

# World Journal of *Gastroenterology*

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Editorial Board Member of *World Journal of Gastroenterology*, Pietro Fusaroli, MD, Associate Professor, Department of Medical and Surgical Sciences, University of Bologna/Hospital of Imola, Via Montericco 4, Imola (BO) 40026, Italy. [pietro.fusaroli@unibo.it](mailto:pietro.fusaroli@unibo.it)

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Retrospective Cohort Study

## Risk factors and prognostic value of acute severe lower gastrointestinal bleeding in Crohn's disease

Jiyoung Yoon, Dae Sung Kim, Ye-Jee Kim, Jin Wook Lee, Seung Wook Hong, Ha Won Hwang, Sung Wook Hwang, Sang Hyoung Park, Dong-Hoon Yang, Byong Duk Ye, Jeong-Sik Byeon, Seung-Jae Myung, Suk-Kyun Yang

**ORCID number:** Jiyoung Yoon 0000-0001-7448-4296; Dae Sung Kim 0000-0002-4881-7883; Ye-Jee Kim 0000-0002-3307-2970; Jin Wook Lee 0000-0002-5312-4053; Seung Wook Hong 0000-0003-1440-9950; Ha Won Hwang 0000-0002-4065-5058; Sung Wook Hwang 0000-0002-6981-7575; Sang Hyoung Park 0000-0002-5366-5749; Dong-Hoon Yang 0000-0001-7756-2704; Byong Duk Ye 0000-0001-6647-6325; Jeong-Sik Byeon 0000-0002-9793-6379; Seung-Jae Myung 0000-0003-0585-4016; Suk-Kyun Yang 0000-0003-2772-2575.

**Author contributions:** Yoon J and Kim DS equally contributed to this article; Yoon J and Kim DS collected and analyzed data, and drafted the manuscript; Kim YJ supervised the research and contributed to analysis; Lee JW, Hong SW, Hwang HW, Hwang SW, Park SH, Yang DH, Ye BD, Byeon JS, and Myung SJ were involved in study patient enrollment, data collection, and data analysis; Yang SK was involved in study design, supervision, and critical revision of the study; all authors read and approved the final version of the manuscript.

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Jiyoung Yoon, Dae Sung Kim, Jin Wook Lee, Seung Wook Hong, Ha Won Hwang, Sung Wook Hwang, Sang Hyoung Park, Dong-Hoon Yang, Byong Duk Ye, Jeong-Sik Byeon, Seung-Jae Myung, Suk-Kyun Yang, Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, South Korea

**Ye-Jee Kim,** Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, South Korea

**Corresponding author:** Suk-Kyun Yang, PhD, Professor, Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea. [sky@amc.seoul.kr](mailto:sky@amc.seoul.kr)

### Abstract

#### BACKGROUND

Acute severe lower gastrointestinal bleeding (LGIB) is an uncommon but challenging complication of Crohn's disease (CD).

#### AIM

To identify the predictors of acute severe LGIB and to evaluate the impact of acute severe LGIB on the subsequent clinical course in CD patients.

#### METHODS

A retrospective inception cohort study was conducted in 75 CD patients with acute severe LGIB and 1359 CD patients without acute severe LGIB who were diagnosed between February 1991 and November 2019 at Asan Medical Center, a tertiary university hospital in Korea. Multivariable analysis with Cox proportional hazard regression was performed to identify the risk factors for acute severe LGIB. A matched analysis using 72 patients with bleeding and 267 matched patients without within the cohort was also conducted to investigate whether acute severe LGIB is a predictor of clinical outcomes of CD.

#### RESULTS

Multivariable Cox regression analysis revealed that early use of thiopurines [hazard ratio (HR): 0.23, 95% confidence interval (CI): 0.12-0.48;  $P < 0.001$ ] and female sex (HR: 0.51, 95%CI: 0.27-0.94;  $P = 0.031$ ) were significantly associated

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with a lower risk of acute severe LGIB. The cumulative risks of behavioral progression and intestinal resection were not significantly different between the two matched groups ( $P = 0.139$  and  $P = 0.769$ , respectively). The hospitalization rate was higher in the bleeding group than in the matched non-bleeding group (22.1/100 vs 13.2/100 patient-years;  $P = 0.012$ ). However, if hospitalizations due to bleeding episodes were excluded from the analysis, the hospitalization rate was not significantly different between the bleeding group and the matched non-bleeding group (14.5/100 vs 13.2/100 patient-years;  $P = 0.631$ ).

## CONCLUSION

Early use of thiopurines may reduce the risk of acute severe LGIB. History of acute severe LGIB may not have a significant prognostic value in patients with CD.

**Key Words:** Gastrointestinal hemorrhage; Lower gastrointestinal tract; Crohn's disease; Risk factors; Cohort studies; Clinical course

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**Core Tip:** A retrospective cohort study was conducted to identify the predictors of acute severe lower gastrointestinal bleeding (LGIB) in Crohn's disease (CD) and the impact of acute severe LGIB on the subsequent clinical course thereof. In multivariable analysis, early use of thiopurines and female sex were associated with a lower risk of acute severe LGIB. Moreover, matched analyses within the cohort demonstrated that the risks of behavioral progression, intestinal resection, and hospitalization due to non-bleeding causes did not significantly differ according to bleeding, which suggests that a history of acute severe LGIB may not have a significant prognostic value in CD.

