High Charlson comorbidity index scores are associated with recurrent colon diverticular bleeding

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Abstract

Background/Aims: Colonic diverticular bleeding (CDB) is a common cause of acute lower gastrointestinal bleeding. Patients with CDB are at increased risk for recurrence. Here, we aimed to evaluate the clinical course of patients with CDB and identify risk factors, including the Charlson comorbidity index (CCI), for recurrent CDB (rCDB).

Methods: We retrospectively included patients who were hospitalized at the Chonnam National University Hospital for management of CDB between January 2005 and March 2020, and data on the underlying disease, drug history, treatment method, post-discharge rCDB, and death were checked.

Results: Among 221 investigated patients (mean age, 68.1 years; 56 females), 56 and 165 had definite and presumptive CDB, respectively, 122 (55.2%) had a right-sided CDB, and 51 (23.3%) experienced rCDB throughout a median period of 339 days (range, 3–4817 days). The most common comorbidities were hypertension (62.4%) and diabetes (33.5%). The median length of hospitalization was 5 days (range, 2–119 days). The CDB-related morality rate was 0.9% at first admission. The cumulative incidence rates of rCDB after 1, 6, 12, 24 months were 4.6%, 9.1%, 12.3%, and 16.9%, respectively. In Cox regression analysis, rCDB more frequently occurred in patients with CCI $\geq$ 4 than in patients with CCI < 4 (adjusted hazard ratio, 2.76; 95% confidence interval, 1.30–5.88; $p < 0.01$).

Conclusions: rCDB occurred frequently at any time in patients with previous CDB. High CCI scores were associated with rCDB. Clinicians need to consider possible rCDB for patients with high CCIs.

Introduction

Despite the decreasing incidence of upper gastrointestinal bleeding, the incidence of lower gastrointestinal bleeding (LGIB) is gradually increasing.[1] Colonic diverticular bleeding (CDB) is a common cause of LGIB,[2] and its risk factors include old age, male sex, obesity, non-steroidal anti-inflammatory drug (NSAID) or antithrombic agent intake, and underlying comorbidities, including cardiovascular diseases, hypertension, or diabetes.[3] Recurrent CDB (rCDB) occurs within 1 year at rates of approximately 4–35%.[4–7] Despite several efforts, including avoiding or decreasing the number of probable triggers, rCDB may occur at various times and clinical situations, leading to increased morbidities, rehospitalizations, and medical costs. Its reported risk factors are similar but inconsistent, as previous studies included a small number of patients, and related clinical situations at each period may be different. In real clinical practice, performing risk stratification for rebleeding in patients with CDB is difficult. Therefore, studies with a larger number of patients considering the overall clinical factors including age, comorbidities, and prescribed medications for patients with CDB are needed.

The Charlson comorbidity index (CCI) was developed to determine the association between the patients' various underlying diseases and 1-year mortality.[8] It is helpful in approaching the patients by classifying and weighing their comorbidities. The CCI has been validated in various disease subgroups, such as cardiac, renal, stroke-related, and liver diseases.[8–12] Therefore, we assumed that the CCI would be a

risk factor for rCDB. Here, we aimed to evaluate the clinical course of patients with CDB and identify risk factors for rCDB, including the CCI, at a referral center.

Methods

Study population

This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board of the Chonnam National University Hospital (IRB No.: CNUH-2020-115).

From January 2005 to March 2020, a total of 3539 consecutive patients with gastrointestinal bleeding were admitted at our center, of which 1572 had obscure GIB or LGIB. After excluding patients with bleeding from small bowel origin, colon cancer, ischemic colitis, inflammatory bowel disease, hemorrhoid, angiodysplasia, colonic ulcer, or others, based on medical chart review, we included 221 patients with CDB (Fig. 1).

We retrospectively reviewed their electronic medical records and extracted information on their demographic factors, clinical characteristics, including comorbidities, medication history or laboratory findings, diagnostic or therapeutic procedural outcomes, and presence and relevance of rCDB with mortality.

Assessment of comorbidity and CCI score

The components of CCI include the following: acquired immunodeficiency syndrome status, cerebrovascular accident, chronic obstructive pulmonary disease, congestive cardiac failure, connective tissue disease, dementia, diabetes, hemiplegia, leukemia, liver disease, lymphoma, peptic ulcer disease, peripheral vascular disease, previous myocardial infarction, renal disease, and solid tumor with or without metastasis. We calculated the CCI score by adding the weights of all comorbid parameters.

