced rebleeding risk ($P = 0.038$), while clipping did not ($P = 0.81$). Multivariate analysis showed coagulation therapy was an independent factor for reducing rebleeding risk (hazard ratio [HR] 0.40; 95% CI 0.16–0.96).
Conclusions Our data showed patients with angioectasia had a greater comorbidity burden and needed more blood transfusions in comparison with those without angioectasia. To reduce rebleeding risk, coagulation therapy can be superior for controlling hematochezia secondary to angioectasia.

Keywords Acute hematochezia · Colonic angioectasia · Rebleeding · Clipping therapy · Coagulation therapy

Abbreviations

ALGIB	Acute lower gastrointestinal bleeding
APC	Argon plasma coagulation
BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
DOAC	Direct oral anticoagulant
eGFR	Estimated glomerular filtration rate
HR	Hazard ratio
OR	Odds ratio
SRH	Stigmata of recent hemorrhage

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Introduction

Gastrointestinal angioectasia are mainly located in the colon, predominantly the cecum and ascending colon [1–3], and colonic angioectasia accounts for 3–40% of patients with acute lower gastrointestinal bleeding (ALGIB) [4–6]. Several studies showed that patients with ALGIB secondary to colonic angioectasia often develop an intermittent and/or recurrent bleeding without abdominal pain [7, 8]. This bleeding from colonic angioectasia may be mild and can stop spontaneously in approximately 40% of patients [9]; nonetheless, as it could be associated with a life-threatening bleeding requiring blood transfusion [10]. Therefore, the prediction factors and management of bleeding angioectasia are important. While some scarce reports showed clinical conditions associated with such bleeding [11–14], contributing factors to acute hematochezia due to colonic angioectasia are not well-understood.

Approximately 40% of patients with ALGIB secondary to angioectasia achieve hemostasis without any interventions [9]; however, therapeutic endoscopy is essential, particularly if there is evidence of acute or chronic blood loss [15]. Although treatment guidelines specialized for gastrointestinal angioectasia are still lacking [16], endoscopic argon plasma coagulation (APC) is considered a first-line treatment for bleeding angioectasia [15, 17]. However, since few studies have focused on colonic angioectasia, the therapeutic impact of APC on clinical outcomes remains unclear. Several studies, including in patients with small intestinal angioectasia, showed no significant differences in long-term outcomes between conservative therapy and APC [18, 19]. Meanwhile, other reports showed that therapeutic endoscopy was effective to initially control bleeding angioectasia, but rebleeding rates may be considerable. A meta-analysis showed a pooled rebleeding rate after endoscopic therapy was 36% during a mean follow-up of 22 months [20]. Several investigations indicated the risk of rebleeding seems to be higher in patients with small intestinal angioectasia than in those with colonic lesions [20, 21], suggesting better outcomes in colonic versus small intestinal angioectasia. While previous studies identified risk factors for rebleeding in patients with small intestinal angioectasia [22–28], contributing factors to the rebleeding in patients with colonic angioectasia have been poorly reported.

A nationwide, multicenter retrospective cohort study (CODE BLUE-J Study: COlonic DivErticular Bleeding Leaders Update Evidence from multicenter Japanese Study) was previously conducted in Japan to understand the usefulness of colonoscopy in patients with acute hematochezia [29, 30], demonstrating that colonoscopy can identify bleeding etiologies in patients with acute hematochezia and enable stratification of patients by risk of adverse clinical outcomes [29, 30].

The present study was designed as a subgroup analysis of patients with angioectasia using the CODE BLUE-J Study database to determine the clinical features and outcomes of patients with acute hematochezia secondary to angioectasia. We assessed efficacies among therapeutic modalities for angioectasia as well as contributing factors to rebleeding.

Materials and methods

Study design and patients

This study was designed as a retrospective, observational, multicenter study of 49 participating Japanese hospitals. We included patients who experienced emergency hospitalization for acute hematochezia between January 2010 and December 2019. The methodology and enrolled patient clinical characteristics were previously described (CODE BLUE-J Study) [29, 30]. The ethics committees of all 49 participating institutions approved this study and the opt-out method of consent (Supplementary Table 1).

Clinical data collection

Baseline factors

All variables were obtained from electronic medical records and endoscopy databases at each participating institution by gastroenterologists or dedicated researchers. The following data were retrospectively collected: age at diagnosis of acute hematochezia, gender, body mass index (BMI), alcohol consumption, smoking status, vital signs, presenting symptoms, history of radiation therapies, comorbidities, medication use within 30 days of admission, laboratory data at the initial admission, hematochezia etiologies, and in-hospital therapies for hematochezia. Chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 lasting more than 3 months [31]. Using the Japanese GFR equation based on serum creatinine [32], eGFR was calculated by serum creatinine levels at the initial admission

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and was categorized into the GFR category defined by the Kidney Disease Improving Global Outcomes (KDIGO) CKD guideline [33].

