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ORIGINAL ARTICLE

The clinical practice of ulcerative colitis in elderly patients: An investigation using a nationwide database in Japan

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Abstract

Background and Aim: The number of elderly patients with ulcerative colitis (UC) is increasing worldwide. The clinical practice of associated treatment is still unclear. Therefore, we aimed to analyze clinical treatment realities and mortality in elderly and non-elderly patients with UC.

Methods: We collected UC patients' data using the diagnosis procedure combination (DPC) database system and divided eligible patients into elderly (≥65 years) and non-elderly (≤64 years) groups. We investigated and compared their therapeutic histories (medical treatments *vs*. surgery). Logistic regression analysis was conducted to identify clinical factors affecting surgery and in-hospital death in each group.

Results: The rates of systemic steroid injection, molecular targeting drug usage, and surgery were not different between the two age groups. Meanwhile, the rate of in-hospital death in elderly patients was higher than that in non-elderly patients (2.7% *vs*. 0.19%, $P < 0.0001$). Multivariate analysis revealed that lower body mass index, treatment at an academic hospital, smoking history, molecular targeting drug use, and treatment with systemic steroid injection affected the rate of surgery in the elderly group. Multivariate analysis also revealed that male and older age affected the rate of in-hospital death in the elderly group. Similar tendencies were also recognized in the non-elderly group.

Conclusions: The clinical practice of treating elderly patients with UC is overall not different from treating non-elderly patients with UC. Although the form of medical treatment and surgery rate for elderly patients with UC may not be significantly different from non-elderly patients, the rate of in-hospital death for elderly patients is higher.

Introduction

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized as a diffuse nonspecific inflammatory disorder of the colon mainly affecting the mucosa by forming erosions and ulcers.[1,2] The first peak of UC onset is seen in patients aged 30–40 years old; the second peak is seen in the elderly.[3–5] Several studies recently reported that the number of elderly-onset patients with UC was increasing worldwide.[6–8] Therefore, it is important for daily practice that clinicians fully understand the characteristics of elderly patients with UC.

Elderly patients are generally more susceptible to developing complications and need to be treated more carefully than younger patients. Although one review reported that disease severity of UC in elderly and non-elderly patients was not different,[9] several studies have reported contradictory results.[7,10–14] Furthermore, the clinical practice of treating elderly patients with UC—including medication, duration of hospital stay, and the rates of surgery and in-hospital death—are still unclear. It is also unclear whether there is a significant difference between the clinical factors that affect the risks of surgery and in-hospital death between elderly and younger patients.

The number of patients with UC in a single-center is too small to analyze; even smaller is the number of fatal cases. In contrast, the diagnosis procedure combination (DPC) is a national database of hospitalizations in Japan[15] containing data on a large number of patients, which are useful for analyzing the clinical practice of treating UC across Japan.

The aims of this study were to use the DPC database to clarify the clinical practice of treating elderly patients with UC and compare the disease outcomes between elderly and younger patients across Japan.

Methods

DPC system. The DPC database, introduced in 2003, is a medical claims database of admissions to acute-care hospitals in Japan. The DPC system was adopted by 1730 hospitals in 2018 and covers approximately 83% of acute-care beds throughout Japan.[16] The DPC database contains data on a patient's demographic, diagnosis, main disease triggering admission, most resource-consuming diagnosis, comorbidities at admission, complications after admission, medications, surgeries, procedures including cytapheresis, and condition at discharge.[15,17–19] Physicians input patient diagnosis data into the DPC database according to the International Classification of Diseases, Tenth Revision (ICD-10). The DPC database has already been used for various clinical studies and its diagnostic validity has been recognized.[15]

Patients. This study included patients with UC who were admitted to DPC-participating hospitals between April 2012 and March 2018. UC was identified using a DPC diagnosis containing the phrase "ulcerative colitis." Entries of UC suspicious cases containing the word "suspicious" were excluded. Eligible patients admitted to the hospital with UC were identified using a DPC diagnosis query containing the phrase "ulcerative colitis" as their main diagnosis, main disease triggering admission, or most resource-consuming diagnosis.

Data collection. We collected the following data on patient and clinical characteristics, procedures, and condition at discharge from the DPC database: age, sex, body mass index (BMI), smoking history (current or ex-smokers *vs*. nonsmokers), Charlson comorbidity index (CCI),[20] hospital type (academic hospital or not), duration of admission, medication (systemic steroid injection or molecular targeting drugs), cytapheresis, rate of surgery, and rate of in-hospital death. The molecular targeting drugs were defined as follows: infliximab, adalimumab, golimumab, vedolizumab, tacrolimus, and tofacitinib.

Data analysis. We classified the eligible patients into two groups (elderly group: ≥65 years and non-elderly group: ≤64 years) according to their age, based on World Health Organization classification.[21] We additionally classified each of the two aforementioned groups into three subgroups (elderly group: 65–69 years, 70–79 years, and ≥80 years; non-elderly group: 60–64 years, 50–59 years, and ≤49 years). We also classified the eligible patients into three groups according to BMI (underweight: <18.5 kg/m^2, normal range: 18.5–24.9 kg/m^2, and overweight: ≥25.0 kg/m^2) based on World Health Organization classification.[22] We investigated the patients' backgrounds and compared their medical therapies, including systemic steroid injection, molecular targeting drugs, cytapheresis, and surgery. We also examined the difference in rate of in-hospital death using the chi-square test, and difference in duration of hospital stay using Wilcoxon's signed-rank test. We also performed a multivariate analysis using logistic regression to identify clinical factors that affect the rates of surgery and in-hospital death in each group and across all patients. The threshold for statistical significance was $P < 0.05$. All analyses were performed using JMP PRO14 (SAS Institute, Tokyo, Japan) software.