Definition of CDB

All patients underwent colonoscopy and abdominal computed tomography (CT) to exclude other diseases, such as colonic inflammatory bowel disease or cancer. Definite CDB was diagnosed by colonoscopic findings of stigmata of recent diverticular hemorrhage (active bleeding, visible vessel, or adherent clot). Presumptive CDB was diagnosed by endoscopic features of a diverticulum with fresh blood clots in the colon, or abdominal CT findings of a colonic extravasation and colonoscopic findings of a diverticulum without other bleeding foci. Additional examinations, including esophagogastroduodenoscopy, abdominal CT, and/or capsule endoscopy, cannot confirm other bleeding foci.[4, 6] rCDB was defined as any rebleeding after initial discharge.

Treatment method

Endoscopic hemostasis, endoscopic clipping (EC), epinephrine injection therapy, and argon plasma coagulation were used. Transarterial embolization was also performed when extravasation was prominent on CT. If bleeding was not controlled by endoscopic treatment or embolization, surgical treatment was performed.

Confirmation of death outside the hospital

The patient's date of death and related disease codes were confirmed by request from the Korea National Statistical Agency. Disease codes were classified by the Korean Standard Classification of Disease and Cause of Death (KCD7).[13, 14]

Statistical analysis

The primary and secondary outcomes were rCDB and mortality after diverticular bleeding, respectively. Continuous and categorical data are expressed as means ± standard deviations or medians (ranges) and absolute or relative frequencies, respectively. Continuous variables were analyzed using Student's t-test. Categorical data were examined using the Fisher exact test or χ^2 test. Rebleeding free days were calculated from the date of first bleeding to the date of recurrence or death using the Kaplan–Meier method. Patients without evidence of recurrence were censored as alive and event-free at the date of last follow-up. Univariate analysis using the log-rank test and multivariate analysis using the Cox proportional hazards model were performed to evaluate the risk factors associated with rCDB. In all statistical tests, a two-sided p-value of < 0.05 was considered statistically significant. Kaplan–Meier analyses were performed using GraphPad Prism (version 5.0; GraphPad Software Inc., San Diego, CA), whereas all other analyses were performed using SPSS (version 25.0; SPSS Inc., Chicago, IL).

Results

Baseline demographic and clinical characteristics

A total of 221 patients (mean age, 68.1 ± 12.4 years; 56 females) were enrolled in the study. The most common comorbidities were hypertension (62.4%) and diabetes (33.5%). Aspirin, thienopyridine, and NSAIDs were administered to 76 (34.4%), 38 (17.2%), and 22 (10.0%) patients, respectively. The mean CCI score was 1.4 ± 1.7 (Table 1). Comorbidities contributing to CCI are shown in Supplement Table 1. Among the patients, 86, 54, 37, 16, 13, 8, and 7 had a CCI score of 0, 1, 2, 3, 4, 5, and ≥ 6, respectively (Fig. 2).

Table 1
Baseline characteristics of patients with colonic diverticular bleeding.

Variables	Total (n = 221)	Patients with rCDB (n = 51)	Patients without rCDB (n = 168)	p-value
Age, years, mean ± SD	68.1 ± 12.4	70.7 ± 10.9	67.2 ± 12.7	0.06
Females, n (%)	56 (25.3)	17 (33.3)	38 (22.6)	0.12
Body mass index, kg/m^2, mean ± SD	24.4 ± 3.4	24.8 ± 3.8	24.5 ± 3.3	0.69
Diagnosis, n (%)	56 (25.3)	13 (25.5)	42 (25.0)	0.94
Definite	165 (74.7)	38 (74.5)	126 (75.0)	
Presumptive				
Location of bleeding, n (%)	122 (55.2)	31 (60.8)	91 (54.2)	0.70
Right colon	29 (13.1)	6 (11.8)	22 (13.1)	
Left colon	70 (31.7)	14 (27.5)	55 (32.7)	
Indeterminate				
Shock on first admission, n (%)	55 (24.9)	13 (25.5)	40 (23.8)	0.81
Hypertension, n (%)	138 (62.4)	32 (62.7)	104 (61.9)	0.91
Diabetes, n (%)	74 (33.5)	15 (29.4)	58 (34.5)	0.50
Cerebrovascular disease, n (%)	27 (12.2)	9 (17.6)	17 (10.1)	0.15
Chronic kidney disease*, n (%)	20 (9.0)	7 (13.7)	12 (7.1)	0.14
Liver disease, n (%)	11 (5.0)	5 (9.8)	6 (3.6)	0.07
Total	3 (1.4)	2 (3.9)	1 (0.6)	0.07
Hepatitis	8 (3.6)	3 (5.9)	5 (3.0)	0.33
Cirrhosis				
Any tumor, n (%)	20 (9.0)	5 (9.8)	15 (8.9)	0.85

CDB, colonic diverticular bleeding; NOAC, new oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; PT, prothrombin time; rCDB, recurrent CDB; SD, standard deviation.