Etiologies of acute hematochezia were primarily determined by endoscopy and included diverticular bleeding, colitis, ulcerative lesion, hemorrhoid, colorectal cancer, angioectasia, radiation proctitis, small intestinal bleeding, miscellaneous and unknown origin. The definition of angioectasia was a slightly elevated or flat, cherry red spot with a fern-like or regular margin which was identified by colonoscopy. While this analysis included angioectasias localized at the colon or terminal ileum, other small intestinal angioectasias were not evaluated. Stigmata of recent hemorrhage (SRH) was defined as active bleeding, non-bleeding visible vessels and adherent clots [34].

Clinical outcomes

Main outcomes included blood transfusion, length of hospital stays, and rebleeding. Rebleeding was defined as significant amounts of fresh, bloody, or wine-colored stools [35–37] occurring during hospitalization or after discharge. Patients with rebleeding did not necessarily have decreased hemoglobin levels, hemodynamic instabilities, and repeat colonoscopies. There were no criteria for blood transfusions in this study; transfusions were administered at the discretion of providers. Data on endoscopic procedures such as coagulation therapy or the clipping method or only endoscopic observation were collected. Coagulation therapy included APC and endoscopic contact-probe methods, such as monopolar electrocoagulation and bipolar electrocoagulation. Endoscopic procedures for acute hematochezia were selected at the discretion of the endoscopist and in accordance with the policies of each participating hospital.

Statistical analysis for outcomes

To identify factors associated with angioectasia, we compared baseline characteristics between acute hematochezia patients with and without angioectasia. Categorical data were compared using the Fisher's exact test, while continuous data were compared using the Mann–Whitney *U* test. Multivariate logistic regression analysis was also performed to include a priori variables based on previous reports (including older age [2, 12–14], cardiovascular diseases [11, 12], and anticoagulation use [12]) as well as all univariate variables with P values < 0.1. Given laboratory data (e.g., serum creatinine levels) are correlated with clinical conditions (e.g., CKD), our multivariate analysis only included clinical conditions to avoid multicollinearity. Then, we compared clinical outcomes between the two groups. Missing observations were imputed using the most recent previous observation (the last observation carried forward analysis). Multivariate logistic regression analysis was also performed to understand factors associated with blood transfusion and the length of hospital stays.

To determine independent factors associated with time to rebleeding in patients with angioectasia, a Cox proportional hazards model was used. In this multivariate analysis, we included a priori factors associated with angioectasia rebleeding (older age [23, 24], chronic heart disease [25, 26], CKD [25], and chronic hepatitis or liver cirrhosis [27]) as well as all variables with P values < 0.10 in our univariate analysis.

The cumulative rebleeding rate during 1 year of follow-up was estimated using the Kaplan–Meier method and calculated from the date of the initial admission for acute hematochezia to the date of rebleeding. In this analysis, the conservative management group was defined as patients who did not undergo any endoscopic intervention but endoscopic observation. Two patients who were treated with both clipping and coagulation were excluded as curves for cumulative rebleeding rates were compared between patients treated with endoscopic clipping or coagulation therapy and patients treated with conservative managements using the log-rank test. We followed up patients from the date of admission to the occurrence of rebleeding and data were censored at the time of the last visit, the end of follow-up, or death.

A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the statistical package IBM SPSS Statistics ver. 28.0 (IBM Corp., Armonk, New York, USA).

Results

Patient characteristics and contributing factors to angioectasia in patients with acute hematochezia

This study evaluated a total of 10,342 adult patients who experienced emergency admission due to acute hematochezia at the 49 hospitals (Supplementary Table 1) [29]. Among them, an initial colonoscopy was performed in 88% of patients. The most common etiology was colonic diverticular bleeding (63.6%), followed by ischemic colitis (9.1%), and postprocedure bleeding (4.5%). Only 5.1% of patients had unknown etiologies [29]. We identified 133 patients with a final diagnosis of angioectasia (1.3%) and colonoscopy was conducted in 97% of these patients. Four patients were diagnosed with angioectasia based on the combination of a previous history of angioectasia and an exclusion of other diseases by CT scan. The four patients were excluded and 129 patients with angioectasia were ultimately included in our analysis. SRH was identified in

76 patients (59%) and 93% of SRHs were located in the colon, with the ascending colon as the most common SRH location (36%). Six SRHs (7%) were located at the terminal ileum (Supplementary Table 2).

