

# Long-Term Prognosis of Patients with Obscure Gastrointestinal Bleeding: A Retrospective Cohort Study

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## Keywords

Obscure gastrointestinal bleeding · Capsule endoscopy · Long-term prognosis

## Abstract

**Aims:** We evaluated the long-term prognosis of patients with obscure gastrointestinal bleeding (OGIB) who underwent capsule endoscopy (CE). **Methods:** In our hospital, 429 patients underwent CE between November 2007 and March 2012. Among them, 259 patients underwent CE as the first examination for OGIB and were then followed at 77 clinics and hospitals. The clinical characteristics were investigated, including age, gender, overt/occult bleeding, the use of anti-thrombotic drugs and NSAIDs, complications (liver cirrhosis and hemodialysis), and CE. We asked the medical institutions for their survival data as of August 2017 (>5 years after CE). **Results:** The prognoses of 240 patients (92.6%) were analyzed. The average follow-up period was 55.7 (1–115)

months. During the follow-up period, 57 patients (23.8%) died and the survival rates were 90.5% at 1 year, 81.7% at 3 years, and 74.7% at 5 years. Age 65 years or older and liver cirrhosis were predictive factors for a poor prognosis. Re-bleeding occurred in 42 patients (17.9%) and small bowel cancer and gastrointestinal stromal tumor were found at 12 and 21 months after CE, respectively. **Conclusions:** Patients with OGIB showed a poor prognosis, especially those who were elderly or who had liver cirrhosis.

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## Introduction

Obscure gastrointestinal bleeding (OGIB) is defined as recurrent or persistent bleeding with negative esophago-gastroduodenoscopy, ileocolonoscopy, and small bowel radiography [1]. Video capsule endoscopy (CE) is the investigation of choice in OGIB, with a high diagnostic

yield compared to other modalities [2]. The causes of OGIB are varied, that is, mucosal ulcer, erosion, aneurysm, angioectasia, etc. [3, 4]. Common background characteristics of OGIB patients include a history of use of antithrombotic drugs, liver cirrhosis, or hemodialysis [5]. Because benign diseases account for the majority of OGIB cases, the survival prognosis of OGIB is generally favorable. However, some patients with OGIB have comorbid conditions in their medical histories, and the prognosis may be poor in such cases. Although the prognosis for rebleeding has been investigated fully [6], the survival prognosis for patients with OGIB has not been thoroughly assessed.

In this study, we evaluated the prognosis of OGIB patients who underwent CE. To avoid bias arising from the brevity of the observation period, we enrolled patients who underwent CE at least 5 years ago. In addition, to studying the cause and time of death accurately, we asked the participating medical institutions for survival data. This is the first report to reveal the prognosis of OGIB patients with a long and accurate period of observation.

## Methods

### Patients

In Chiba University Hospital (Japan), 429 patients underwent CE between November 2007 and March 2012. Among them, 259 patients underwent CE as the first examination for OGIB. These patients had recently undergone at least 1 upper-gastrointestinal tract endoscopy and at least 1 colonoscopy, which showed negative findings. None of the patients had contraindications for CE. Clinical characteristics were investigated, including age, gender, overt/occult bleeding, the use of antithrombotic drugs and NSAIDs, complications (liver cirrhosis and hemodialysis), and CE. The patients were followed at 77 clinics and hospitals. The medical institutions were asked to provide survival data for the patients as of August 2017 (>5 years after CE).

### Study Design

The primary endpoint of this study was the survival prognosis of patients with OGIB. We determined the predictive factors for prognosis by Cox regression analysis. This study was reviewed and approved by the institutional review board of Chiba University School of Medicine. This study was registered at University Hospital Medical Information Network (UMIN000028443).

### CE and Diagnostic Definition

CE was performed with a Pillcam SB (Given Imaging, Yoqneam, Israel). CE studies were performed according to our unit's protocol, which includes an overnight fast and bowel preparation (magnesium citrate 34 g) [5]. On the day of CE examination, patients ingested 1 L of polyethylene glycol (Niflec®). Studies were read separately by 2 individuals with experience in CE. When dis-

crepancies occurred, the findings were reviewed simultaneously by both examiners and a consensus was reached. The outcome of CE was determined according to the definition reported by Macdonald et al. [7] with slight modification. CE findings were classified according to standard practice as highly relevant lesions (P2) or less-relevant lesions (P1, P0).