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## INTRODUCTION

Acute severe lower gastrointestinal bleeding (LGIB) is an uncommon manifestation that occurs in 0.6%-6.0% of patients with Crohn's disease (CD); however, it is a challenging problem with high rates of recurrence (21.4%-41.4%)[1-5], surgery (7.1%-39.7%)[1-4], and mortality (0%-8.2%)[2,3]. Despite this clinical importance, acute severe LGIB in CD has not been well-studied. Two studies have evaluated the risk factors for acute severe LGIB[1,3]; however, because the patient populations in these studies were not inception cohorts, it is still unknown what characteristics at the time of CD diagnosis predispose a patient to acute severe LGIB. Moreover, no previous studies have evaluated the impact of acute severe LGIB on the subsequent clinical course of CD. Therefore, by using a well-defined hospital-based inception cohort, we aimed to identify the risk factors for acute severe LGIB in CD and to investigate whether a history of acute severe LGIB is a predictor of a worse clinical course for CD.

## MATERIALS AND METHODS

### Patients

Between February 1991 and November 2019, a total of 4010 patients with CD were registered at the Inflammatory Bowel Disease (IBD) Center of Asan Medical Center, a tertiary university hospital in Seoul, Korea. Of these 4010 patients, 1437 had been first diagnosed and/or first treated with CD at Asan Medical Center. Among them, 78



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patients experienced acute severe gastrointestinal (GI) bleeding and 1359 patients did not. Of the 78 patients, 75 with acute severe LGIB were finally selected for this study after those with postoperative bleeding ( $n = 1$ ), upper GI bleeding ( $n = 1$ ), or anal bleeding ( $n = 1$ ) were excluded.

To identify the risk factors for acute severe LGIB, we performed a retrospective cohort study in the 75 patients with acute severe LGIB and 1359 patients without acute severe LGIB. In addition, to investigate whether acute severe LGIB is a predictor of a worse clinical course of CD, a matched cohort analysis was performed by matching patients without acute severe LGIB to those with acute severe LGIB at a ratio of 4:1 in terms of sex, age at CD diagnosis ( $\pm 5$  years), calendar year of CD diagnosis ( $\pm 5$  years), and disease location and behavior at CD diagnosis. According to the matching conditions, a total of 72 patients with acute severe LGIB were matched to 267 patients without. The selection process for our study population is shown as a flowchart (Figure 1). The study protocol was approved by the Institutional Review Board of Asan Medical Center.

### Data collection

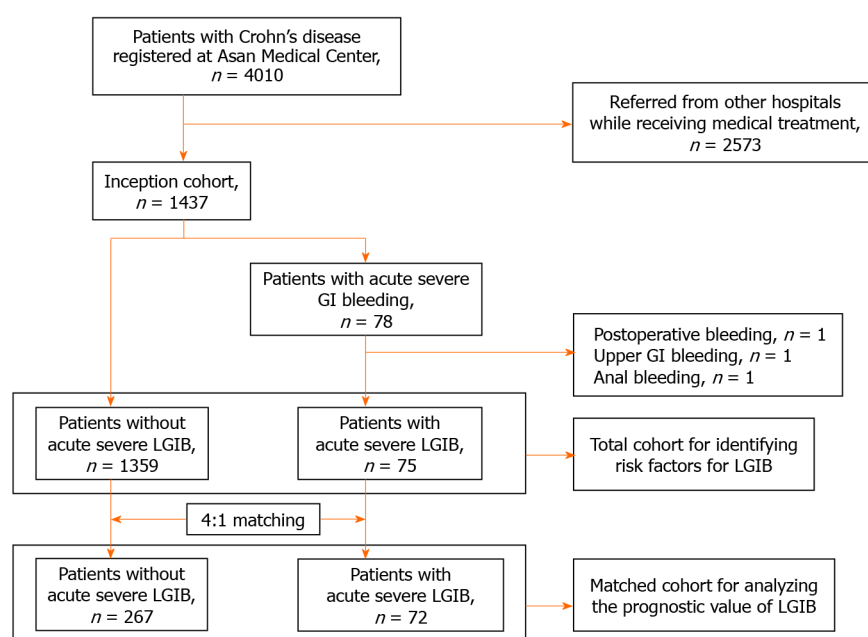
The patients' demographic and clinical information were retrieved from the Asan IBD Registry, which has been prospectively maintained since 1997. Information missing in the IBD registry was obtained by reviewing the medical records. To identify the risk factors for acute severe LGIB, we retrieved data on sex, date of birth, date of CD diagnosis, date of acute severe LGIB, disease location and behavior at diagnosis, smoking status at diagnosis, early use of medications including corticosteroids, thiopurines, and anti-tumor necrosis factor (TNF) agents, diagnostic modalities for identification of bleeding site, identified bleeding site, and date of final follow-up. In addition, to investigate whether acute severe LGIB is a predictor of a worse clinical course of CD, we additionally retrieved data on medications (*i.e.*, corticosteroids, thiopurines, and anti-TNF agents), progression of disease behavior, intestinal resection, and hospitalization.