The total number includes patients who died on initial admission to CDB, patients with rCDB, and patients without rCDB.

* Chronic kidney disease was defined as a serum creatinine level > 3.0 mg/dL or if the patient was on dialysis.

Variables	Total (n = 221)	Patients with rCDB (n = 51)	Patients without rCDB (n = 168)	p-value
Chronic lung disease, n (%)	7 (3.2)	2 (3.9)	5 (3.0)	0.74
Charlson comorbidity index, mean ± SD	1.4 ± 1.7	1.7 ± 1.9	1.4 ± 1.8	0.39
Laboratory findings, mean ± SD				
Hemoglobin(mg/dL)	10.0 ± 2.5	9.9 ± 2.6	10.0 ± 2.4	0.81
Platelet count(mm3)	205.0 ± 69.6	217.1 ± 80.6	203.1 ± 64.2	0.26
PT (INR)	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.6	0.40
Creatinine (mg/dL)	1.0 ± 0.7	1.1 ± 1.0	1.0 ± 0.5	0.13
Anti-thrombotic agents, n (%)				
Aspirin	76 (34.4)	13 (25.5)	61 (36.3)	0.15
Thienopyridine	38 (17.2)	8 (15.7)	28 (16.7)	0.87
Cilostazol	5 (2.3)	2 (3.9)	3 (1.8)	0.37
Warfarin	14 (6.3)	5 (9.8)	9 (5.4)	0.26
NOAC	7 (3.2)	2 (3.9)	5 (3.0)	0.74
Number of anti-thrombotic agents, mean ± SD	0.8 ± 0.8	0.8 ± 0.8	0.8 ± 0.8	0.90
Steroids, n (%)	9 (4.1)	4 (7.8)	4 (2.4)	0.07
NSAIDs, n (%)	22 (10.0)	4 (7.8)	18 (10.7)	0.55
CDB, colonic diverticular bleeding; NOAC, new oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; PT, prothrombin time; rCDB, recurrent CDB; SD, standard deviation.				
The total number includes patients who died on initial admission to CDB, patients with rCDB, and patients without rCDB.				
* Chronic kidney disease was defined as a serum creatinine level > 3.0 mg/dL or if the patient was on dialysis.				

Definite and presumptive CDB were diagnosed in 56 (25.3%) and 165 (74.7%) patients, respectively, and the CDB was right-sided, left-sided, and indeterminate in 122 (55.2%), 29 (13.1%), and 70 (31.7%) patients, respectively. Fifty-five (24.9%) patients had experienced shock at admission, and 166 (75.1%) patients had undergone urgent colonoscopy within 24 hours of admission. Of the total 221 patients with CDB at first admission, bleeding stopped spontaneously in 150 (67.9%) patients. Urgent endoscopic, radiologic, and surgical interventions were performed in 56 (25.3%), 11 (5.0%), and 2 (0.9%) patients, respectively.

The median duration of hospitalization was 5 days (range, 2–119 days). rCDB requiring a second hospitalization occurred in 51 (23.1%) patients, of which 18 (8.1%) patients required a third hospitalization (Fig. 3). The CDB-related mortality rate at first admission was 0.9% (2/221).

rCDB

After excluding two patients who died at first admission, 219 patients were analyzed to evaluate the variables associated with rCDB. rCDB occurred in 51 (23.3%) patients. Mean follow-up after first admission in patients with rCDB and without rCDB was 20.0 ± 27.6 months and 56.0 ± 36.5 months, respectively. Median follow-up after first admission in patients with rCDB and without rCDB was 11 months (range, 0.1–160.6) and 47 months (range, 8.4–157.1), respectively. The cumulative incidence rates of rCDB at 1, 6, 12, and 24 months were 4.6% (n = 10), 9.1% (n = 20), 12.3% (n = 27), and 16.9% (n = 37), respectively.

There were no significant differences between rCDB-positive and rCDB-negative groups in terms of baseline characteristics, including demographic factors, underlying comorbidities, laboratory findings, use of antithrombotic agents or NSAIDs, and variables contributing to the CCI score (Table 1 and Supplement Table 1). There were also no significant differences between the two groups in terms of endoscopic (25.5% vs. 25.0%, p = 0.94), radiologic (5.9% vs. 4.2%, p = 0.61), and surgical (2.0% vs. 0.6%, p = 0.58) interventions performed.

