Outcomes of small bowel angioectasia

Frequency and risk factors for rebleeding events in patients with small bowel angioectasia


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Abstract:

Background:

Small bowel angioectasia is reported as the most common cause of bleeding in patients with obscure gastrointestinal bleeding. Although the safety and efficacy of endoscopic treatment have been demonstrated, rebleeding rates are relatively high. To establish therapeutic and follow-up guidelines, we investigated the long-term outcomes and clinical predictors of rebleeding in patients with small bowel angioectasia.

Methods:

A total of 68 patients were retrospectively included in this study. All the patients had undergone CE examination, and subsequent control of bleeding, where needed, was accomplished by endoscopic argon plasma coagulation. Based on the follow-up data, the rebleeding rate was compared between patients who had/had not undergone endoscopic treatment. Multivariate analysis was performed using Cox proportional hazard regression model to identify the predictors of rebleeding. We defined the OGIB as controlled if there was no further overt bleeding within 6 months and the hemoglobin level had not fallen below 10 g/dl by the time of the final examination.

Results:

The overall rebleeding rate over a median follow-up duration of 30.5 months
(interquartile range 16.5–47.0) was 33.8% (23/68 cases). The cumulative risk of rebleeding tended to be lower in the patients who had undergone endoscopic treatment than in those who had not undergone endoscopic treatment, however, the difference did not reach statistical significance ($P = 0.14$). In the majority of patients with rebleeding (18/23, 78.3%), the bleeding was controlled by the end of the follow-up period.

Multiple regression analysis identified multiple lesions ($\geq 3$) (OR 3.82; 95% CI 1.30–11.3, $P = 0.02$) as the only significant independent predictor of rebleeding.

**Conclusion:**

In most cases, bleeding can be controlled by repeated endoscopic treatment. Careful follow-up is needed for patients with multiple lesions, which is considered as a significant risk factor for rebleeding.

(290 words)

**Key words:**
capule endoscopy (CE), balloon-assisted endoscopy (BAE), small bowel angioectasia, obscure gastrointestinal bleeding (OGIB), argon plasma coagulation (APC)
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1. **Background:**

Obscure gastrointestinal bleeding (OGIB), defined as persistent or recurrent bleeding with negative findings on upper and lower gastrointestinal endoscopic evaluations [1], accounts for about 5% of all cases of gastrointestinal bleeding [2]. Capsule endoscopy (CE), introduced in 2000, has become established as the examination modality of first choice for the investigation of OGIB [3-6] and other small bowel abnormalities [7-10]. The diagnostic yield of CE has been reported to range from 45% to 80% [6, 11-15], as high as that of balloon-assisted enteroscopy (BAE) [16, 17].

Angioectasia is the most commonly occurring vascular malformation of the gastrointestinal tract [18]. Although small bowel angioectasia was previously considered to be rare, with recent advances in endoscopic modalities (e.g. CE and BAE), this condition is being detected at an increasing frequencies nowadays. Recent studies have revealed that small bowel angioectasia is the most common cause of bleeding in patients with OGIB, which is sometimes life-threatening [19, 20]. Although several studies have demonstrated the safety and efficacy of endoscopic treatment for small bowel angioectasia [21, 22], not all patients with OGIB can receive endoscopic treatment, because the procedure is complex and time-consuming. Moreover, the predictors of rebleeding in patients with small bowel angioectasia have not yet been
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fully investigated. Relatively high rebleeding rates have been reported in patients with small bowel angioectasia [23-26]. Therefore, there is a need for therapeutic and follow-up guidelines to be established.

The long-term outcomes in patients with small bowel angioectasia should be determined in a large cohort study. Therefore, we conducted the present study to determine the efficacy of endoscopic treatment and the long-term outcomes in patients with small bowel angioectasia. In addition, the clinical predictors of rebleeding were evaluated to select patients who would need close follow-up.
Methods:

Patients

Of 386 consecutive patients with OGIB who underwent CE at Yokohama City University Hospital and four tertiary hospitals (Yokohama Rosai Hospital, Chigasaki Municipal Hospital, Odawara Municipal Hospital and Hiratsuka City Hospital) between October 2007 and October 2012, we enrolled 74 patients who were detected to have at least one small bowel angioectasia. All of the patients had undergone upper and lower endoscopic examinations prior to the CE, with negative findings. To investigate the long-term outcome and risk factors for rebleeding in patients with small bowel angioectasia, patients with other definitive lesions (e.g. ulcer, Dieulafoy’s lesion, varices, arteriovenous malformation, diverticulum or tumor) were excluded. In addition, patients with failed examinations due to CE retention, incomplete small bowel transit or poor bowel preparation were also excluded. The study protocol was approved by the Ethics Committee of each of the participating hospitals. Written informed consent was obtained from all of the subjects prior to their participation in the study.