### Definitions and classifications

CD was diagnosed using standard clinical, radiological, endoscopic, and histopathological criteria[6]. Acute severe LGIB was defined as acute overt rectal bleeding that resulted in (1) an abrupt decrease in the hemoglobin level to  $< 9$  g/dL or at least 2 g/dL below the baseline; and/or (2) transfusion of at least two units of blood within 24 h[1]. The ligament of Treitz was regarded as the anatomic landmark separating LGIB from upper GI bleeding. Postoperative bleeding was defined as bleeding that occurred within 1 mo after intestinal surgery. The lesion found was defined as the bleeding site when it showed active bleeding or adherent blood clot[2]. Early use of corticosteroids was defined as the initiation of treatment within 3 mo of diagnosis[7]; early use of thiopurines or anti-TNF agents was defined as the initiation of therapy within 6 mo of diagnosis[8,9] and at least 6 mo before the first intestinal resection and acute severe LGIB episode[7,10]. In the matched analysis, each matched patient in the non-bleeding group was given an index date that corresponded to the date of acute severe LGIB in the matched patient in the bleeding group, such that the time interval between CD diagnosis and the index date of each non-bleeding patient was equal to that between CD diagnosis and the acute severe LGIB date for the matched bleeding patient. Disease location and behavior were defined according to the Montreal classification[11]. Behavioral progression was defined as the development of stricturing or penetrating disease in patients who had non-stricturing, non-penetrating disease at the start of follow-up. Hospitalization was defined as care in a hospital setting for  $\geq 3$  d for flare-ups or complications of CD[12]. Hospitalizations only for disease evaluation or due to conditions unrelated to CD were excluded. Index hospitalization was defined as the first hospitalization for acute severe LGIB.

### Statistical analyses

Categorical variables are expressed as numbers with percentages, and continuous variables are expressed as medians with interquartile ranges (IQRs). The Chi-squared test or Fisher's exact test was used to compare categorical variables, as appropriate, and the *t*-test was used to compare continuous variables. Multivariable analysis with Cox proportional hazard regression was performed to identify the risk factors for acute severe LGIB and to calculate their hazard ratios (HRs) and 95% confidence intervals (CIs). All variables with *P* values  $< 0.2$  in the univariate analysis were included in the multivariable analysis, and backward elimination was performed. In the matched analyses, the balance in the distribution of baseline characteristics



**Figure 1** Flowchart of study patients. GI: Gastrointestinal; LGIB: Lower gastrointestinal bleeding.

between the matched groups was quantified using the standardized mean difference (SMD). An SMD < 0.1 was regarded to indicate a fair balance of confounders between the matched groups[13]. Disease courses such as medication use, behavioral progression, and intestinal resection before the bleeding/index date were compared between the matched groups using conditional logistic regression analysis. Cumulative risks of medication use, behavioral progression, and intestinal resection after the bleeding/index date were calculated using the Kaplan-Meier method, and the values were compared between the matched groups using the log-rank test. Hospitalization rates *per* 100 patient-years of follow-up were calculated in both the bleeding group and the non-bleeding group, and the relative rates and associated CIs were estimated using Poisson regression with generalized estimating equation. *P* values < 0.05 were considered statistically significant. Statistical evaluations were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, United States) and R version 3.6.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria). The statistical methods of this study were reviewed by Kim YJ from the Department of Clinical Epidemiology and Biostatistics at Asan Medical Center, University of Ulsan College of Medicine.

## RESULTS

### **Characteristics of patients and bleeding episodes**

During a median follow-up of 84.8 mo (IQR 43.2-141.8), 75 (5.2%) of 1437 patients developed the first episode of acute severe LGIB. The cumulative risks of bleeding at 1, 5, 10, and 20 years after CD diagnosis were 3.0%, 4.4%, 5.9%, and 11.6%, respectively. Sixty-three of the 75 patients were men, yielding a male-to-female ratio of 5.2:1. The median age at the first bleeding episode was 27.0 years (IQR 21-34), and the median duration of CD at the first bleeding episode was 7.7 mo (IQR 0-42.1). After excluding 26 patients who were first diagnosed with CD at the time of bleeding, the median duration of disease at the first bleeding episode in the other 49 patients was 31.0 mo (IQR 8.0-66.0).

Of the 75 patients with acute severe LGIB, bleeding sites were identified in 19 (25.3%) patients through ileocolonoscopy, computed tomography, angiography, bleeding scan, and surgery. Capsule endoscopy or double-balloon enteroscopy was not used in the evaluation of acute severe LGIB. In the patients as a whole, the sites of bleeding were the jejunum in 2, the ileum in 12, and the colon in 5. Ileocolonoscopy was performed in 66 patients and revealed bleeding sites in 7 (10.6%) patients (colon, *n* = 5; terminal ileum, *n* = 2). Computed tomography was performed in 55 patients and revealed bleeding sites in 6 (10.9%) patients (jejunum, *n* = 2; ileum, *n* = 4). Mesenteric



angiography was performed in 14 patients and identified bleeding sites in the ileum in 4 (28.5%) patients. Radionuclide bleeding scan was performed in 22 patients and identified bleeding sites in the ileum in 4 (18.2%) patients. Surgery was performed to control bleeding in 4 patients and revealed ileal ulcers with adherent blood clots in 2 (50%) patients.