If the cause of or explanation for OGIB was observed, such as angiodysplasia, Dieulafoy's lesion, varix, arteriovenous malformation, tumor, polyp, ulceration, multiple (>3) erosions, diverticulum, or the presence of blood and/or blood clots in the lumen of the small bowel, this finding was classified as a P2 lesion. When a definite abnormality was identified but was not thought to be the cause of or explanation for blood loss, it was assigned as P1 status. Minor mucosal changes or abnormalities that were not diagnostic were also categorized as P1 lesions, and nonspecific mucosal changes including isolated red spots, mucosal breaks, and visible submucosal veins were regarded as P1 status. In our hospital, rebleeding was defined as a documented fall in Hb of 2 g/dL from baseline, evidence of melena or hematochezia, and the need for blood transfusion. In other institutes, the definition of rebleeding was left to the discretion of the physician at each institute.

### Statistical Analysis

Baseline data are presented as mean  $\pm$  SD. Logistic regression analysis was used for statistical analyses as appropriate with the statistical program SPSS 21.0 (SPSS Inc., Chicago, IL, USA); a *p* value of less than 0.05 was considered statistically significant.

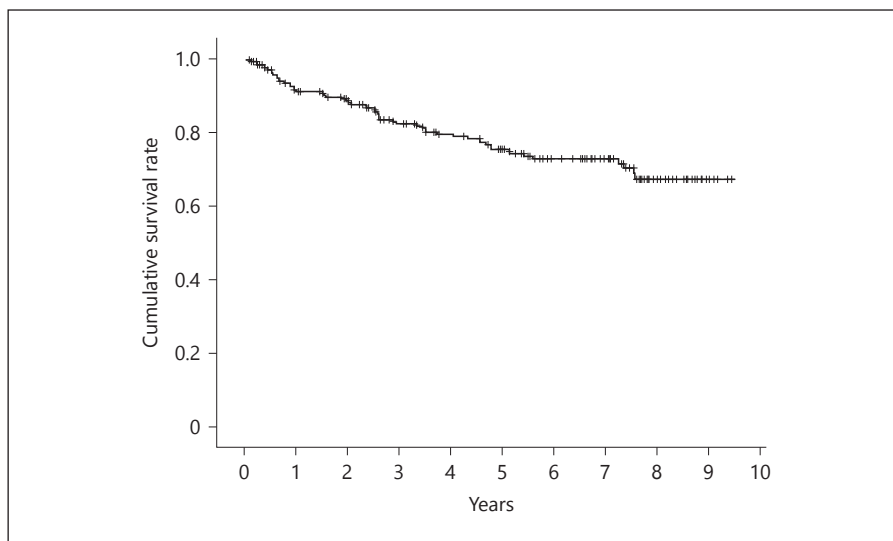
## Results

### Prognosis of Patients with OGIB

Until the end of September 2017, 69 of the medical institutes (89.6%) replied to our enquiries and the prognoses of 240 patients (92.6%) could be analyzed. The clinical characteristics of patients with OGIB are shown in Table 1. The average follow-up period was 55.7 (1–115) months. During the follow-up period, 57 patients (23.8%) died. The survival rates were 90.5% at 1 year, 81.7% at 3 years, and 74.7% at 5 years (Fig. 1). Using the cohort survival rate table for Japan in 2007 after matching age and sex (<https://ganjoho.jp/public/index.html>), the survival rates for Japan were  $98.0 \pm 2.0\%$  at 1 year,  $94.0 \pm 6.4\%$  at 3 years, and  $89.3 \pm 10.9\%$  at 5 years. Compared with the survival rates for Japan, the prognosis of patients with OGIB seemed poor.