Clinical information

We registered patient data from the database, including the type of OGIB, age, sex, smoking history, alcohol history, blood transfusion history, minimum hemoglobin
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concentration, presence/absence of comorbidities, and the current medication history at the time of the initial CE. According to the bleeding pattern, the OGIB was classified into two categories; overt, manifesting as melena or hematochezia, and occult, manifesting as recurrent IDA and/or a positive fecal occult blood test without any visible bleeding. In addition to the information in the database, follow-up data, including the data at the final examination, change in the hemoglobin level, presence/absence of overt bleeding and the treatment history were obtained retrospectively from the hospital medical records or questionnaires collected by the doctors of other hospitals/clinics. The follow-up duration was defined as the time between the first CE examination and the last medical examination.

Capsule endoscopy

The patients were instructed to swallow the CE capsule (PillCam SB or SB2; Given Imaging, Yoqneam, Israel) with a solution of dimethicone after overnight fasting, with no other bowel preparation. They were allowed to drink clear liquids 2 hours after swallowing the capsule, and eat a light meal 4 hours after. Two CE experts (with experience of reporting more than 150 CE videos) separately read and interpreted the complete CE videos. When there were discrepancies in the interpretation, the findings were reviewed simultaneously by both the CE experts and a consensus was reached.
Definition of small bowel angioectasia

Angioectasia is a venous lesion that requires cauterization; Dieulafoy's lesions and arteriovenous malformations may cause arterial bleeding, and require clipping or surgical treatment. According to a previous report [27], angioectasia is a punctate (<1 mm) or patchy (a few mm) erythematous lesion (Figure 1) with or without oozing, that is diagnosed by CE and/or BAE, because histologic confirmation cannot be obtained for most of these lesions. In the present study, both punctate and patchy erythema were considered as definitive diagnostic findings, and the location and size of the angioectasia were recorded according to the results of the CE examination. Each of the CE videos was divided into two segments of equal length according to the small-bowel transit time; the first segment was defined as the proximal small bowel and the other as the distal small bowel.

Treatment for small bowel angioectasia

In this study, all the patients had undergone CE examination prior to any endoscopic treatment. Subsequent endoscopic treatment was performed when active bleeding was identified by CE. In addition, endoscopic treatment was also performed for patients with on-going overt bleeding (within three days) and/or drop of the hemoglobin level more than 2 g/dl within two weeks after first OGIB episode. If endoscopic treatment was
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needed to control small bowel bleeding, single-balloon endoscopy (SBE) (SIF-Q260, Olympus Optical, Tokyo, Japan) was performed within 5 days of the initial CE examination. The insertion route was determined by the location of the lesions detected by the CE. If a definitive bleeding source could not be identified by one route, another route was used. For cases where a bleeding source was clearly detected during the procedures, we did not always attempt total enteroscopy. For angioectasias, we performed endoscopic argon plasma coagulation (APC). We basically attempted to treat all the angioectasias detected by SBE, although some non-bleeding small angioectasias were left if there were too many lesions to treat. No serious complications were encountered in any of the patients during the study.