### **Risk factors for acute severe LGIB**

**Table 1** shows the baseline demographic and clinical characteristics according to the presence of acute severe LGIB. The proportions of male patients and patients with ileal disease at diagnosis were significantly higher in the bleeding group ( $P = 0.045$  and  $P = 0.002$ , respectively), whereas the proportion of patients with early use of thiopurines was significantly higher in the non-bleeding group ( $P < 0.001$ ). There were no significant differences between the two groups in terms of age at diagnosis, disease behavior at diagnosis, smoking status at diagnosis, early use of corticosteroids, and early use of anti-TNF agents.

Multivariable Cox regression analysis revealed that female sex (HR: 0.51, 95%CI: 0.27-0.94;  $P = 0.031$ ) and early use of thiopurines (HR: 0.23, 95%CI: 0.12-0.48;  $P < 0.001$ ) were significantly associated with a lower risk of acute severe LGIB (**Table 2**). In addition, patients with ileal disease at diagnosis showed a trend toward a higher risk of bleeding compared with those with colonic disease at diagnosis (HR: 6.58, 95%CI: 0.90-48.12;  $P = 0.063$ ).

### **Impact of acute severe LGIB on the clinical course of CD**

In the matched analysis between patients in the non-bleeding group and the bleeding group, the baseline characteristics including age at diagnosis, sex, disease location at diagnosis, and disease behavior at diagnosis were well-balanced between the matched groups (**Table 3**). The median duration of follow-up from CD diagnosis to the bleeding/index date was 7.1 mo (IQR 0.9-38.6) among 72 patients with acute severe LGIB and 8.7 mo (IQR 0.01-38.6) among 267 matched patients without ( $P = 0.423$ ). During the follow-up period before the bleeding/index date, there were no significant differences in the rates of medication use, behavioral progression, intestinal resection, and hospitalization between the two matched groups (**Tables 4 and 5**).

The median duration of follow-up from the bleeding/index date to the last follow-up was 105.2 mo (IQR 50.7-135.3) in the bleeding group and 84.4 mo (IQR 46.7-144.2) in the matched non-bleeding group ( $P = 0.766$ ). During the follow-up period after the bleeding/index date, the cumulative risks of receiving corticosteroids and thiopurines were not significantly different between the two matched groups ( $P = 0.068$  and  $0.248$ , respectively; **Figure 2A and B**). In contrast, the cumulative risk of receiving anti-TNF agents was significantly higher in the bleeding group ( $P = 0.035$ ; **Figure 2C**). The cumulative risk of behavioral progression did not significantly differ between the two matched groups ( $P = 0.139$ ; **Figure 3A**). Intestinal resection was performed in 13 (18.1%) of the 72 patients in the bleeding group and 53 (19.9%) of the 267 patients in the matched non-bleeding group ( $P = 0.86$ ). Four (30.8%) of the 13 patients who underwent intestinal resection in the bleeding group underwent surgery due to acute severe LGIB. The cumulative risks of intestinal resection did not significantly differ between the two matched groups ( $P = 0.769$ ; **Figure 3B**). The hospitalization rate after the bleeding/index date was significantly higher in the bleeding group than in the matched non-bleeding group (22.1/100 vs 13.2/100 patient-years;  $P = 0.012$ ), even when the index hospitalization was excluded from the analysis. However, if all hospitalizations due to bleeding episodes were excluded from the analysis, the hospitalization rate did not significantly differ between the bleeding group and the matched non-bleeding group (14.5/100 vs 13.2/100 patient-years;  $P = 0.631$ ; **Table 5**).

## **DISCUSSION**

In this study, we investigated the risk factors for acute severe LGIB in CD and the impact of acute severe LGIB on the subsequent clinical course of CD by using a well-defined hospital-based inception cohort. To our knowledge, this is the first study that evaluated the prognostic value of acute severe LGIB in CD. Our results demonstrated that early use of thiopurines and female sex were negatively associated with the risk of bleeding and that there were no significant differences in the clinical course of CD including the rates of medication use (*e.g.*, corticosteroids and thiopurines), behavioral progression, intestinal resection, and hospitalization due to non-bleeding causes between patients who experienced acute severe LGIB and those who did not.