Kaplan–Meier analysis showed that rCDB occurred more in patients with CCI scores ≥ 4 than in patients with CCI scores < 4 (95% confidence interval [CI], 1.37–9.32; hazard ratio [HR], 3.58; p < 0.01) (Fig. 4), even after adjusting for other factors, including age, sex, antithrombotic use, steroid use, NSAID use, hemostatic intervention, and bleeding location (95% CI, 1.30–5.88; adjusted HR, 2.76; p < 0.01) (Table 2).

Table 2
Univariate and multivariate analyses of the risk factors for increase in diverticular rebleeding using Cox regression.

Variables	cHR	95% CI	p-value	aHR	95% CI	p-value
Age	1.02	0.99–1.06	0.18	1.02	0.99–1.05	0.12
Male sex	1.68	0.75–3.78	0.21	1.35	0.62–2.93	0.45
CCI ≥ 4	2.67	1.20–5.96	0.02	2.76	1.30–5.88	< 0.01
Number of antithrombotics	1.01	0.61–1.66	0.98	0.95	0.58–1.57	0.85
Steroids	0.31	0.07–1.38	0.12	0.39	0.12–1.34	0.13
NSAIDs	1.28	0.34–4.84	0.72	1.25	0.40–3.89	0.70
Hemostasis	1.39	0.67–2.88	0.38	1.21	0.61–2.39	0.59
Location of bleeding	1.69	0.67–4.27	0.27	1.39	0.57–3.40	0.47

cHR, crude hazard ratio; aHR, adjusted hazard ratio; CCI, Charlson comorbidity index; CI, confidence interval.

Causes of death

Two patients died at first admission because of diverticular bleeding and acute myocardial infarction, respectively. During follow-up after discharge, 31 out of the remaining 219 patients died, of which 11 (21.6%) had rCDB and 20 (11.8%) did not have rCDB (p = 0.08). One patient with rCDB had a CDB-related death. The most common cause of death during follow-up was pneumonia (n = 5, 16.1%) (Supplement Table 2).

Discussion

This study presented the clinical course of 221 patients with CDB over 13 years in a tertiary referral center. The recurrence rate was as high as 23%. CCI ≥ 4 was found to be significantly associated with an increased risk of rCDB.

The incidence of CDB is increasing because of the increase in the incidence of colonic diverticulosis, elderly population, and antithrombotic agent use.[3] Approximately 70–90% of diverticular bleeding events spontaneously stop, complicating the definite diagnosis of diverticular bleeding.[15–17] In our study, only 25% of the patients were diagnosed with definite CDB, which was similar to proportions in previous studies (19–42%),[6, 18, 19] and CDB spontaneously stopped in 80% of the patients. Despite this, about 25% of the patients with CDB experienced hypovolemic shock at admission, which was also similar to that in a previous study (25.6%).[7] Moreover, two patients with CDB died at first admission (one with CDB and another with myocardial infarction). Therefore, any changes in symptoms or vital signs should be closely monitored and adequate resuscitation should be provided for all patients with CDB.

While left-sided colonic diverticulosis is more common in Western countries, right-sided colonic diverticulosis is more common in Asia.[18, 20–22] CDB is more commonly right-sided,[23, 24] and our study showed similar results.

Endoscopic hemostasis can achieve a high rate of active bleeding control[25, 26] and is typically considered the first-line treatment for CDB management.[27, 28] In this study, 75% of patients had undergone urgent colonoscopy examination within 24 hours. Although aggressive colonoscopic evaluation was performed as the first evaluation, endoscopic intervention was performed in only a third of the patients. A literature review reported an endoscopic hemostasis rate ranging from 20.8 to 32.8% in Western countries [29, 30] and 16.8 to 34.1% in Eastern countries,[31, 32] which were similar to the rates in our study. Angiographic treatment and surgical resection can be the other modalities used if endoscopic hemostasis fails.[33, 34] In our study, radiological intervention was performed in 11 (5.0%) patients and surgical intervention in 2 (0.9%).

In our study, the 1-year incidence of rCDB was 12.3%. In other studies, the 1-year incidence of rCDB varied between 4% and 35%.[4–7] Although NSAIDs, steroids, antithrombic agents, obesity, hypertension, and CKDs are risk factors for rCDB, each study showed inconsistent results,[4–6, 35] suggesting that considering the overall patient condition, rather than each variable, is necessary.