We conducted a univariate analysis to understand contributing factors to angioectasia and found that the frequencies of the following factors were significantly higher in patients with angioectasia than in patients without angioectasia: age $\geq$ 70 years old, female, systolic blood pressure $\leq$ 100 mmHg, chronic heart failure, CKD, liver disease, hypertension, warfarin use, and direct oral anticoagulant (DOAC) use. Meanwhile, the frequencies of male, BMI $\geq$ 25, current alcohol drinker, and abdominal pain were significantly lower in patients with angioectasia compared to patients without angioectasia (Table 1). In terms of laboratory data, hemoglobin levels, white blood cell counts, platelet counts, and albumin levels were significantly lower in patients with anigioectasia than in those without angioectasia (Table 1). Regarding kidney function at the initial admission, creatinine levels in patients with angioectasia were significantly higher than that in patients without angioectasia. Consistently, the proportions of patients who had $\geq$ G3b in the GFR category and required hemodialysis for CKD were significantly higher in patients with angioectasia compared with patients without angioectasia ($P < 0.001$ and $P = 0.021$, respectively). (Supplementary Table 3).

The multivariate analysis revealed that the following factors were significantly associated with angioectasia: female (odds ratio [OR] 2.14; 95% confidence interval [CI] 1.36–3.35; $P < 0.001$), CKD (OR 3.03; 95% CI 1.95–4.69; $P < 0.001$), liver disease (OR 6.95; 95% CI 4.22–11.5; $P < 0.001$), warfarin use (OR 5.70; 95% CI 3.48–9.35; $P < 0.001$), and DOAC use (OR 3.45; 95% CI 1.81–6.56; $P < 0.001$) (Table 2). Meanwhile, BMI $\geq$ 25 and abdominal pain were inversely associated with angioectasia (OR 0.56; 95% CI 0.32–0.99; $P = 0.047$ and OR 0.33; 95% CI 0.14–0.77; $P = 0.010$, respectively) (Table 2).

Clinical outcomes between acute hematochezia patients with and without angioectasia

We compared clinical outcomes between acute hematochezia patients with and without angioectasia. As a result, patients with angioectasia were more likely to require blood transfusion ($P < 0.001$) and larger amounts of transfused blood ($P < 0.001$), and needed longer hospital stays ($P = 0.012$) compared to those without angioectasia (Table 3). There were no significant differences in rebleeding rates during hospitalization, 1-year, and 2-year follow-up after initial hemostasis between the two groups (Table 3).

Logistic regression models adjusted for contributing factors to angioectasia showed that patients with angioectasia had a significant risk of blood transfusions (OR 2.61; 95% CI 1.69–4.02; $P < 0.001$) and their blood transfusion volumes were significantly higher than the volume in those without angioectasia (OR 1.04; 95% CI 1.02–1.06; $P < 0.001$) (Table 3). Our multivariate analysis assessing contributing factors to the risk of blood transfusions among patients with angioectasia showed no significant risk factors. Although the risk of blood transfusion was higher in patients with CKD and male patients, but not significant (OR 2.19; 95% CI 0.95–5.01; $P = 0.065$ and OR 2.03; 95% CI 0.93–4.44; $P = 0.075$, respectively) (Supplementary Table 4).

Contributing factors to rebleeding among patients with acute hematochezia due to angioectasia

Among 129 patients with angioectasia, we identified 36 patients (27.9%) who experienced rebleeding during a 1-year follow-up period after initial hemostasis. To identify contributing factors to the rebleeding events, we conducted a univariate analysis. This revealed that patients treated with coagulation therapies were less likely to experience the rebleeding events than patients who were not treated with coagulation ($P = 0.031$). Furthermore, our multivariate analysis showed that coagulation therapies significantly reduced the risk of rebleeding in patients with angioectasia (Hazard ratio (HR) 0.40; 95% CI 0.16–0.96; $P = 0.039$) (Table 4). Age, chronic heart failure, CKD and liver disease were not associated with rebleeding events in this analysis (Table 4).

Effectiveness of therapeutic endoscopy for acute hematochezia due to angioectasia

Data regarding therapies for angioectasia showed that endoscopic clipping, coagulation therapies, and conservative management were selected in 20.9% (27/129), 32.6% (42/129), and 45.0% (58/129) of patients, respectively. We compared the cumulative rebleeding rate between angioectasia patients treated with endoscopic interventions and those treated with conservative management using Kaplan–Meier curves. Median follow-up time in all groups was 12 months (range 0.067–12). The rates of patients who lost to follow up within 1 year were 26% in the clipping group, 40% in the coagulation group, and 33% in the conservative management group ($P = 0.45$).