**Table 1 Demographic and clinical characteristics of patients with Crohn's disease according to the presence of acute severe lower gastrointestinal bleeding**

	Bleeding group (n = 75)	Non-bleeding group (n = 1359)	P value
Age at diagnosis, years (median, IQR)	23.6 (18.9-31.9)	23.2 (18.6-33.5)	0.952
Sex, male, n (%)	63 (84.0)	1000 (73.6)	0.045
Disease location at diagnosis, n (%)			0.002
Ileum	34 (45.3)	377 (27.7)	
Colon	1 (1.3)	81 (6.0)	
Ileocolon	40 (53.4)	901 (66.3)	
Upper GI modifier at diagnosis, n (%)	15 (20)	355 (26.1)	0.238
Disease behavior at diagnosis, n (%)			0.157
Non-stricturing, non-penetrating	59 (78.6)	1012 (74.5)	
Stricturing	11 (14.7)	155 (11.4)	
Penetrating	5 (6.7)	192 (14.1)	
Perianal modifier at diagnosis, n (%)	32 (42.7)	686 (50.5)	0.204
Smoking status at diagnosis, n (%)			0.540
Never smokers	51 (68.0)	874 (64.3)	
Ex-smokers	3 (4.0)	99 (7.3)	
Current smokers	21 (28.0)	386 (28.4)	
Early use of medications, n (%)			
Corticosteroids	21 (28.0)	399 (29.4)	0.840
Thiopurines	10 (13.3)	649 (47.8)	< 0.001
Anti-TNF agents	1 (1.3)	43 (3.2)	0.560

IQR: Interquartile range; GI: Gastrointestinal; TNF: Tumor necrosis factor.

However, the use of anti-TNF agents was more common in the bleeding group.

To date, only two studies have investigated the risk factors of acute severe LGIB in CD[1,3], with Kim *et al*[1] reporting that the use of thiopurines was associated with a lower risk of bleeding[1] and Li *et al*[3] confirming this result[3]. Li *et al*[3] also reported that left colon involvement and a history of bleeding were associated with a higher risk of bleeding. Similar to the results of previous studies, our present study demonstrated that early use of thiopurines was associated with a lower risk of bleeding. Thiopurines are effective for maintaining remission in patients with CD[14,15], and some studies have also reported that early use of thiopurines is associated with a lower risk of intestinal resection in patients with CD, albeit there are some disagreements in the literature[7,10,16]. Given the results of these previous studies, it can be assumed that early use of thiopurines can lower the risk of bleeding in patients with CD.

Another risk factor for bleeding in our study was male sex. In most population-based cohort studies, sex was not associated with the risk for surgery in patients with CD[7,17,18]. As a result, sex has not been considered a prognostic factor of CD[19]. However, sex differences in the phenotypic characteristics and clinical course of CD are increasingly being recognized[20]. Mazon *et al*[21] reported that only male sex was independently associated with complicated diseases such as stricturing disease, penetrating disease, perianal disease, and abdominal surgery[21]. Some studies have also shown that male sex was significantly associated with a higher risk for surgery[22-24]. These results collectively suggest that male sex may be a real risk factor for bleeding. Further studies are required to confirm whether male sex is an independent risk factor for bleeding in patients with CD.

In the present study, patients with ileal disease at diagnosis had a higher risk of bleeding compared with those with colonic disease at diagnosis, although the result did not reach statistical significance. This is in line with the results of previous studies

**Table 2 Risk factors of acute severe lower gastrointestinal bleeding in patients with Crohn's disease**

	Univariate analysis		Multivariable analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age at diagnosis	1.01 (0.98-1.03)	0.663		
Sex				
Male	Reference		Reference	
Female	0.51 (0.28-0.95)	0.035	0.51 (0.27-0.94)	0.031
Disease location at diagnosis				
Colon	Reference		Reference	
Ileum	7.56 (1.04-55.26)	0.046	6.58 (0.90-48.12)	0.063
Ileocolon	3.60 (0.50-26.22)	0.206	3.86 (0.53-28.09)	0.182
Upper GI modifier at diagnosis				
No	Reference			
Yes	0.78 (0.45-1.38)	0.401		
Disease behavior at diagnosis				
Non-stricturing, non-penetrating	Reference			
Stricturing	1.10 (0.58-2.10)	0.763		
Penetrating	0.45 (0.18-1.13)	0.067		
Perianal modifier at diagnosis				
No	Reference		Reference	
Yes	0.71 (0.45-1.12)	0.142	0.74 (0.42-1.19)	0.209
Smoking status at diagnosis				
Never smokers	Reference			
Ex-smokers	0.59 (0.18-1.88)	0.368		
Current smokers	0.93 (0.56-1.55)	0.783		
Early use of medications				
Corticosteroids	0.94 (0.57-1.58)	0.840		
Thiopurines	0.17 (0.09-0.34)	0.001	0.23 (0.12-0.48)	< 0.001
Anti-TNF agents	0.41 (0.12-3.21)	0.560		

HR: Hazard ratio; CI: Confidence interval; GI: Gastrointestinal; TNF: Tumor necrosis factor.

that ileal disease is a predictor of complicated behavior[25] and surgery[17,26,27], whereas colonic disease is a predictor of a milder disease course[17,28]. However, other studies reported contrasting results in that bleeding was more common in patients with colonic involvement than in those with isolated small bowel disease[2,29]. These conflicting results warrant further targeted investigation.