We used the CCI score to reflect the overall status of comorbidities. The CCI score was calculated according to the severity of various underlying diseases and was originally developed to analyze the 1-year mortality of hospitalized patients.[8] Recently, it has been used to predict the prognosis in various patient groups,[9–12, 36] with high CCI scores becoming a risk factor for severe CDB.[37] In this study, the CCI scores of the two patients who died at first admission were 4 and 5. A high CCI score is also a risk factor for rCDB.[38]

In our study, the incidence of rCDB was 2.7 times higher in patients with CCI scores ≥ 4 than in those with CCI scores < 4, after adjusting for several known risk factors, such as age, sex, medication intake, hemostasis, and location of CDB. Furthermore, we showed a significant increase in mortality even in patients with CDB with CCI scores of ≥ 4. A CCI score of ≥ 4 was usually confirmed in patients with multiple or serious comorbidities, suggesting that multiple comorbidities affect the incidence of rCDB in patients.

In this study, CDB-related death occurred in two patients, and the overall mortality rate was twice as high in patients with rCDB compared to that in patients without rCDB. Although CDB itself was not the immediate cause of death, increased hospitalization and morbidity due to CDB may have affected the increase in mortality.

Our study had two limitations. First, this was a retrospective cohort study conducted at a single referral center. However, a larger number of cases were evaluated in this study than in previous studies. Second, this study did not reflect the effects of variable endoscopic hemostatic methods, such as endoscopic band ligation, endoscopic detachable snare ligation, use of topical hemostatic agents, and over-the scope

clip.[31, 39–41] We typically performed endoscopic hemostasis using EC or endoscopic injection therapy. Recent studies showed that endoscopic band ligation was more helpful in decreasing early rCDB.[18, 34]

Conclusion

rCDB occurred frequently at any time in patients with previous CDB. High CCI scores were associated with rCDB. Clinicians need to consider possible rCDB for patients with high CCIs.

Abbreviations

CCI	Charlson comorbidity index
CDB	colonic diverticular bleeding
CI	confidence interval
CKD	chronic kidney disease
CT	computed tomography
HR	hazard ratio
LGIB	lower gastrointestinal bleeding
NSAIDs	nonsteroidal anti-inflammatory drugs
NOAC	new oral anticoagulant
rCDB	recurrent CDB

Declarations

•**Ethics approval and consent to participate:** The Ethics Committee of the Chonnam National University Hospital approved this study (IRB No. CNUH-2020-115). The need for informed consent was waived by the Chonnam National University Hospital Institutional Review Board due to the retrospective nature of the study. All the study protocol was in accordance with Declaration of Helsinki.

•**Consent for publication**: Not Applicable.

•**Availability of data and material**: The datasets used and/or analyzed during the current study are not currently available due to their containing information that could compromise the privacy of research participants, but are available from the corresponding author on reasonable request.

•**Competing interests**: The authors have no conflicts of interests.

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DHK and HSY developed the concept of the study, analyzed electronic medical records, and wrote the manuscript. CHP and SKC made substantial contributions to the conception and design of the study, interpreted data, wrote the paper, and revised it critically for intellectual content. SYP and HSK performed the literature review and collected clinical data. All authors (DHK, HSY, SYC, CHP, SYP, HSK, and SKC) have read and approved the final manuscript.

