

A Case-control Study on the Risk Factors for Ischemic Colitis

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Objective: Ischemic colitis (IC) is a relatively common acute inflammation disorder of the intestine. It was considered to be a disorder of elderly people with risk factors for arteriosclerosis; however, a considerable number of young people with IC have been reported recently. We performed a case-control study to determine the risk factors for IC and compare the risk factors between elderly and non-elderly people.

Methods: The study included 209 consecutive patients diagnosed with IC between December 2004 and March 2017 at Tokai University Hospital. The study also included 209 randomly selected controls in the same calendar year so as to match age and sex. Possible risk factors for IC were identified and compared between age groups.

Results: The mean age of IC group was 64.9 with 60 males and 115 elderly patients aged 65 or more in each group. On multivariable conditional logistic regression analysis, drinking, abdominal surgery, hypertension, and malignant diseases were risk factors for IC in all ages. In non-elderly patients, only hypertension and laxative/enema use were significant factors, while in elderly, abdominal surgery, hypertension, COPD, malignant disease and antiplatelet drugs were significant.

Conclusion: The risk factors in elderly people might be quite different from younger ones, while hypertension seemed to be a common risk in all ages.

Key words: ischemic colitis, risk factor, age

INTRODUCTION

Ischemic colitis (IC), which is also referred to as colonic ischemia, is one of the most common intestinal disorders and is thought to be caused by reduced blood flow followed by reperfusion injury [1, 2]. IC is typically characterized by the sudden onset of left lower abdominal pain with diarrhea and hematochezia, and the condition tends to recover rather quickly with intestinal rest in most cases. However, in some severe cases, surgery might be needed or the condition might be fatal. The left colon is the most commonly affected segment, and longitudinal ulcers or erosions are typical endoscopic findings.

There have been case-control studies on the risk factors for IC [3-7]. Cardiovascular disease-related factors, such as diabetes, dyslipidemia, heart failure, peripheral vascular disease, and aspirin or digoxin use, were thought to be risk factors for IC. Surgery for an abdominal aortic aneurysm was also thought to increase the chance of IC. Other than these factors, constipation, coagulopathy, use of illicit and prescription drugs such as cocaine, and endurance athletics have been evaluated as risk factors for IC.

The features of IC are commonly noted in elderly people with a previous history of atherosclerotic disease, and there is a female dominance [8]. However, some patients experience the disease at a young age. The risks for IC might differ between young and elderly people. However, the results of previous studies

have been controversial. For example, constipation was found to be a risk factor in elderly people and not in young people in a previous report [7] but was found to be a risk factor in both young and elderly people in another previous report [9].

Thus, the present study aimed to determine the risk factors for IC and to compare the risk factors between young and elderly people.

PATIENTS AND METHODS

Participants were identified by screening the electronic records of colonoscopy performed in the endoscopy room of Tokai University Hospital between December 2004 and March 2017. A total of 209 consecutive patients diagnosed with IC were included in the IC group. The diagnosis was based on comprehensive assessments of the clinical course, physical findings, blood data, and colonoscopy findings. Using the same electronic records, 14,782 candidates were screened with the objective of choosing control patients; no special findings were noted, except for the presence of hemorrhoid. Each patient with IC was assigned an age- and sex-matched control in the same calendar-year with a caliper of 3 years in age.

The following information was obtained from the electronic medical records of each participant: age; sex; histories of smoking, drinking, and abdominal surgery; comorbidities, including hypertension, hyperlipidemia, hyperuricemia, diabetes mellitus, coronary heart disease, congestive heart failure, atrial fibrilla-