The impact of acute severe LGIB on the subsequent clinical course of CD has not been investigated to date. To investigate this issue after controlling for potential confounders, we performed a matched cohort study. In our matched analyses, the cumulative risks of behavioral progression and intestinal resection after the bleeding/index date did not significantly differ between the bleeding group and the matched non-bleeding group. In particular, although 31% of the patients in the bleeding group who underwent intestinal resection received surgery due to bleeding, the overall rate of intestinal resection in the bleeding group was not significantly higher than that in the matched non-bleeding group. Moreover, when we excluded the hospitalizations due to bleeding episodes from the analysis, the hospitalization rate was not significantly different between the two matched groups. These results suggest that a history of acute severe LGIB may not have a significant prognostic value in patients with CD. However, a definite conclusion on this issue cannot be made

**Table 3 Comparison of the baseline parameters between patients with acute severe lower gastrointestinal bleeding and matched patients without**

	Before matching			After matching		
	Bleeding group (n = 75)	Non-bleeding group (n = 1359)	SMD	Bleeding group (n = 72)	Non-bleeding group (n = 267)	SMD
Age at diagnosis, years (median, IQR)	23 (18-32)	23 (18-33)	0.009	22 (18-31.5)	23 (18-30)	0.061
Male, n (%)	63 (84.0)	1000 (73.6)	0.257	63 (87.5)	234 (87.6)	0.004
Disease location at diagnosis, n (%)			0.391			0.020
Ileum	34 (45.3)	377 (27.7)		31 (43.1)	111 (41.6)	
Colon	1 (1.3)	81 (6.0)		1 (1.4)	4 (1.5)	
Ileocolon	40 (53.3)	901 (66.3)		40 (55.6)	152 (56.9)	
Disease behavior at diagnosis, n (%)			0.301			0.030
Non-stricturing, non-penetrating	59 (78.7)	1012 (74.5)		58 (80.6)	219 (82.0)	
Stricturing	11 (14.7)	155 (11.4)		9 (12.5)	32 (12.0)	
Penetrating	5 (6.7)	192 (14.1)		5 (6.9)	16 (6.0)	

SMD: Standardized mean difference; IQR: Interquartile range.

**Table 4 Comparison of the outcome parameters between patients with acute severe lower gastrointestinal bleeding and matched patients without during the period before the bleeding/index date**

	Bleeding group (n = 72)	Non-bleeding group (n = 267)	Matched OR (95%CI)	P value
Use of medications, n (%)				
Corticosteroids	19/72 (26.4)	78/267 (29.2)	0.82 (0.43-1.57)	0.55
Thiopurines	27/72 (37.5)	108/267 (40.4)	0.74 (0.36-1.51)	0.40
Anti-TNF agents	6/72 (8.3)	27/267 (10.1)	0.68 (0.24-1.91)	0.47
Behavioral progression, n (%)	10/58 (17.2)	21/219 (9.6)	1.96 (0.87-4.44)	0.10
Intestinal resection, n (%)	13/72 (18.1)	30/267 (11.2)	1.83 (0.73-4.58)	0.20

OR: Odds ratio; CI: Confidence interval; TNF: Tumor necrosis factor.