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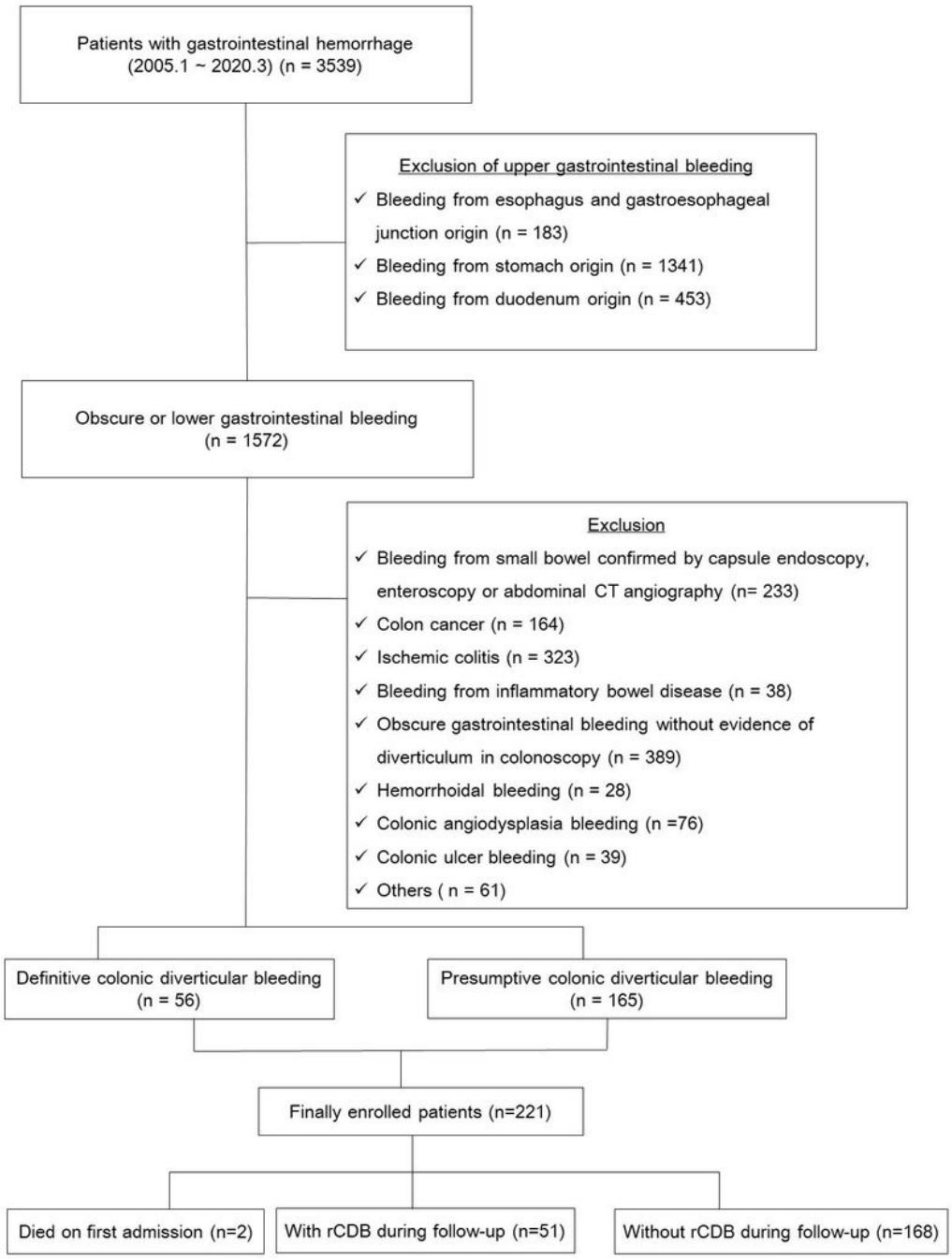
Figures



CT, computed tomography; rCDB, recurrent colonic diverticular bleeding.

Figure 1

Patient enrollment flowchart.