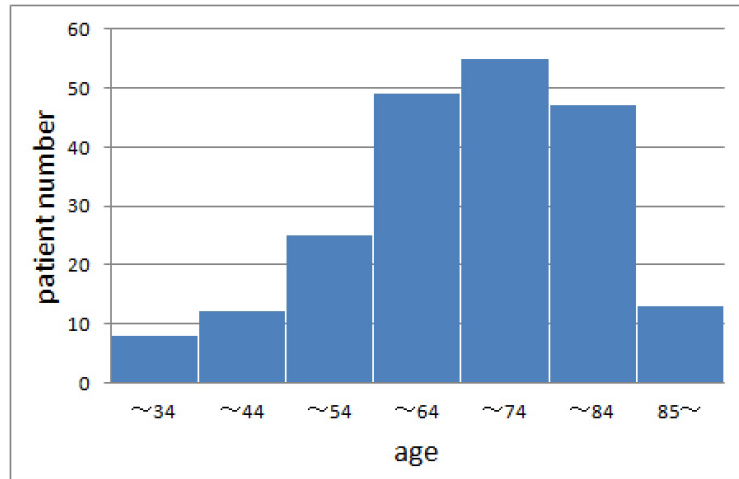


Fig. 1 Age distribution of the patients with ischemic colitis.

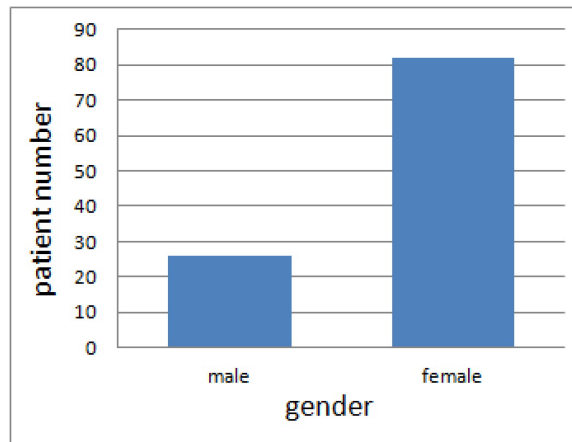


Fig. 2 Sex of the patients with ischemic colitis.

tion, liver disease, chronic kidney disease (creatinine level ≥ 2.0 mg/dL), chronic obstructive pulmonary disease, brain stroke, malignant disease, and irritable bowel syndrome; and medications/procedures, including laxatives/enema, oral contraceptives, nonsteroidal anti-inflammatory drugs, antiplatelet drugs, including low-dose aspirin (LDA), anticoagulants, and antidepressants.

Each characteristic was simply compared between the IC and control groups, and univariate analyses were performed using Fisher's exact test or Student's *t*-test. Risk factors associated with IC were elucidated via a multivariable conditional logistic regression analysis involving a backward elimination method with an alpha level of 0.5 using SAS University Edition (SAS Institute Inc., Cary, NC, USA. Released in April 2018.).

RESULTS

The IC group included 209 patients, and the control group included 209 controls. The age distribution and sex of patients in the IC group are shown in Figs. 1 and 2, respectively. Female sex was dominant, and with regard to age distribution, a major peak was noted for the patients around 70. Risk factors for IC in younger and elder people might be different and the risk factor analyses of the non-elderly participants (age < 65 years) and elderly participants (age ≥ 65 years)

were separately performed after the all-age analysis.

The mean age of the patients with IC was 64.9 years (standard deviation [SD], 14.33 years), while the mean age of the controls was 64.9 years (SD, 14.31 years; Table 1). In both groups, over 70% of the participants were female. Thus, the age and sex-matched controls appeared to have been selected properly. Table 1 shows comparisons of the possible risk factors between the IC and control groups according to univariate analysis. History of abdominal surgery, hypertension, coronary heart disease, chronic kidney disease, and antiplatelet drug use were more frequent in the IC group than in the control group, while drinking was less frequent in the IC group than in the control group.