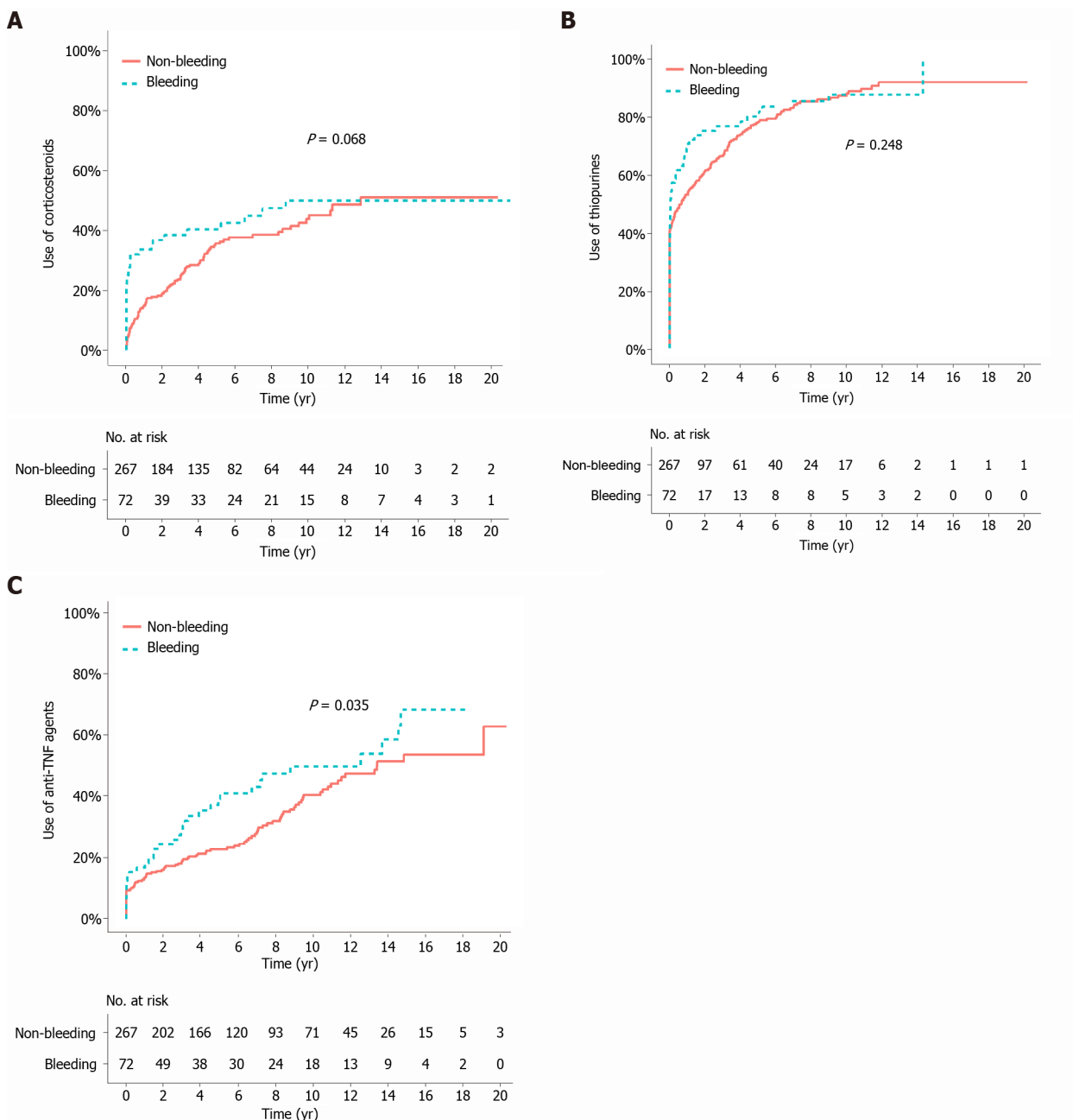
because anti-TNF agents were more commonly used in the bleeding group than in the matched non-bleeding group. In addition, the rate of all-cause hospitalization was higher in the bleeding group than in the matched non-bleeding group; this is an expected result considering the high recurrence rates (21.4%-41.4%) of acute severe LGIB reported in previous studies[1-5]. A higher need for anti-TNF agents and a higher rate of hospitalization in the bleeding group indicate that a history of acute severe LGIB may have some prognostic value. Regardless of whether acute severe LGIB in CD is a poor prognostic factor, it is a common practice to use anti-TNF agents to lower the risk of rebleeding in CD patients who develop acute severe LGIB[1,5,30-32], and major disease outcomes including behavioral progression and intestinal resection in the bleeding group are comparable with those in the non-bleeding group.

The strength of our present study is that we used a well-defined inception cohort, which enabled us to identify the patients' demographic and clinical characteristics at the time of or at an early stage of CD diagnosis that could predict the occurrence of acute severe LGIB. However, our study has some limitations. First, although our results suggested that male sex was associated with a higher risk of bleeding, we cannot exclude the possibility that this difference was derived from non-biological

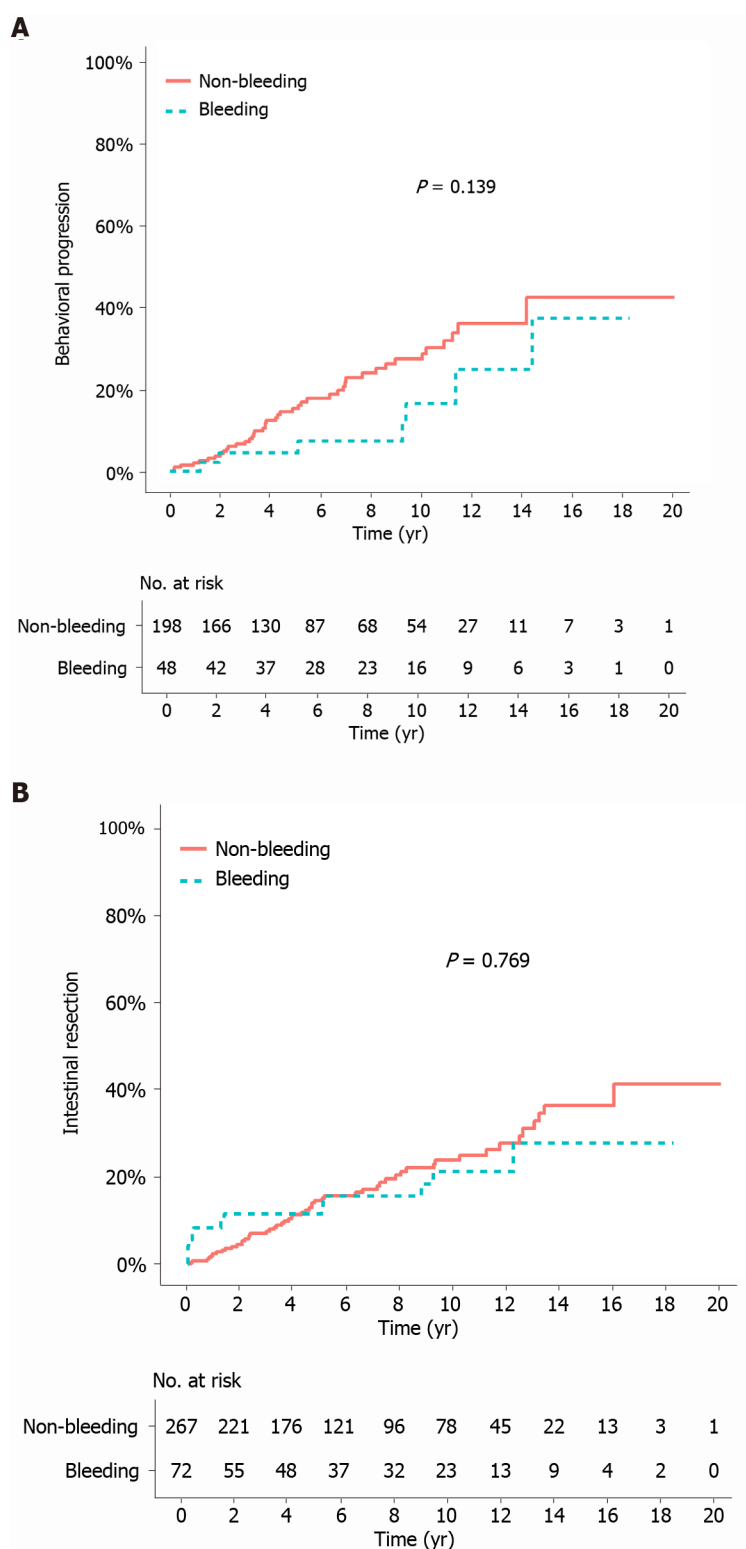
**Table 5 Comparison of the hospitalization rate between patients with acute severe lower gastrointestinal bleeding and matched patients without**