The 1-year cumulative rebleeding rates were 37.0% (10/27) in the clipping group, 14.3% (6/42) in the coagulation group, and 32.8% (19/58) in the conservative management group. While there were no differences in the cumulative incidence curves for rebleeding between patients treated

Table 1 Comparative analysis between acute hematochezia patients with and without angioectasia

	All acute hematochezia patients (n = 10,338)		P value
	Angioectasia (+) (n = 129)	Angioectasia (−) (n = 10,209)	
Age ≥ 70 years	100 (78)	6239 (61)	**< 0.001**
Sex (male/female)	57/72 (44/56)	6259/3950 (61/39)	**< 0.001**
BMI ≥ 25	21 (17)	2359 (25)	**0.047**
Current drinker	34 (32)	4096 (47)	**0.003**
Current smoker	24 (21)	1637 (18)	0.47
Hemodynamics			
Systolic blood pressure ≤ 100 mmHg	26 (21)	1286 (13)	**0.012**
Heart rate ≥ 100 bpm	22 (18)	1977 (20)	0.65
Symptom			
Loss of consciousness	5 (4)	662 (7)	0.28
Abdominal pain	10 (8)	1654 (16)	**0.010**
History of colorectal radiation therapy	4 (3)	237 (2)	0.55
Comorbidity			
Diabetes mellitus	26 (20)	1907 (19)	0.66
Cerebrovascular disease	22 (17)	1453 (14)	0.38
Chronic obstructive pulmonary disease	7 (5)	308 (3)	0.12
Dementia	4 (3)	561 (6)	0.33
Connective tissue disease	9 (7)	409 (4)	0.11
Chronic heart failure	34 (26)	818 (8)	**< 0.001**
Chronic kidney disease*	51 (40)	1454 (14)	**< 0.001**
Liver disease	28 (22)	395 (4)	**< 0.001**
Hypertension	84 (65)	5755 (56)	**0.050**
Hyperlipidemia	32 (25)	2789 (27)	0.55
Medication			
Low dose aspirin	33 (26)	2023 (20)	0.12
Thienopyridines	11 (9)	1003 (10)	0.77
Cilostazol	2 (2)	241 (2)	0.77
Warfarin	40 (31)	665 (7)	**< 0.001**
DOAC	18 (14)	596 (6)	**< 0.001**
Corticosteroid	11 (9)	568 (6)	0.17
Initial laboratory data			
Hemoglobin (g/dL), median (range)	7.6 (3.4–13.3)	11.4 (2.7–19.3)	**< 0.001**
White blood cell (/μL), median (range)	5300 (1140–19,310)	7200 (600–167,910)	**< 0.001**
Platelets (10^4 /μL), median (range)	15.6 (3.5–45.0)	20.8 (0.2–133)	**< 0.001**
Albumin (g/dL), median (range)	3.4 (1.6–4.5)	3.7 (1.0–8.8)	**< 0.001**
Creatinine (mg/dL), median (range)	1.03 (0.4–11.7)	0.84 (0.07–15.2)	**< 0.001**
eGFR (ml/min/1.73m^2), median (range)	44.1 (3.4–131.0)	62.9 (2.65–745)	**< 0.001**
C-reactive protein (mg/dL), median (range)	0.12 (0.0–14.5)	0.16 (0.0–48.9)	**0.087**

Data are presented as n (%). Bold values indicate $p < 0.1$. Analyzed using Fisher's exact test and Mann–Whitney U test

Low-dose aspirin included enteric-coated aspirin and buffered aspirin

Thienopyridine included clopidogrel and ticlopidine

DOAC included dabigatran etexilate, rivaroxaban, apixaban, and edoxaban

BMI body mass index, *DOAC* direct oral anticoagulant, *eGFR* estimated glomerular filtration rate

*Chronic kidney disease defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 lasting more than 3 months

Table 2 Multivariate logistic regression model to identify contributing factors to angioectasia

Variables	Adjusted OR	95% CI	*P* value
Age ≥ 70 years	1.12	0.68–1.86	0.66
Sex (female)	2.14	1.36–3.35	**< 0.001**
BMI ≥ 25	0.56	0.32–0.99	**0.047**
Current drinker	0.84	0.52–1.35	0.47
Systolic blood pressure ≤ 100 mmHg	1.42	0.85–2.37	0.18
Abdominal pain	0.33	0.14–0.77	**0.010**
Chronic heart failure	1.07	0.62–1.83	0.82
Chronic kidney disease*	3.03	1.95–4.69	**< 0.001**
Liver disease	6.95	4.22–11.5	**< 0.001**
Hypertension	0.94	0.60–1.46	0.78
Warfarin	5.70	3.48–9.35	**< 0.001**
DOAC	3.45	1.81–6.56	**< 0.001**

Values are the number and (%). Bold values indicate $p < 0.05$

Each of the ORs is obtained by multivariate logistic regression analysis. Adjustment for the 12 factors of age ≥ 70 years, sex, BMI ≥ 25, current drinker, systolic blood pressure ≤ 100 mmHg, abdominal pain, chronic heart disease, chronic kidney disease, liver disease, hypertension, use of warfarin and use of DOAC, which were shown to have $p < 0.1$ in the univariate analysis