### Cause of Death in Patients with OGIB

The causes of death were malignant tumors ( $n = 16$ , 28.1%), cardiovascular disease ( $n = 9$ , 15.8%), cerebrovascular disease ( $n = 8$ , 14.0%), liver failure ( $n = 6$ , 10.5%), injury ( $n = 3$ , 5.3%), and pneumonia ( $n = 3$ , 5.3%). The organs affected by malignant tumors are list-



**Fig. 1.** Kaplan-Meier analysis for the survival prognosis of OGIB patients.

**Table 1.** Clinical characteristics of patients with OGI

	(n = 240)
Age, years	64.7±15.5
Gender, male/female, n	142/98
Observation period, months	55.7 (1–115)
Overt/occult	191/49
Timing of CE examination after bleeding (overt; over 28/15-28/8-14/4-7/0-3 days)	73/43/27/26/22
Prognosis (dead/alive)	57/183
Drug, n (%)	
Antithrombotic drug	56 (23.3)
NSAID	9 (3.8)
Liver cirrhosis, n (%)	31 (12.9)
Child-Pugh classification (A/B)	15/15
Etiology (HCV/HBV/alcohol/ NASH/others)	18/1/6/1/5
History of hepatocellular carcinoma, n	4
Hemodialysis, n (%)	13 (5.4)
CE finding (P2/P1, P0)	82/158
Rebleeding, n (%)	42 (17.5)

OGIB, obscure gastrointestinal bleeding; CE, capsule endoscopy; NSAID, nonsteroidal anti-inflammatory drug.

ed in Table 2. There were 2 patients who died of colon cancer. One patient showed gastrointestinal bleeding during chemotherapy for postoperative recurrence. In upper GI endoscopy and colonoscopy, there was no finding. In CE, an ulcer in the small intestine was found. The patient died 11 months after CE. The other patient had alcohol-related liver cirrhosis and chronic kidney disease. Because he showed repeated gastrointestinal

bleeding, upper GI endoscopy, colonoscopy, CE, double-balloon enteroscopy (oral and anal), and nonenhanced CT were performed. Although there were multiple colon diverticula, the cause of bleeding was undetermined. CE was performed 3 times in total, but the cause of bleeding could not be identified. GI bleeding subsequently reoccurred and he was admitted to the hospital. At 24 months after a detailed examination, colonoscopy detected advanced cancer in the descending colon. Because of liver dysfunction (Child-Pugh C), active treatment could not be performed, and he died of cancer and liver failure.

#### Factors Associated with Death of Patients with OGIB

Univariate analysis showed that age, liver cirrhosis, and hemodialysis were predictive factors for prognosis. Multivariate analysis showed that age 65 years or older (hazard ratio 2.98, 95% CI 1.54–5.78) and liver cirrhosis (hazard ratio 2.22, 95% CI 1.19–4.14) were predictive factors for a poor prognosis (Table 3). CE findings and bleeding type (overt/occult) were not predictive factors for prognosis. There were significant differences in survival prognosis between patients 65 years of age or older versus younger (log-rank test,  $p = 0.001$ , Fig. 2a), with or without liver cirrhosis (log-rank test,  $p = 0.003$ , Fig. 2b). Among those with liver cirrhosis, 14 patients died during the follow-up period. The causes of death were liver failure ( $n = 9$ ), HCC ( $n = 3$ ), other malignant tumor ( $n = 1$ ), renal failure ( $n = 1$ ), injury ( $n = 1$ ), brain bleeding ( $n = 1$ ), and unknown ( $n = 1$ ; the causes overlapped in some cases). Among the 4 patients with a past history of HCC treatment, only 1 patient died due to HCC. Fifteen were

**Table 2.** Causes of death in patients with OGIB

	(n = 57), n (%)
Malignant tumor, n (%) (4 liver, 3 blood, 2 pancreas, 2 colon, 1 sarcoma, 1 ovary, 1 melanoma, 1 mammary, 1 lung), n (%)	16 (28.1)
Cardiovascular disease	9 (15.8)
Cerebrovascular disease	8 (14.0)
Liver failure	6 (5.2)
Injury	3 (5.2)
Pneumoniae	3 (1.8)
Respiratory failure	1 (1.8)
Bleeding	1 (1.8)
Senility	1 (1.8)
Renal failure	1 (1.8)
Unknown	8 (10.5)

**Table 3.** Univariate and multivariate analyses of risk factors associated with survival prognosis in patients with OGIB

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age, years	2.96 (1.53–5.72)	0.001	2.98 (1.54–5.78)	0.001
Gender (male)	0.96 (0.57–1.62)	0.88		
Bleeding (overt)	1.60 (0.75–3.41)	0.22		
Drug				
Antithrombotic drug	1.55 (0.89–2.69)	0.19		
NSAID	1.02 (0.25–4.18)	0.98		
Liver cirrhosis	2.46 (1.33–4.51)	0.004	2.22 (1.19–4.14)	0.012
Hemodialysis	2.25 (0.90–5.64)	0.08	2.22 (0.86–5.72)	0.10
CE finding (P2)	1.09 (0.64–1.86)	0.75		

OGIB, obscure gastrointestinal bleeding; CE, capsule endoscopy; NSAID, nonsteroidal anti-inflammatory drug.