Hospitalization rate (per 100 patient-years)	Bleeding group (n = 72)	Non-bleeding group (n = 267)	Hospitalization rate ratio (95%CI)	P value
Before bleeding/index date (95%CI)	21.0 (14.5-30.5)	23.6 (19.0-29.2)	0.89 (0.58-1.37)	0.599
After bleeding/index date (95%CI)				
Excluded: Index hospitalization	22.1 (16.5-29.4)	13.2 (11.2-15.5)	1.67 (1.20-2.33)	0.012
Excluded: Hospitalizations due to bleeding	14.5 (10.3-20.4)	13.2 (11.2-15.5)	1.10 (0.75-1.60)	0.631

CI: Confidence interval.

**Figure 2 Cumulative risks of receiving medications after the bleeding/index date according to bleeding.** A: Corticosteroids ( $P = 0.068$ ); B: Thiopurines ( $P = 0.248$ ); C: Anti-tumor necrosis factor agents ( $P = 0.035$ ). TNF: Tumor necrosis factor.





**Figure 3** Cumulative risks of behavioral progression and intestinal resection after the bleeding/index date according to bleeding. A: Behavioral progression ( $P = 0.139$ ); B: Intestinal resection ( $P = 0.769$ ).

causes such as sex differences in access to health care or adherence to therapy in patients with IBD[33-35]. Second, our result that male sex is a risk factor for bleeding may not be generalized in Western patients considering the sex-related differences between Asian and Western patients with CD. For example, the male predominance in the incidence of CD is evident in Asian populations but not in Western populations [36].

## CONCLUSION

Our results suggest that early use of thiopurines may reduce the risk of acute severe LGIB. In addition, a history of acute severe LGIB may not have a significant impact on the subsequent clinical course of patients with CD in terms of behavioral progression, intestinal resection, and hospitalization due to non-bleeding causes. Further studies are needed to determine whether our results on the prognostic value of acute severe LGIB were biased by the differential use of anti-TNF agents between patients with acute severe LGIB and those without.

## ARTICLE HIGHLIGHTS

### Research background

Acute severe lower gastrointestinal bleeding (LGIB) is an uncommon but challenging complication of Crohn's disease (CD).

### Research motivation

Acute severe LGIB in CD has not been well-studied.

### Research objectives

To identify the predictors of acute severe LGIB and to evaluate the impact of acute severe LGIB on the subsequent clinical course in patients with CD.

### Research methods

A hospital-based retrospective inception cohort study was conducted. Multivariable analysis with Cox proportional hazard regression was performed to identify the predictors of acute severe LGIB. A matched analysis within the cohort was also conducted to investigate whether acute severe LGIB is a predictor of clinical outcomes of CD. Disease courses were compared using conditional logistic regression analysis.

### Research results

Early use of thiopurines and female sex were associated with a decreased risk of acute severe LGIB. The risks of behavioral progression, intestinal resection, and hospitalization due to non-bleeding causes did not significantly differ between the bleeding group and the matched non-bleeding group.

### Research conclusions

Early use of thiopurines may reduce the risk of acute severe LGIB. History of acute severe LGIB may not have a significant prognostic value in patients with CD.

### Research perspectives

Further studies are needed to investigate whether our findings on the possible null prognostic value of acute severe LGIB in CD was biased by the differential use of anti-tumor necrosis factor agents between patients with acute severe LGIB and those without.

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