Definition of rebleeding and control rate

The main outcome variable of this study was the incidence of recurrent bleeding. Rebleeding was defined as evidence of recurrent visible gastrointestinal bleeding (hematochezia or melena) with recent negative upper and lower endoscopic examinations and/or a recurrent drop of the hemoglobin level by more than 2 g/dl from the baseline. We defined the OGIB as controlled if there was no further overt bleeding within 6 months and the hemoglobin level had not fallen below 10 g/dl by the time of the final examination.
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1 **Statistical analysis**

2 The differences in the values of the clinical parameters were calculated by Fisher’s exact test and unpaired student’s $t$-test. Follow-up data related to the rebleeding-free interval were analyzed by the Kaplan-Meier method and log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazard regression models to identify the predictors of rebleeding in patients with small bowel angioectasia. For the multivariate analysis, only variables identified by the univariate analyses to be significant with $P$ values of $<0.1$ were included. Unless otherwise specified, $P$ values of $<0.05$ were considered to denote statistical significance. All the analyses were performed using the SPSS, ver. 11.0 (SPSS Inc., Chicago IL, USA).
Results:

Patients

Of the 74 patients enrolled in this study, 6 patients who were followed up for less than 1 year, were lost to follow-up, or died of other causes were excluded. Finally, a total of 68 patients were included for the analysis in this study (Figure 2).

Demographic characteristics and clinical data

The demographic and clinical characteristics of the patients with small bowel angioectasia are shown in Table 1. Of the 68 patients, 22 (32.4%) received endoscopic treatment, while 46 (67.6%) were managed conservatively with or without iron replacement therapy. While 17 patients who underwent endoscopic treatment (77.3%) required blood transfusion, only 14 patients who did not undergo endoscopic treatment (30.4%) needed blood transfusion \((P < 0.001)\). The minimum hemoglobin level in the patients who had undergone endoscopic treatment was significantly lower than that in the patients who had not undergone endoscopic treatment \((8.0 \pm 2.0\) vs. \(9.9 \pm 2.9, P = 0.006)\). There were no significant differences in the prevalence of comorbidities or rates of medication use between the patients who had/had not undergone endoscopic treatment, except for hypertension \((86.4\% \text{ vs. } 58.7\%, P = 0.03)\).

Association between rebleeding rate and endoscopic treatment
The overall rebleeding rate over a median follow-up duration of 30.5 months was 33.8% (23/68 cases) (interquartile range 16.5–47.0). In most cases, the first rebleeding episode occurred within 24 months after the CE, with a median time to rebleeding of 9.0 months (range 3.0–28.0). Although the rebleeding rate in the patients who had undergone endoscopic treatment was slightly lower than that in the patients who had not undergone endoscopic treatment, the difference did not reach statistical significance (22.7% vs. 39.1%, \( P = 0.27 \)). As shown in Figure 3, the cumulative risk of rebleeding tended to be lower in the patients who had undergone endoscopic treatment than those who had not undergone endoscopic treatment, however, again, the difference did not reach statistical significance (\( P = 0.14 \)).

**Treatment after rebleeding**

The clinical outcomes after rebleeding in patients with small bowel angioectasia are shown in Table 2. The overall rebleeding modes were as follows: overt (hematochezia or melena), 52.2% (12/23) and occult (drop of hemoglobin by more than 2 g/dl), 47.8% (11/23). Of the 23 patients who developed rebleeding, 8 (34.8%) received additional endoscopic treatment. In the majority of patients (18/23, 78.3%), by the end of the follow-up period, with a significant increase of the hemoglobin level from 9.1 ± 2.4 g/dl to 11.4 ± 2.1 g/dl (\( P < 0.001 \)).
Location of small bowel angioectasia

A total of 239 small bowel angioectasias were identified in this study (Table 3). The lesions were multiple in 83.8% (57/68 cases) of the patients, and were present in both the proximal and distal bowel in 42.6% (29/68 cases). The angioectasias occurred more frequently in the proximal small bowel than in the distal small bowel (64.0% vs. 36.0%). Therefore, antegrade SBE was more frequently performed to treat small bowel angioectasia (35.2% vs. 23.2%).

Factors predicting rebleeding in patients with small bowel angioectasia

The selected variables and results are shown in Table 4. Univariate analysis conducted in patients with small bowel angioectasia identified a past history of blood transfusion (odds ratio [OR] 3.16; 95% confidence interval [CI] 1.30–7.69, \( P = 0.01 \)), multiple lesions (\( \geq 3 \)) (OR 4.31; 95% CI 1.60–11.6, \( P = 0.004 \)), chronic kidney disease (CKD) \( \geq \) stage 4 (OR 2.94; 95% CI 1.29–6.71, \( P = 0.01 \)) and history of warfarin use (OR 3.30; 95% CI 1.29–8.40, \( P = 0.01 \)) as significant factors predictive of rebleeding. Multiple logistic regression analysis identified only multiple lesions (\( \geq 3 \)) (OR 3.82; 95% CI 1.30–11.3, \( P = 0.02 \)) as an independent significant factor predictive of rebleeding.
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Discussion:

Herein, we have presented the results of a relatively large, long-term, cohort study focusing on bleeding from small bowel angioectasia. Our aim was to evaluate the significance of endoscopic treatment and reveal the long-term outcomes in patients with small bowel angioectasia. It is worthy of note that in contrast to previous reports [23-26], we excluded patients with other vascular lesions such as Dieulafoy’s lesion, varices and anteriovenous malformation, and could therefore obtain important information on how to manage bleeding from small bowel angioectasia.

There have been several reports of studies carried out to evaluate the outcomes after the initial bleeding episode in patients with OGIB. According to these reports, the long-term rebleeding rates ranged widely from 17% to 40% [23-26, 28-31]. This could be explained by patient heterogeneity, and differences in the duration of follow-up, management strategies and definition of rebleeding. Importantly, the reported rebleeding rates associated with vascular lesions are higher than those associated with other lesions, such as erosions/ulcers and tumors [23-26]. Consistent with previous reports, we confirmed a relatively high rebleeding rate (33.8%) in patients with small bowel angioectasia.

Our results indicated that initial endoscopic treatment was not sufficient to control
the risk of rebleeding from small bowel angioectasia. This might be attributable to the
following reasons. Firstly, in some patients, even if the lesions thought to be responsible
for the bleeding are treated appropriately, other tiny lesions can bleed later. Consistent
with a previous report [32], multiple lesions were frequently observed in this study
(83.8%) and 42.6% of the patients had angioectasias both in the proximal and distal
small bowel. Therefore, all of the lesions, especially some of the tiny lesions, could not
be treated in a single endoscopic treatment session, even though we tried to treat all the
definitive lesions. In the present study, the size of the angioectasia was not found to be a
factor associated with rebleeding. Moreover, Shiozaki et al. reported that tiny lesions
rather than larger lesions bleed more frequently [25]. These results suggest that
aggressive endoscopic treatment of tiny lesions is important to prevent future rebleeding.

In addition, careful follow-up is required when only tiny lesions are detected as the
bleeding source. Secondly, definitive lesions could be overlooked by the first CE
examination in patients with OGIB. Fujimori et al. reported that some angioectasias
could be diagnosed only later even after combined CE and double-balloon enteroscopy
(DBE) examination [33]. Small bowel angioectasia is reported to occur more frequently
in the proximal small bowel than in the distal small bowel [23, 34]. Because of rapid
capsule transit or reduced bowel visibility due to the presence of bile and bubble
artifacts [35], small bowel lesions are more likely to be overlooked by CE, especially those located in the proximal small bowel. Recently, improved visibility and detectability of small bowel angioectasia has been reported with the use of computed virtual chromoendoscopy systems, such as flexible spectral imaging color enhancement (FICE) [36, 37]. Additional studies are needed to evaluate whether the use of such image-enhancing modalities could contribute to reducing the risk of rebleeding from small bowel angioectasia. Finally, the lower diagnostic yield of SBE could have affected the outcomes of the patients enrolled in this study. SBE was subsequently introduced to avoid the time-consuming and complex DBE procedure. Although SBE and DBE appear to be equivalent in terms of the therapeutic outcomes and re-bleeding rates for small bowel lesions [38, 39], decreased rates of total enteroscopy was observed in cases examined by SBE.

Consistent with a previous report [25], multiple lesions were identified as a significant risk factor for the presence of rebleeding. In the present study, while the first rebleeding episode occurred after 1 year in approximately 50% of the cases, in the majority of cases, rebleeding occurred within 2 years, suggesting that patients with small bowel angioectasia should be closely followed up for at least 2 years after the initial treatment, especially those with multiple lesions. Although our results suggested
that rebleeding could be controlled with repeated endoscopic treatment and iron
replacement therapy in the majority of patients with small bowel angioectasia, some
patients are unsuitable for endoscopic treatment, because angioectasia is frequently
detected in patients older than 60 years of age [32] and is often accompanied by severe
comorbidities such as chronic renal failure [40] and cardiac valvular disease [41].
Pharmacological treatments such as thalidomide and octreotide might serve as
attractive options for these patients [42, 43].