DOAC included dabigatran etexilate, rivaroxaban, apixaban, and edoxaban

OR odd ratio, *CI* confidence interval, *BMI* body mass index, *DOAC* direct oral anticoagulant

*Chronic kidney disease defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 lasting more than 3 months

Table 3 Comparative analysis regarding clinical outcomes of acute hematochezia with and without angioectasia

Clinical outcome	Angioectasia (+) (*n* = 129)	Angioectasia (−) (*n* = 10,209)	*P* value	Adjusted OR*	95% CI	*P* value
Blood transfusion during admission, *n* (%)	77 (60)	3001 (29)	**< 0.001**	2.61	1.69–4.02	**< 0.001**
Blood transfusion (units), median (range)	4.0 (0–34)	0.0 (0–94)	**< 0.001**	1.04	1.02–1.06	**< 0.001**
Length of stay (days), median (range)	8.0 (1–96)	7.0 (0–299)	**0.012**	1.00	0.99–1.02	0.90
In-hospital rebleeding, *n* (%)	20 (16)	1554 (15)	0.91			
1-year rebleeding**, *n* (%)	36 (28)	2863 (28)	0.99			
2-year rebleeding**, *n* (%)	38 (30)	3246 (32)	0.63			

Bold values indicate $p < 0.05$. Analyzed using Fisher's exact test and Mann–Whitney *U* test

Each of the ORs is obtained by multivariate logistic regression analysis

DOAC included dabigatran etexilate, rivaroxaban, apixaban, and edoxaban

OR odd ratio, *CI* confidence interval, *DOAC* direct oral anticoagulant

*ORs were adjusted for the contributing factors to angioectasia; age ≥ 70 years, sex, body mass index ≥ 25, current drinker, systolic blood pressure ≤ 100 mmHg, abdominal pain, chronic heart disease, chronic kidney disease, liver disease, hypertension, use of warfarin and use of DOAC (Table 1)

**Missing data were analyzed using the last observation carried forward

with endoscopic clipping and the conservative management group (HR 1.10; 95% CI 0.51–2.36; $P = 0.81$), patients treated with coagulation therapies were at significantly decreased risk of rebleeding over time (HR 0.39; 95% CI 0.16–0.98; $P = 0.038$) (Fig. 1).

Discussion

This nationwide cohort study showed that 129 patients among 10,342 patients with acute hematochezia were finally diagnosed with angioectasia by colonoscopy. Angioectasia was mainly identified by colonoscopies and

Table 4 Univariate and multivariate analyses to assess risk factors for 1-year rebleeding after admission for an initial hemostasis in patients with angioectasia (n = 129)

Angioectaisa patients (n = 129)	Rebleeding (+) (n = 36)	Rebleeding (−) (n = 93)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age ≥ 70 years	27 (75)	73 (79)	0.81 (0.38–1.72)	0.59	0.83 (0.38–1.79)	0.63
Sex (female)	22 (61)	50 (54)	1.23 (0.63–2.41)	0.54		
BMI ≥ 25	3 (9)	18 (20)	0.48 (0.15–1.58)	0.23		
Current drinker	11 (33)	23 (32)	0.96 (0.46–1.97)	0.90		
Current smoker	9 (26)	15 (19)	1.35 (0.63–2.87)	0.44		
Hemodynamics						
Systolic blood pressure ≤ 100 mmHg	8 (23)	18 (20)	1.24 (0.56–2.73)	0.60		
Heart rate ≥ 100 bpm	8 (23)	14 (16)	1.39 (0.63–3.07)	0.41		
Symptom						
Loss of consciousness	1 (3)	4 (4)	0.63 (0.086–4.57)	0.64		
Abdominal pain	4 (11)	6 (7)	1.43 (0.51–4.04)	0.50		
Endoscopic findings at initial hemostasis						
SRH	16 (44)	47 (51)	0.79 (0.41–1.53)	0.49		
Active bleeding	12 (33)	35 (38)	0.77 (0.38–1.53)	0.45		
Clipping therapy*	10 (29)	17 (19)	1.50 (0.72–3.13)	0.28		
Coagulation therapy*	6 (17)	36 (39)	0.38 (0.16–0.91)	**0.031**	0.40 (0.16–0.96)	**0.039**
History of colorectal radiation therapy	2 (6)	2 (2)	1.89 (0.45–7.86)	0.38		
History of angioectasia	7 (19)	15 (16)	1.38 (0.61–3.16)	0.44		
Comorbidity						
Diabetes mellitus	4 (11)	22 (24)	0.48 (0.17–1.37)	0.17		
Cerebrovascular disease	7 (19)	15 (16)	1.48 (0.65–3.38)	0.36		
Chronic obstructive pulmonary disease	1 (3)	6 (6)	0.45 (0.06–3.27)	0.43		
Chronic heart failure	6 (17)	28 (30)	0.54 (0.22–1.29)	0.17	0.58 (0.23–1.49)	0.26
Chronic kidney disease**	15 (42)	36 (39)	1.06 (0.55–2.06)	0.86	1.25 (0.63–2.50)	0.52
Liver disease	9 (25)	19 (20)	1.06 (0.50–2.26)	0.88	1.03 (0.47–2.23)	0.95
Hypertension	21 (58)	63 (68)	0.70 (0.36–1.37)	0.30		
Hyperlipidemia	6 (17)	26 (28)	0.55 (0.23–1.32)	0.18		
Medication						
Low-dose aspirin	6 (17)	27 (29)	0.61 (0.25–1.46)	0.27		
Thienopyridines	1 (3)	10 (11)	0.30 (0.04–2.22)	0.24		
Warfarin	10 (28)	30 (32)	0.74 (0.35–1.53)	0.41		
DOAC	3 (8)	15 (16)	0.50 (0.15–1.63)	0.25		
Corticosteroid	5 (14)	6 (6)	1.50 (0.58–3.87)	0.40		