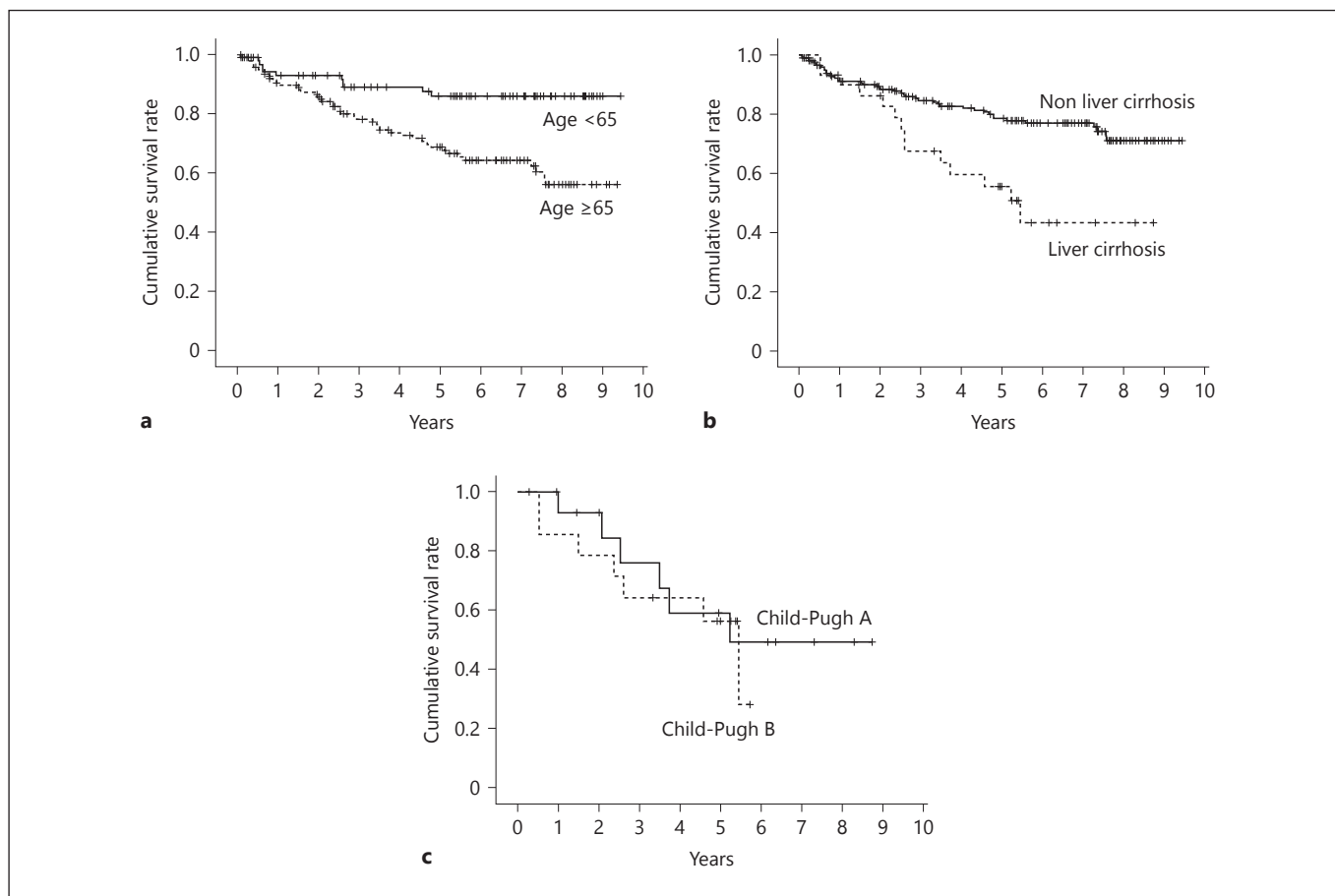
stage A and 15 were stage B according to Child-Pugh classification. There was no significant difference in the survival prognosis between the 2 groups (log-rank test, Fig. 2c).