The present study has some limitations. First, it was a retrospective study, therefore,
selection bias was inevitable. Second, the number of patients enrolled in this study was
not sufficiently large which could have limited our conclusions. Finally, the choice of
treatment and follow-up procedures were not selected based on randomized controlled
protocol. To establish medical management of bleeding from small bowel angioectasia,
large prospective randomized controlled trials are needed.
Conclusions:

Our results indicated that OGIB patients with small bowel angioectasia show relatively high rebleeding rates. Although a single session of endoscopic treatment was not sufficient to control future rebleeding, in most cases, rebleeding could be controlled with repeated endoscopic treatment and/or iron replacement therapy. Careful follow-up is needed for patients with multiple lesions, which was identified as a significant risk factor for rebleeding.
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Abbreviations:

Capsule endoscopy, CE; obscure gastrointestinal bleeding, OGIB; single-balloon endoscopy, BAE; balloon-assisted endoscopy; SBE; double-balloon endoscopy, DBE; APC, argon plasma coagulation; IQR, interquartile range; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; LDA, low-dose aspirin; NSAIDs, nonsteroidal anti-inflammatory drugs; H2-blockers, histamine H2 receptor antagonists; PPIs, proton pump inhibitors; FICE, flexible spectral imaging color enhancement
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Competing interests:

None of the authors have any potential conflict of interests that are relevant to the submission of this manuscript.

Authors’ contributions:

ES, HE and HT designed the study. ES wrote the article. YH, HN and TN participated in the critical revision of the manuscript. HK, LT, AE, TK, KI, JA, EY, HO and TK participated in the study as physicians who treated and followed OGIB patients. ES and TH performed the statistical analysis. HE and AN were responsible for the design of the study. All authors read and approved the submission of the final manuscript.

Authors’ information:

ES and HE are physicians specializing in small bowel diseases, and belong to the Gastroenterology division, Yokohama City University School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama, 236-0004 Japan.

Acknowledgement:

We thank Dr. Hiraga for her assistance in the clinical data management.
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lesions detected by capsule endoscopy in patients with chronic kidney disease.


Figure legends:

Figure 1. Capsule endoscopic findings of small bowel angioectasia.

A: punctate angioectasia (arrow). B: patchy angioectasia (arrowhead).

Figure 2. Study flow diagram.

*Patients with other definitive small bowel lesions, such as ulcers, Dieulafoy’s lesions, varices, anteriovenous malformations, diverticula and tumors, were excluded.

Figure 3. Cumulative rebleeding rates according to the choice of therapeutic management.