The all-age analysis with a multivariable regression model was performed, and the results are shown in Table 2. No drinking ($p = 0.0451$), history of abdominal surgery ($p = 0.0180$), hypertension ($p = 0.0024$), and no malignant disease ($p = 0.0184$) were related with IC. In elderly patients (age ≥ 65 years), history of abdominal surgery ($p < 0.0041$), hypertension ($p = 0.0026$), COPD ($p = 0.0419$), no malignant disease ($p = 0.0314$) and antiplatelet drug use ($p = 0.0360$) were positively related with IC (Table 3). In non-elderly patients (age < 65 years), only hypertension ($p = 0.0238$) and laxative/enema use ($p = 0.0033$) were positively related with IC (Table 4). Possible risk factors by age

Table 1 Comparison of various factors between the patients with ischemic colitis and controls

	Ischemic colitis (n = 209)	Controls (n = 209)	P-values
Age, years	64.9	64.9	0.9918
Male sex	60	60	1.0000
History			
Smoking	22	30	0.2995
Drinking	29	55	0.0022
Abdominal surgery	68	46	0.0209
Comorbidities			
Hypertension	115	74	< 0.0001
Hyperlipidemia	55	44	0.2499
Hyperuricemia	3	1	0.6232
Diabetes	36	31	0.5941
Coronary heart disease	23	9	0.0156
Congestive heart failure	12	6	0.2275
Atrial fibrillation	16	9	0.2152
Liver disease	2	1	1.0000
Chronic kidney disease	13	4	0.0446
COPD	8	2	0.1052
Brain stroke	22	12	0.1062
Malignant disease	22	31	0.2394
Irritable bowel syndrome	6	1	0.1219
Medications			
Laxatives/ enema	64	49	0.1229
Oral contraceptives	0	4	0.1232
Antidepressants	25	21	0.6396
NSAIDs	22	15	0.3015
Antiplatelet drugs including LDA	46	17	0.0001
Anticoagulants	9	9	1.0000
Steroid	12	9	0.6553

t-test for age, Fisher's exact test for the other factors

Significant p-values are indicated in bold text.

COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; LDA, low-dose aspirin

Table 2 Multivariate analysis of the risk factors for ischemic colitis

	Odds ratio	Confidence Interval	P-value
Smoking	0.740	0.320-1.710	0.4811
Drinking	0.488	0.242-0.984	0.0451
Abdominal surgery	1.887	1.115-3.193	0.0180
Hypertension	2.248	1.334-3.788	0.0024
Diabetes	0.771	0.399-1.488	0.4377
Coronary heart disease	1.457	0.544-3.901	0.4536
Congestive heart failure	1.976	0.551-7.084	0.2956
Chronic kidney disease	1.806	0.445-7.339	0.4083
COPD	2.308	0.288-18.466	0.4306
Brain stroke	1.784	0.648-4.910	0.2627
Malignant disease	0.396	0.183-0.855	0.0184
Irritable bowel syndrome	4.042	0.436-37.445	0.2187
Laxatives/ enema	1.271	0.754-2.142	0.3685
Antiplatelet drugs including LDA	1.762	0.759-4.093	0.1877
Anticoagulants	0.593	0.162-2.166	0.4294
Steroid	1.566	0.577-4.251	0.3790

Conditional logistic regression

Risk factors were selected by a backward elimination with an alpha level of 0.5

Significant p-values are indicated in bold text

COPD, chronic obstructive pulmonary disease; LDA, low-dose aspirin

Table 3 Multivariable analysis of the risk factors for ischemic colitis in elderly patients (age ≥ 65 , 115 cases and controls)

	Odds ratio	Confidence Interval	P-value
Drinking	0.366	0.111-1.211	0.0997
Abdominal surgery	3.233	1.452-7.195	0.0041
Hypertension	3.350	1.525-7.359	0.0026
Hyperlipidemia	0.646	0.283-1.473	0.2987
Diabetes	0.620	0.252-1.527	0.2987
Atrial fibrillation	1.918	0.645-5.710	0.2416
COPD	15.580	1.106-219.538	0.0419
Malignant disease	0.317	0.111-0.903	0.0314
Laxatives/ enema	0.593	0.291-1.209	0.1503
Antidepressants	0.609	0.186-1.996	0.4124
Antiplatelet drugs including LDA	2.863	1.071-7.651	0.0360