Values are the number and (%). Bold values indicate $p < 0.05$

Each of the HRs is obtained by COX hazard analysis. Adjusted for age ≥ 70 years, coagulation therapy, chronic heart disease, chronic kidney disease, and liver disease, most of which were shown to be associated with rebleeding in past studies and only coagulation therapy was shown to be significant in univariate analysis ($p < 0.05$)

Low-dose aspirin included enteric-coated aspirin and buffered aspirin

Thienopyridine included clopidogrel and ticlopidine

DOAC included dabigatran etexilate, rivaroxaban, apixaban, and edoxaban

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *SRH* stigmata of recent hemorrhage, *DOAC* direct oral anticoagulant

*Two patients treated both clipping and coagulation were excluded

**Chronic kidney disease defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 lasting more than 3 months

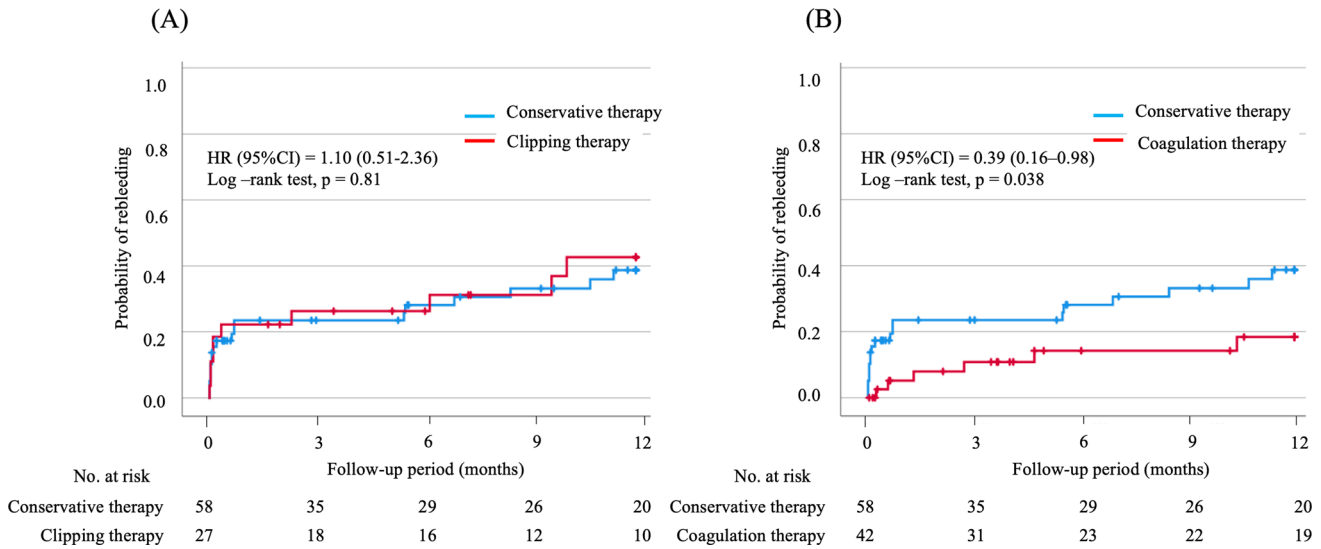

Fig. 1 Effectiveness of therapeutic endoscopy for the time to 1-year rebleeding after initial hemostasis in patients with angioectasia (n = 129). **A** Kaplan–Meier curve comparing the 1-year cumulative rebleeding rate between angioectasia patients treated with endoscopic clipping therapy and those with conservative therapy. **B** Kaplan–Meier curve comparing the 1-year cumulative rebleeding rate between angioectasia patients treated with endoscopic coagulation therapy and those with conservative therapy