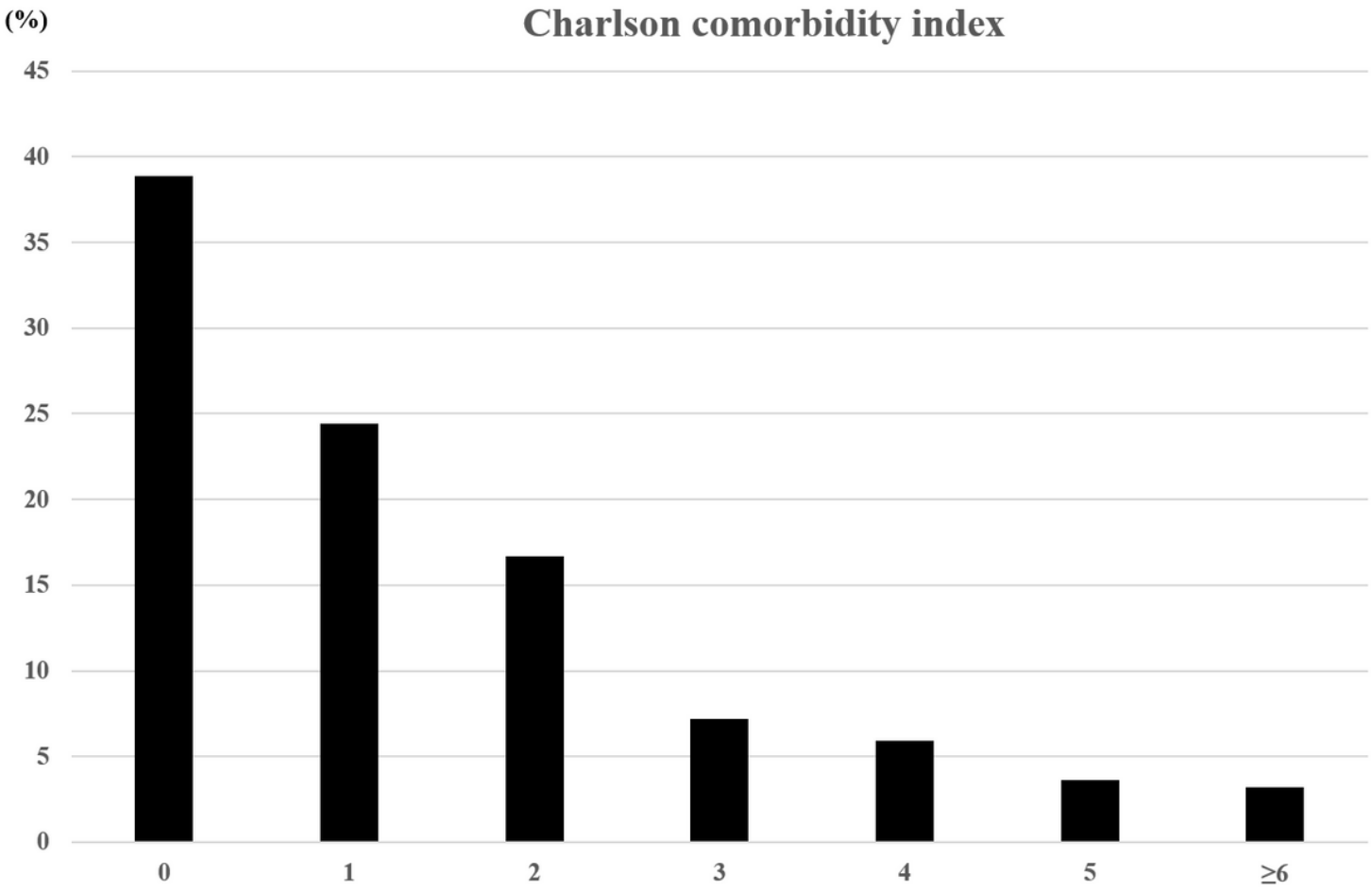
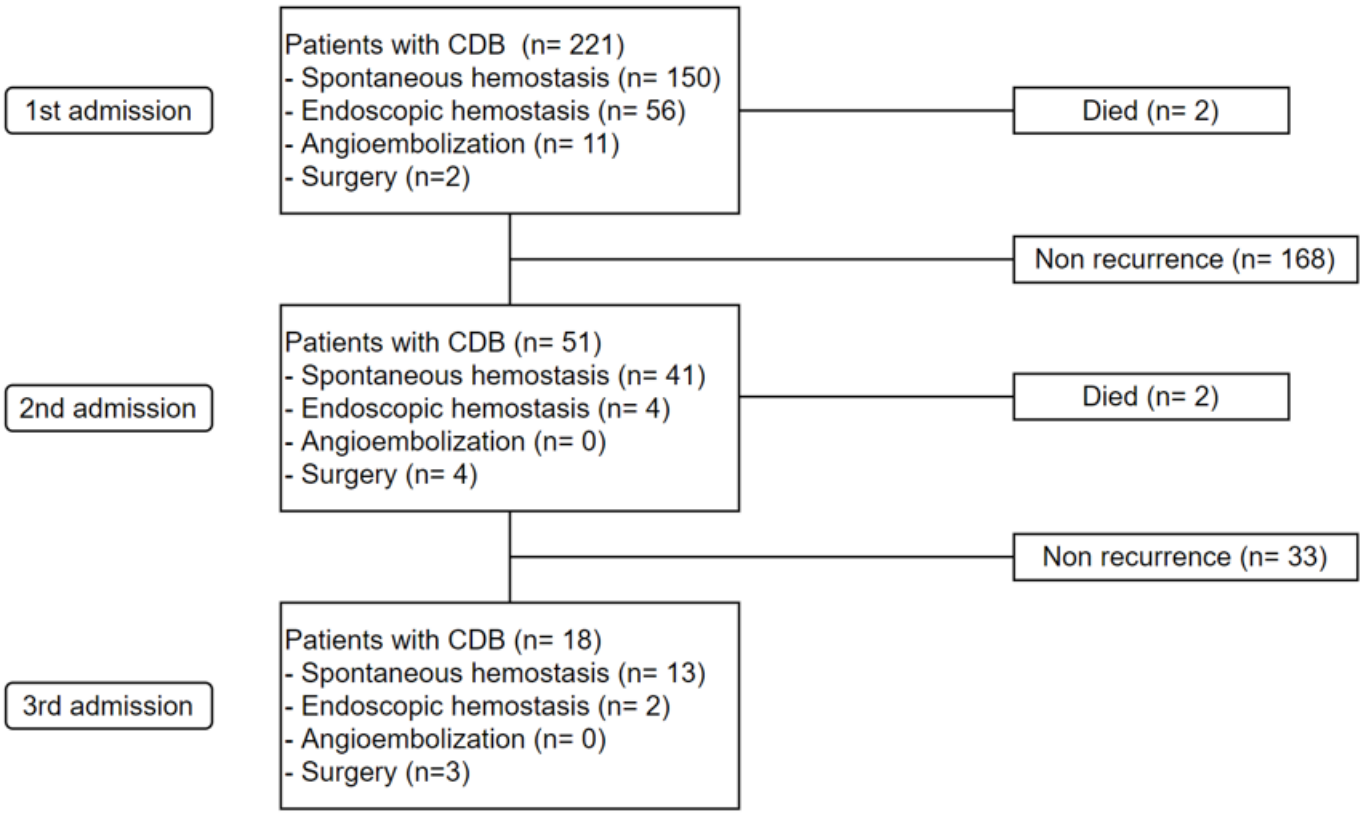