Conditional logistic regression

Risk factors were selected by a backward elimination with an alpha level of 0.5

Significant p-values are indicated in bold text

COPD, chronic obstructive pulmonary disease; LDA, low-dose aspirin

Table 4 Multivariable analysis of the risk factors for ischemic colitis in non-elderly patients (age ≤ 64 , 94 cases and controls)

	Odds ratio	Confidence Interval	P-value
Smoking	0.484	0.165-1.420	0.1864
Hypertension	3.060	1.160-8.068	0.0238
Brain stroke	2.876	0.304-27.229	0.3571
Malignant disease	0.340	0.092-1.255	0.1054
Laxatives/ enema	3.993	1.584-10.066	0.0033
Antidepressants	1.628	0.593-4.469	0.3447
Antiplatelet drugs including LDA	2.455	0.409-14.742	0.3262

Conditional logistic regression

Risk factors were selected by a backward elimination with an alpha level of 0.5

Hyperuricemia and liver disease were excluded because all patients had no disease

Significant p-values are indicated in bold text

LDA, low-dose aspirin

interactions for IC were analyzed, and the results are shown in Table 5. Only COPD ($p = 0.0127$) and laxative/enema use ($p = 0.0030$) were significantly different between the two age groups. These results suggested that the possible risk factors for IC were no drinking, history of abdominal surgery, hypertension, and no malignant disease not depending on age, and that in only elderly or non-elderly IC was COPD or laxative/enema use, respectively.

DISCUSSION

There have been several reports on the risk factors for IC [3-7]. Generally, IC is more often observed in elderly people, and it shows a female dominance [8]. IC was thought to be associated with transient insufficiency of blood flow to the colon, and the risk factors for arteriosclerosis were highly suggested as risk factors for IC [1, 2]. A recent retrospective, case-control study from Spain indicated that diabetes, dyslipidemia, heart failure, peripheral vascular disease, and use of aspirin, and digoxin were associated with the development of IC [4]. A large cohort case-control study from the US indicated that multiple atherosclerotic disease-related factors, such as hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease,

congestive heart failure, smoking, and diabetes, were associated with IC [3]. In two previous reports from the US, irritable bowel syndrome and constipation were shown to be risk factors for IC [5, 7]. In a report using the UK primary care database, inflammatory bowel disease and heart failure were shown to be associated with IC [6]. According to these case-control studies, atherosclerosis-related risk factors, history of abdominal surgery, and bowel disorders affecting bowel habits appear to be related with IC; however, the results remain controversial.

Many factors, such as race, climate, eating habits, and age constitution, might influence the results. Thus, it might be beneficial to attempt to assess the risk factors for IC in different countries or districts with a reliable study approach. We therefore performed this case-control study in the southern Kanto area of Japan. In our study, history of abdominal surgery, hypertension, no drinking and no malignant disease were found to be risk factors for IC. These results were partly different from the results of previous studies. On searching the PubMed database with the keywords IC, case-control study, and Japan, we found limited case-control studies on the risk factors for IC in Japan. We identified a small sample report focusing

Table 5 Risk factor by age interactions for ischemic colitis

	Subgroup	Odds ratio	Confidence Interval	P-value
Drinking	Elderly	0.294	0.107-0.812	0.1049
	Non-elderly	0.798	0.392-1.628	
Abdominal surgery	Elderly	3.398	1.682-6.866	0.0954
	Non-elderly	1.426	0.678-3.000	
Hypertension	Elderly	2.371	1.240-4.534	0.8156
	Non-elderly	2.662	1.233-5.748	
COPD	Elderly	6.214	0.924-41.766	0.0127
	Non-elderly	0.187	0.010-3.605	
Malignant disease	Elderly	0.339	0.140-0.819	0.5648
	Non-elderly	0.517	0.161-1.661	
Laxatives/ enema	Elderly	0.679	0.354-1.303	0.0030
	Non-elderly	3.462	1.466-8.172	
Antiplatelet drugs	Elderly	2.117	0.928-4.826	0.5594
	Non-elderly	4.228	0.461-38.750	