#### *Tumors of the Small Intestine after the Negative CE Results*

In patients with negative CE results, 2 were diagnosed as having tumor of the small intestine. One case was a 75-year-old man who had undergone CE examination for evaluation of overt OGIB, but there were no specific CE findings. He was advised to undergo enhanced CT but refused to do so. After CE, he was not followed by the hospital, and rebleeding could not be

evaluated. At 21 months later, multiple liver tumors and intraperitoneal tumors were detected, and a pathological examination of the liver tumor led to a diagnosis of gastrointestinal stromal tumor (Fig. 3a). Multiple intraperitoneal tumors were suspected to be tumors of the small intestine.

The other case, a 49-year-old man, showed anemia without obvious gastrointestinal bleeding, and again there were no specific CE findings. Because he suffered from chronic kidney disease, he could not be evaluated by enhanced CT. His anemia persisted after CE had been performed. Twelve months after CE, a tumor in the small intestine was detected by CT and resected surgically. It was located at the jejunum (Fig. 3b, c).



**Fig. 2.** Kaplan-Meier analysis for the survival prognosis of OGIB patients. **a** Age, **(b)** liver cirrhosis, **(c)** liver cirrhosis with Child-Pugh A or B. **a** There were significant differences in survival prognosis between patients aged 65 years or older (dotted line) versus

younger (log-rank test,  $p = 0.001$ ; **b**) with or without liver cirrhosis (dotted line; log-rank test,  $p = 0.003$ ). **c** There was no significant difference between patients with stage A and B (dotted line) Child-Pugh classification, (log-rank test, Fig. 2c).

## Discussion

OGIB has multiple causes including a history of use of antithrombotics, hemodialysis, liver cirrhosis, and tumor [3, 4]. CE is used widely for detecting the cause of OGIB, and some cases can be cured using endoscopic techniques. However, in many cases, the underlying cause of OGIB cannot be determined. An in-depth analysis of re-bleeding among patients with OGIB was reported in a prior study [6]. At our institute, we found that to optimize the diagnostic yield, CE should be performed within a short time after bleeding, and that negative CE on examination in patients with OGIB is closely related to the use and cessation of low-dose aspirin prior to CE [8].

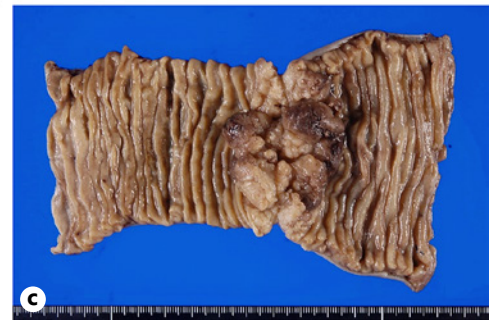
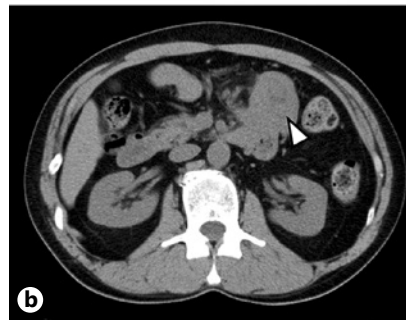
The survival prognosis of patients with OGIB has not been thoroughly examined. In a study of OGIB patients, Niikura et al. [9] reported that 19 patients (5.9%) died

during the follow-up period (mean follow-up period of 20.4 months) and that the cumulative incidence of death was 4.0% at 12 months, 9.5% at 36 months, and 10.9% at 60 months. In our study, 57 patients (23.8%) died, while the cumulative incidence of death was 9.0% at 12 months and 18.0% at 36 months. This represents a worse prognosis than previously reported, even though the patients' average ages and clinical backgrounds were similar between the 2 studies. We speculate that our longer follow-up period (55.7 months) and investigation at medical institutes would produce the more reliable survival rate among OGIB patients.