the colonic SRH was dominant (93%). While few studies focusing on colonic angioectasia have been conducted, this study predominantly included colonic angioectasia. We found that the following factors were significantly associated with the risk of acute hematochezia due to angioectasia: painless hematochezia, oral anticoagulant use, CKD, chronic liver disease, BMI < 25, and female gender. Our analysis regarding laboratory data at the initial admission showed decreases in all elements of the blood counts, serum albumin levels, and kidney functions in patients with angioectasia. Furthermore, our data revealed that patients with angioectasia were more likely to require blood transfusion compared to those without angioectasia. We suggest that these findings may be associated with the higher prevalence of comorbidities such as liver disease or CKD among patients with angioectasia. Given coagulation therapy significantly reduced the risk of recurrent bleeding in patients with angioectasia, coagulation therapy can be an appropriate procedure to control hematochezia.

According to previous investigations, patients with ALGIB due to colonic angioectasia often develop an intermittent, recurrent, and painless hematochezia [8]. Furthermore, angioectasia bleeding was associated with cardiovascular diseases [11, 12], multiple angioectasia lesions [11–13], older age [12–14], and anticoagulant use [12]. A case-controlled study revealed that liver cirrhosis can be a predictor for colonic angioectasia, but this was not necessarily associated with bleeding [11]. While the number of angioectasia was lacking in our data set, our multivariate analysis including such risk factors showed patients with angioectasia were less likely to have abdominal pain. Our analysis also confirmed that oral anticoagulant use was significantly associated with the risk of acute hematochezia due to angioectasia. In addition, we found that risk factors for bleeding angioectasia included chronic liver disease, CKD, female gender, and BMI < 25. In patients with liver cirrhosis, portal hypertensive colopathy was reported as colorectal mucosal lesions [38]. Its endoscopic features resemble vascular ectasia and these lesions are thought to be a cause of lower gastrointestinal hemorrhage [39, 40]. CKD was described as a risk factor of bleeding in patients with small intestinal angioectasia [3, 41] and some mechanisms, including platelet dysfunction, were suggested [42]. We posit that such mechanisms may also be extrapolated to patients with colonic angioectasia.

As for gender, the most common cause of acute hematochezia was colonic diverticular bleeding (64%) in the CODE BLUE J-Study [29] and male patients dominated this category (70%) [43], which may explain why female patients in the angioectasia group were relatively numerous compared to the non-angioectasia group. Some studies showed the beneficial effects of estrogen–progesterone combinations to control angioectasia bleeding as a rescue therapy [44, 45], suggesting that female hormones may restore the continuity of the endothelium of abnormal vessels [46]. Given these hormone levels are decreased in the postmenopausal period, this finding implicates that decreased levels of estrogen and progesterone can be related to the risk of angioectasia bleeding, particularly among elderly female patients. Our findings also showed that BMI < 25 was associated with angioectasia bleeding.

To the best of our knowledge, no previous studies demonstrated the association between angioectasia and BMI. Given the Japanese health check-up data shows that BMI is lower in female than in men [47], the association of BMI < 25 and anigoectasia may be attributed to the greater proportion of female patients in the angioectasia group.

In terms of clinical outcomes, while the rebleeding rate between acute hematochezia patients with and without angioectasia was not significantly different, those with angioectasia had a higher risk of blood transfusion compared with the non-angioectasia group. We presumed a greater comorbidity burden may be associated with a large amount of blood loss or chronic anemia in patients with acute hematochezia due to angioectasia. Our univariate analysis found that the proportion of CKD was higher in patients who required blood transfusion (47%) than in those who did not need transfusion (29%), although multivariate analysis showed no significant association between CKD and the risk of blood transfusion. This suggests that platelet dysfunction due to CKD may cause impaired hemostasis and can be associated with an increased need for blood transfusion. It may also be due to the fact that many patients with CKD might have underlying renal anemia with lower baseline hemoglobin and thus meet the threshold for transfusion with only modest blood loss. Indeed, we found that hemoglobin levels at the initial admission were lower in the angioectasia group than in the non-angioectasia group. The rates of $>$ G3b in the GFR category and hemodialysis were higher in the former group as well, suggesting that renal anemia may influence on the threshold for blood transfusion.