Conditional logistic regression

Explanatory variables are smoking, drinking, abdominal surgery, hypertension, hyperlipidemia, diabetes, coronary heart disease, congestive heart failure, atrial fibrillation, chronic kidney disease, COPD, brain stroke, malignant disease, irritable bowel syndrome, laxatives/ enema, antidepressants, antiplatelet drugs, anticoagulants, steroid, and risk factor by age interactions in the table.

The main effect terms are the selected factors in the whole population or the age subgroup analyses.

The interaction terms are significant factors in the whole population or the age subgroup analyses.

P-values are for risk factor by age interactions, testing the equality of odds ratios between age groups.

Significant p-values are indicated in bold text

COPD, chronic obstructive pulmonary disease

on abdominal fat accumulation, which suggested only dyslipidemia, other than fat accumulation, as a risk factor for IC [10]. Our findings were different from those of this study but were similar to those of global studies at least in regard with the two factors history of abdominal surgery and hypertension. As for the other 2 factors, drinking and malignant disease, the interpretation seemed to be very difficult.

Few reports have compared IC risk factors between young and elderly people. Habu *et al.* examined 68 consecutive IC cases and found that atherosclerosis-related factors were common in elderly patients, while chronic constipation and history of abdominal surgery were common in both young and elderly patients [9]. A case-control study by Chang *et al.* suggested that colon-related factors, such as intestinal excision and irritable bowel syndrome, were more evident in young patients than in elderly patients [7]. IC is caused by transient insufficient blood supply to the colon, and its pathogenesis may be divided into decreased blood supply and increased burden on the colon, which indicate blood supply-related and colon-related factors, respectively. In our study, two of the significant risk factors in whole ages, history of abdominal surgery and hypertension, seemed to be more blood supply related, while the other two were very hard to be explained. In elderly people, four out of the five significant factors, abdominal surgery, hypertension, COPD, and antiplatelet drug use, were blood supply-related. In the non-elderly people, only 2 factors, hypertension and laxatives/enema use, were significant and the former was blood-supply related, while the latter was colon-related. These data suggested that blood-supply related factors were closely related with IC in elderly people, while colon related factors might be also important in addition to blood-supply related ones in non-elderly IC. These results were at least partially consistent with the

findings of previous studies and supported the hypothesis that the pathogenesis of IC in the elderly is related with atherosclerosis. The pathogenesis of IC in younger people might be partially different from that in elderly people.

The present study had some limitations. First, the patient data, such as medical history and drug use, were dependent on medical records, including information from questionnaires written by the patients and their families, which was confirmed by the nurses in the clinic. The accuracy of the data was not supported by objective evidence or records. Second, the population of the control group might have bias. Individuals with no special findings on colonoscopy were used as controls in this study. However, there is a possible bias as the individuals received colonoscopy, and this bias might have affected the results. Third, the diagnosis of IC was mainly dependent on colonoscopy findings supported by the clinical course, and this approach cannot completely exclude the possible presence of other disorders. However, the reliability of the diagnostic procedures has been reported to be considerably high [1], and this might not be a large issue in this study. Fourth, the bowel preparation containing laxatives itself may cause IC. But there were no such cases in the IC group in the study.

In conclusion, overall, history of abdominal surgery, hypertension, no drinking, and no malignant disease were suggested to be risk factors for IC. COPD and laxative/enema use may be unique risk factors for IC among elderly and non-elderly people, respectively. Our findings indicate that the risk factors in elderly people might be more related with atherosclerosis, while those in young people might be also related with the burden on the colon. Further studies will be needed to confirm this in the future.

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