A 2015 report on demographic statistics in Japan (<http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei15/index.html>) showed that the top 5 causes of death in the country were malignant tumors (28.7%), heart diseases (15.2%), pneumoniae (9.4%), cerebrovas-



Color version available online



**Fig. 3.** Malignant tumors in the small intestine were found a considerable time after CE. **a** Multiple liver tumors and intraperitoneal tumors at 21 months after a negative CE result (arrowheads). **b** and **c** Tumor of the small intestine in a CT scan at 12 months after negative CE result (arrowhead) and surgical resection of the specimen.

cular disease (8.7%), and senility (6.6%), which were not different from those of OGIB patients in this study. Because the causes of death in OGIB patients were not different from those of the overall Japanese population, we speculate that OGIB might worsen disease conditions but is not a direct cause of death. It should be noted that effective management for bleeding in patients with OGIB by double-balloon endoscopy or other methods might prevent them from dying directly due to gastrointestinal bleeding. In fact, in a previous study, patients with OGIB were managed efficiently, and endoscopic hemostasis was performed for gastrointestinal bleeding [10].

The top cause of death in OGIB patients was malignant tumors. Because the number of complication involving chronic liver disease and hematopoietic tumors was high in this study, the rates of liver and blood in malignant tumors' organ were high. Liver cirrhosis and age were exacerbating factors for a poor prognosis in patients with OGIB, which would be reasonably expected. Previous reports identified liver cirrhosis as a risk factor in both occult and overt OGIB [11, 12]. The prognosis for patients with Child-Pugh A liver cirrhosis versus those with Child-Pugh B is markedly different, which

has been amply demonstrated in systematic reviews [13, 14]. D'Amico and associates reported 1-year cumulative survival rates for Child-Pugh A and B of 95 and 80%, respectively, and 2-year cumulative survival rates of 90 and 70%, respectively [13]. Interestingly, the prognosis of OGIB patients with Child-Pugh A was poor; as a result, there was no significant difference in the prognosis of OGIB patients between Child-Pugh A and B. Child-Pugh classification evaluates prothrombin time, serum albumin, serum total bilirubin, ascites, and hepatic encephalopathy, and it is one of the most reliable classifications for prognosis in patients with liver cirrhosis. Because OGIB is not related to these factors directly, it could be a valid predictive factor for a poor prognosis in patients with liver cirrhosis, especially compensated cirrhosis.

In this study, 2 tumors of the small intestine were found after obtaining negative CE results. Rebleeding after negative CE results has been thoroughly investigated, but the diagnostic yield of CE for tumors is unknown. Diagnosis of small intestinal tumors is often delayed [15, 16]; approximately 50% of small bowel cancers have already undergone distant metastasis at diagnosis [17]. Johnston and coworkers estimated a di-

agnostic delay of up to 1.5 years for malignant small bowel tumors [18], which might be caused by their slow and extraluminal growth. Some tumors that have not been detected by CE may be detected by other modalities [19]. For this reason, in the clinical guidelines for Japan, the combined use of CE and enhanced CT is recommended for screening of small bowel tumors [20, 21]. In one case with a small intestinal tumor in this study, enhanced CT could not be performed because of renal dysfunction, which might have led to a delay in the diagnosis.

The prevalence of P2 was lower than in previous reports [22, 23]. We speculated that it was due to the late timing of CE. In this study, 73 of 191 overt OGIB cases (38.6%) underwent CE more than 1 month after gastrointestinal bleeding. The diagnostic yield of CE in overt OGIB is influenced by the timing of CE after overt bleeding [24]. In this study, the timing of CE for OGIB was late, which we had pointed out as one of the causes for low diagnostic yield in our previous study [5].

There are some limitations of this study. First, there were a large number of patients with liver cirrhosis. Our hospital is one of the high-volume centers for liver disease in Japan; therefore, we manage many patients with liver cirrhosis. The high rate of patients with liver cirrhosis might influence the overall prognosis of patients with OGIB because they had a high risk of liver failure and hepatocellular carcinoma. Second, this study was

performed at a university hospital; 58 of 240 patients (24%) were followed at a university hospital after CE because of various complications. Therefore, the patients in this study represent a typical group of patients, which might have influenced the overall prognosis. Third, the diagnostic yield of CE was lower than in previous studies. Identification of the cause of OGIB could have led to treatment by double-balloon enteroscopy or other methods, which might have influenced the patients' prognosis.

In conclusion, this study is the first to report a poor long-term survival prognosis in patients with OGIB, especially the elderly and those with liver cirrhosis. In patients with liver cirrhosis, OGIB could be a predictive factor for a poor prognosis. We must heed the possibility that a malignant tumor in the small intestine will be found a considerable time after CE.

### Acknowledgments

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### Disclosure Statement

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