Figure 2

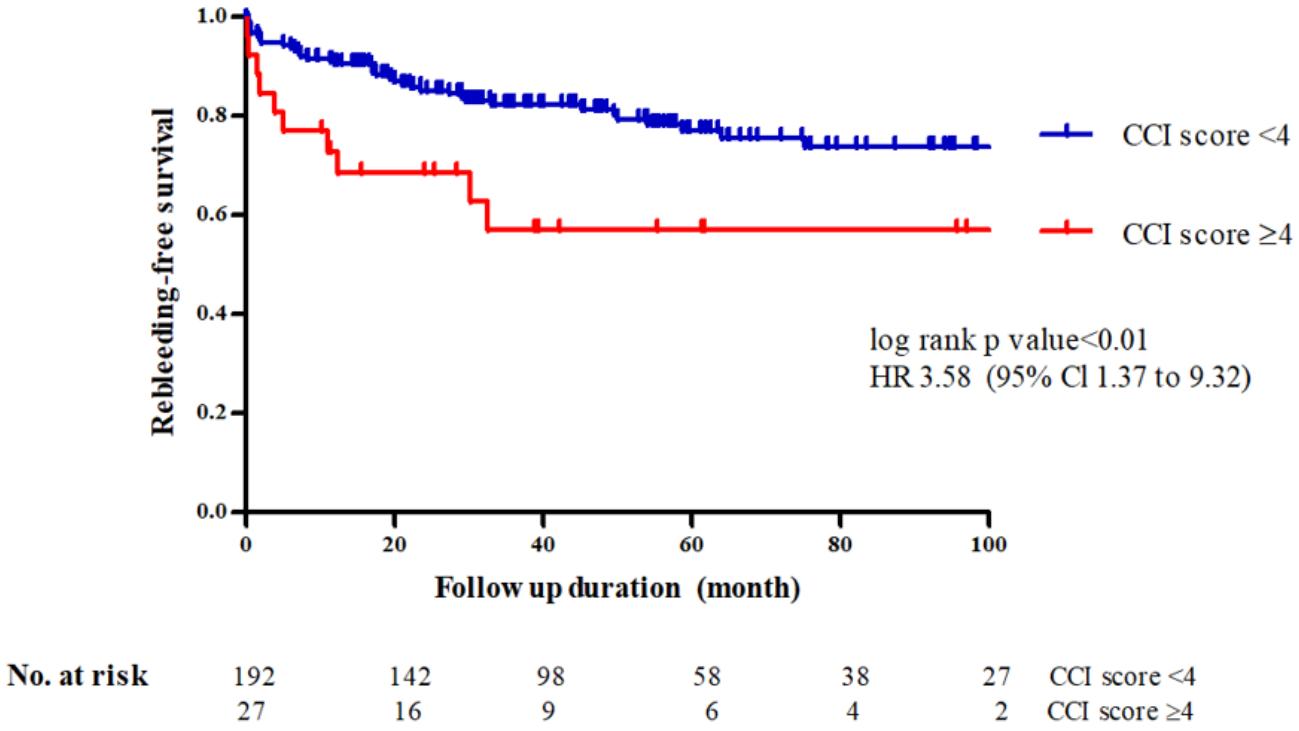
Distribution of Charlson comorbidity index scores.



CDB, recurrent colonic diverticular bleeding.

Figure 3

Long-term outcomes of re-admission and therapeutic modalities in study population



CCI, Charlson comorbidity Index; CI, confidence interval; HR, hazard ratio.

Figure 4

Comparison of rebleeding-free survival rate according to the Charlson comorbidity index scores of ≥ 4 or < 4 using the Kaplan-Meier graph.

Supplementary Files

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- supplementtable.docx