The risk of rebleeding tended to be lower in the patients who had undergone endoscopic treatment than in those who had not undergone without endoscopic treatment, although the difference did not reach statistical significance ($P = 0.14$, log rank test).
Table 1. Demographic and clinical characteristics of studied patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Endoscopic treatment (+)</th>
<th>Endoscopic treatment (-)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>68</td>
<td>22</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Bleeding pattern (overt/occult)</td>
<td>40 / 28</td>
<td>19 / 3</td>
<td>21 / 25</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of angioectasia, mean (median)</td>
<td>3.4 (2.5)</td>
<td>4.0 (2.0)</td>
<td>3.1 (3.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Age, year, mean ± SD</td>
<td>67.6 ± 12.8</td>
<td>66.9 ± 10.9</td>
<td>66.5 ± 13.6</td>
<td>0.30</td>
</tr>
<tr>
<td>Sex, Male/Female</td>
<td>38 / 30</td>
<td>11 / 11</td>
<td>27 / 19</td>
<td>0.60</td>
</tr>
<tr>
<td>Drinking history (%)</td>
<td>23 (33.8)</td>
<td>11 (50.0)</td>
<td>12 (26.0)</td>
<td>0.06</td>
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<tr>
<td>Smoking history (%)</td>
<td>24 (35.3)</td>
<td>7 (31.8)</td>
<td>17 (37.0)</td>
<td>0.79</td>
</tr>
<tr>
<td>Blood transfusion (%)</td>
<td>31 (45.6)</td>
<td>17 (77.3)</td>
<td>14 (30.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Minimum hemoglobin value, g/dl</td>
<td>9.3 ± 2.7</td>
<td>8.0 ± 2.0</td>
<td>9.9 ± 2.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Follow-up duration, month, median (IQR)</td>
<td>30.5 (16.5-47.0)</td>
<td>34.0 (21.0-46.5)</td>
<td>30.0 (18.0-46.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Rebleeding rate, number (%)</td>
<td>23 (33.8)</td>
<td>5 (22.7)</td>
<td>18 (39.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Iron replacement therapy after OGIB, number (%)</td>
<td>59 (86.8)</td>
<td>20 (91.0)</td>
<td>39 (84.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>Comorbidity, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>46 (67.6)</td>
<td>19 (86.4)</td>
<td>27 (58.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (22.1)</td>
<td>7 (31.8)</td>
<td>8 (17.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>18 (26.5)</td>
<td>8 (36.4)</td>
<td>10 (21.7)</td>
<td>0.25</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>9 (13.2)</td>
<td>3 (13.6)</td>
<td>6 (13.0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>CKD, ≥stage 4</td>
<td>17 (86.4)</td>
<td>8 (36.4)</td>
<td>9 (19.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>3 (4.4)</td>
<td>1 (4.5)</td>
<td>2 (4.3)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Medication used, Number (%)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>9 (13.2)</td>
<td>4 (18.2)</td>
<td>5 (10.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>LDA</td>
<td>27 (39.7)</td>
<td>10 (45.5)</td>
<td>17 (37.0)</td>
<td>0.60</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>9 (13.2)</td>
<td>3 (13.6)</td>
<td>6 (13.0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>7 (10.3)</td>
<td>2 (9.1)</td>
<td>5 (10.9)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>H2-blockers</td>
<td>17 (25.0)</td>
<td>5 (22.7)</td>
<td>12 (26.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>PPIs</td>
<td>25 (36.8)</td>
<td>8 (36.4)</td>
<td>17 (37.0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Rebamipide</td>
<td>10 (14.7)</td>
<td>4 (18.2)</td>
<td>6 (13.0)</td>
<td>&gt;0.99</td>
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</table>
Abbreviations: IQR, interquartile range; CKD, chronic kidney disease; LDA, low-dose aspirin; NSAIDs, nonsteroidal anti-inflammatory drugs; H2-blockers, histamine H2 receptor antagonists; PPIs, proton pump inhibitors.

Variable definitions: Alcohol history was defined as positive if the subject’s alcohol consumption exceeded 20 g/day. Smoking history was defined as positive if the subject had smoked more than 10-pack years and was still smoking or had quit within the past 10 years. History of antiplatelet drug and/or NSAID use was defined as positive if the patient had been taking at least 1 pill per day for more than 1 week within 1 month prior to the CE. History of anticoagulant drug use was defined as positive if the patient had been taking at least 1 pill per day within one week prior to the CE.

*Differences between endoscopic treatment (+) and (-) were calculated by Fisher's exact test or unpaired student t-test.
Table 2. Clinical outcomes after rebleeding in patients with small bowel angioectasia.

<table>
<thead>
<tr>
<th></th>
<th>Patients with rebleeding</th>
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<tr>
<td>Number</td>
<td>23</td>
</tr>
<tr>
<td>Bleeding pattern (overt/occult)</td>
<td>12 / 11</td>
</tr>
<tr>
<td>Blood transfusion, number (%)</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td>Minimum hemoglobin value after rebleeding, g/dl</td>
<td>9.1 ± 2.4</td>
</tr>
<tr>
<td>Endoscopic treatment, number (%)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>Controlled by the end of the follow-up period*, number (%)</td>
<td>18 (78.3)</td>
</tr>
<tr>
<td>Iron replacement therapy after rebleeding, number (%)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Hemoglobin value at the end of the follow-up period, g/dl</td>
<td>11.4 ± 2.1</td>
</tr>
</tbody>
</table>

* We defined OGIB as controlled if there was no further overt bleeding within 6 months and the hemoglobin level had not fallen below 10 g/dl by the final examination.
Table 3. Location of small bowel angioectasias.