With regard to rebleeding, the following factors have been reported to contribute to rebleeding in small intestinal angioectasia [22]: older age [23, 24], chronic heart disease [25, 26], CKD [25], chronic hepatitis or liver cirrhosis [27], and multiple angioectasia lesions [28]. On the other hand, few risk factors for rebleeding have been reported in colonic angioectasia. Our univariate and multivariate analyses including such risk factors only found coagulation therapy significantly reduced the risk of rebleeding. A meta-analysis showed that the rebleeding rates in gastrointestinal and small intestinal angioectasia after the initial endoscopic therapy were 36% and 45%, respectively [20]. Meanwhile, a study focused only on colonic angioectasia reported a rebleeding rate of 10% after endoscopic coagulation therapy [21]. A prospective observational study, including 100 patients with colonic angioectasia, also demonstrated that the probability of remaining free of rebleeding at 1- and 2-year follow-up after APC therapy was 98% and 90%, respectively [21]. These findings were consistent with our findings (14.3% of 1-year cumulative rebleeding rate in the coagulation group).

Notably, we demonstrated that coagulation therapy significantly reduced the risk of rebleeding in patients with acute hematochezia due to angioectasia, whereas endoscopic clipping did not decrease the rebleeding risk compared to the conservative management group. Since our study predominantly included colonic angioectasia, we suggest that coagulation therapy might be a superior endoscopic approach for acute hematochezia secondary to colonic angioectasia to reduce the likelihood of rebleeding. On the other hand, a retrospective study by Ismail et al. reported clinical outcomes between patients with gastrointestinal angioectasia treated with APC and those with endoscopic clipping, showing that the overall rebleeding rate was higher in the APC group (47%) than in the clipping group (33%) [48]. Their subgroup analysis, which included only patients who resumed antithrombotic agents after colonoscopy, revealed lower risks of rebleeding in patients treated with a combination of APC plus clipping compared to APC alone [48]. Therefore, future investigations based on risk stratification are needed to better discriminate between endoscopic modalities for acute hematochezia due to angioectasia to prevent rebleeding.

There were several strengths and limitations to this study. A significant strength is the size of this large-scale cohort study, which included 10,342 acute hematochezia cases, and such higher numbers may mean a more accurate description of clinical angioectasia characteristics and outcomes among patients with acute hematochezia. It was also a strength that our comparative analysis using the conservative management group demonstrated the effectiveness of coagulation therapy for angioectasia, suggesting that coagulation therapy might improve clinical outcomes. However, we acknowledge the limitations inherent to the retrospective nature of this multicenter study, conducted primarily on tertiary endoscopic centers in Japan, which limited data for some cases. In particular, the data regarding the number and exact localization of angioectasia lesions were limited, although it has been previously reported that patients with multiple angioectasia lesions had a greater risk for acute hematochezia due to colonic angioectasia [12, 13]. Second, it was also unclear if the rebleeding occurred during the same angioectasia in which initial bleeding developed. Third, some cases were not followed up for 1 year, although the follow-up rates were not significantly different among the groups. Fourth, detailed data on coagulation methods (e.g., APC or endoscopic contact-probe methods) was also not always available. Finally, baseline hemoglobin, erythropoietin use, albuminuria and creatinine levels before the initial admission for assessing renal anemia and CKD stage were also unknown. Hence, further prospective studies are warranted to validate and generalize our findings.

In conclusion, we conducted a nationwide cohort study focusing on acute hematochezia due to angioectasia. This analysis found that patients with angioectasia had a greater comorbidity burden and needed more blood transfusions in comparison with those without angioectasia, suggesting that their comorbidities may be associated with the risk of transfusion. Our study also demonstrated that coagulation therapy significantly reduced the risk of rebleeding in patients with angioectasia, implying that coagulation therapy might be the current best endoscopic modality for patients with acute hematochezia due to colonic angioectasia.

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Author contributions NN was the principal investigator and designed the study. MK (University of Tsukuba Hospital), SA, TN and NN conducted the literature search and conducted the study. MK (University of Tsukuba Hospital) and SA performed all data analysis and created all figures and tables. MK (University of Tsukuba Hospital), SA, TN, KK (Bokutoh hospital), AY, JO, TI, TA (Hiroshima City Asa Citizens Hospital), NT, YS (St Marianna University School of Medicine), TK, NI, TS, MM, AT, KM, KK (Fukuoka University Chikushi Hospital), SF, TU, MF, HS, SS, JH, TF, YK, AM, SK, TM, RG, HF, YF, NG, YT, KN (National Defense Medical College), NM, KN (Suita Municipal Hospital), TK, YS (National Hospital Organization Kyushu Medical Center), SF, KK (Kitasato University), TM, YK, KM, KW and MK (Nippon Medical School) collected and interpreted the data. MK (University of Tsukuba Hospital), SA and NN drafted the article. MK (University of Tsukuba Hospital), SA, TN, NI, KT and NN critically revised. All authors read and approved the submitted version of the manuscript.

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Declarations

Conflict of interest All authors have no conflict of interest to disclose.

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