<table>
<thead>
<tr>
<th></th>
<th>Proximal</th>
<th>Distal</th>
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<tbody>
<tr>
<td>Total number</td>
<td>153</td>
<td>86</td>
</tr>
<tr>
<td>Prevalence, number (%)</td>
<td>54 (79.4)</td>
<td>43 (63.2)</td>
</tr>
<tr>
<td>Endoscopic treatment, number (%)</td>
<td>19 (35.2)</td>
<td>10 (23.2)</td>
</tr>
<tr>
<td>Rebleeding, number (%)</td>
<td>21 (38.9)</td>
<td>18 (41.8)</td>
</tr>
</tbody>
</table>

NOTE: Each of the CE videos was divided into two segments of equal length according to the small-bowel transit time. The first segment was defined as the proximal small bowel and the other as the distal small bowel.
### Table 4. Predictors of rebleeding in patients with small bowel angioectasia.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate (OR 95% CI)</th>
<th>P value</th>
<th>Multivariate (OR 95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>1.38 (0.54-3.52)</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>2.11 (0.87-5.15)</td>
<td>0.10</td>
<td>2.52 (0.95-6.70)</td>
<td>0.07</td>
</tr>
<tr>
<td>Overt bleeding</td>
<td>2.00 (0.79-5.08)</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>3.16 (1.30-7.69)</td>
<td>0.01</td>
<td>1.08 (0.32-3.63)</td>
<td>0.91</td>
</tr>
<tr>
<td>Minimum hemoglobin value &lt; 8 g/dl</td>
<td>2.03 (0.89-4.60)</td>
<td>0.09</td>
<td>2.43 (0.95-6.19)</td>
<td>0.06</td>
</tr>
<tr>
<td>Size of angioectasia ≥1mm</td>
<td>0.80 (0.36-1.75)</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of angioectasias ≥3</td>
<td>4.31 (1.60-11.6)</td>
<td>0.004</td>
<td>3.82 (1.30-11.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Drinking history</td>
<td>1.72 (0.75-3.95)</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>1.71 (0.75-3.87)</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.63 (0.64-4.17)</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.95 (0.35-2.55)</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.89 (0.80-4.48)</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1.68 (0.57-4.95)</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage ≥4</td>
<td>2.94 (1.29-6.71)</td>
<td>0.01</td>
<td>1.72 (0.58-5.06)</td>
<td>0.33</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>3.77 (0.87-16.3)</td>
<td>0.08</td>
<td>3.44 (0.60-19.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>3.30 (1.29-8.40)</td>
<td>0.01</td>
<td>2.48 (0.79-7.79)</td>
<td>0.12</td>
</tr>
<tr>
<td>LDA</td>
<td>1.00 (0.43-2.31)</td>
<td>&gt;0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>1.99 (0.74-5.38)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.32 (0.39-4.46)</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2-blockers</td>
<td>0.75 (0.28-2.01)</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIs</td>
<td>1.45 (0.64-3.32)</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rebamipide</td>
<td>1.17 (0.40-3.45)</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NOTE: For the multivariate Cox proportional hazard regression analysis, only the variables with P value <0.1 were included.

Abbreviations: OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; LDA, low-dose aspirin; NSAIDs, nonsteroidal anti-inflammatory drugs; H2-blockers, histamine H2 receptor antagonists; PPIs, proton pump inhibitors.

Variable definitions: Alcohol history was defined as positive if the subject’s alcohol consumption exceeded 20 g/day. Smoking history was defined as positive if the subject had smoked more than 10-pack years and was still smoking or had quit within the past 10 years. History of antiplatelet drug and/or NSAID use was defined as positive if the patient had been taking at least 1 pill per day for more than 1 week within 1 month prior to the CE. History of anticoagulant drug use was defined as positive if the patient had been taking at least 1 pill per day within one week prior to the CE.
Figure 2

Patients with OGIB patients (N = 386)

Exclusion* (N = 312)

Patients with angioectasia (N = 74)

Follow-up for less than 1 year (N = 6)

Endoscopic treatment (+) (N = 22)

- Rebleeding (+) (N = 5)
  - Rebleeding (-) (N = 17)

Endoscopic treatment (-) (N = 46)

- Rebleeding (+) (N = 18)
  - Rebleeding (-) (N = 28)