Ethical considerations

The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (2019-1-415). Owing to the anonymous nature of the data, informed consent was waived for approval.

Results

Patient characteristics. We finally included 84 035 eligible patients, of whom 17 648 were assigned to the elderly group and the remaining 66 387 to the non-elderly group. The characteristics of the study population are summarized in Table 1. The backgrounds of the two groups demonstrated small differences in the rate of diabetes without complication and paraplegia. The rate of academic hospital usage by the elderly group was significantly higher than that of the non-elderly group (27.3% *vs*. 25.2%, $P < 0.0001$).

Comparison of clinical events and medications between elderly and non-elderly groups. Comparisons of clinical events and medications between the two groups are summarized in Table 2. The rate of in-hospital death was significantly higher in the elderly group (2.7% *vs*. 0.19%, $P < 0.0001$). The average length of hospital stay in the elderly group was longer than that of the non-elderly group (17 *vs*. 16 days, $P < 0.0001$). On the contrary, the rate of surgery was the same between the two groups. There were also no differences in the rates of systemic steroid injection, molecular targeting drug use, and cytapheresis.

Multivariate analysis for surgery and in-hospital death in elderly patients. The results of multivariate analysis of surgery risk in elderly patients are summarized in Table 3. On multivariate analysis, being underweight (odds ratio [OR] = 1.77, 95% confidence interval [CI]: 1.39–2.26, $P < 0.0001$), attending an academic hospital (OR = 2.84, 95% CI: 2.27–3.54, $P < 0.0001$), smoking (OR = 1.51, 95% CI: 1.21–1.90, $P = 0.0003$), using one or more molecular targeting drugs (OR = 1.38, 95% CI: 1.08–1.77, $P = 0.011$), and being treated with systemic steroid injection (OR = 3.57, 95% CI: 2.83–4.49, $P < 0.0001$) were identified as clinical factors affecting surgical risk.

The results of multivariate analysis of in-hospital death in elderly patients are summarized in Table 4. On multivariate analysis, being male and old-aged were identified as clinical factors affecting the risk of in-hospital death.

The results of multivariate analyses of surgery risk and in-hospital death for all patients are summarized in Tables S1 and S2, respectively. Although elderly age did not affect surgery risk, it was identified as a clinical factor affecting in-hospital death (OR = 14.4, 95% CI: 11.8–17.6, $P < 0.0001$).

Multivariate analysis for surgery and in-hospital death in non-elderly patients. The results of multivariate analysis of surgical risks in non-elderly patients are summarized

Table 1 Comparison of clinical characteristics of study population between elderly and non-elderly patients

	Hospital admission due to ulcerative colitis Total *n* = 84 035		
	Elderly *n* = 17 648	Non-elderly *n* = 66 387	*P* value
Sex (male/female)	10 103/7522	37 850/28 837	0.07
Body mass index (BMI) (mean ± SD)	21.5 ± 4.3 (kg/m^2)	21.5 ± 5.4 (kg/m^2)	0.29
BMI categories			
Overweight (over 25.0 kg/m^2)	2944	10 969	
Normal range (18.5–24.9 kg/m^2)	10 273	38 998	
Underweight (below 18.5 kg/m^2)	3940	14 510	
Charlson comorbidity index			
Acute myocardial infarction (%)	144 (0.84)	559 (0.87)	0.78
Heart failure (%)	428 (2.5)	1601 (2.5)	0.93
Peripheral vascular disease (%)	135 (0.79)	498 (0.77)	0.84
Cerebral vascular disease (%)	461 (2.7)	1728 (2.7)	0.96
Dementia (%)	175 (1.0)	735 (1.1)	0.19
Pulmonary disease (%)	629 (3.7)	2345 (3.6)	0.85
Connective tissue disorder (%)	321 (1.9)	1181 (1.8)	0.72
Peptic ulcer (%)	1297 (7.6)	4844 (7.5)	0.59
Liver disease (%)	648 (3.8)	2398 (3.7)	0.71
Diabetes without complication (%)	1459 (8.5)	5147 (8.0)	**0.027**
Diabetes with complication (%)	187 (1.1)	787 (1.22)	0.17
Paraplegia (%)	51 (0.3)	134 (0.21)	**0.037**
Renal disease (%)	255 (1.5)	932 (1.5)	0.69
Cancer (%)	851 (5.0)	3141 (4.9)	0.63
Metastatic cancer (%)	289 (1.7)	1082 (1.7)	0.94
Severe liver disease (%)	39 (0.23)	126 (0.26)	0.39
Human immunodeficiency virus (%)	5 (0.03)	22 (0.03)	1
Smoking (yes/no)	5891/11 226	21 694/42 783	0.091
Academic hospital (yes/no)	4833/12 324	16 740/47 737	**<0.0001**

The bold value means statistical significance (< 0.05).

in Table 5. On multivariate analysis, being underweight (OR = 1.34, 95% CI: 1.17–1.52, $P < 0.0001$), attending an academic hospital (OR = 3.24, 95% CI: 2.89–3.63, $P < 0.0001$), smoking (OR = 1.34, 95% CI: 1.20–1.51, $P < 0.0001$), having two or more positive points of CCI (OR = 1.32, 95% CI: 1.12–1.55, $P = 0.0008$), using one or more molecular targeting drugs

Table 2 Comparison of clinical event and medications between elderly and non-elderly groups

	Hospital admission due to ulcerative colitis Total *n* = 84 035		
	Elderly *n* = 17 648	Non-elderly *n* = 66 387	*P* value
Systemic steroid injection (%)	2957 (17.2)	11 218 (17.4)	0.63
Biologics (%)	2185 (12.7)	8356 (13.0)	0.44
Infliximab (%)	1589 (9.3)	5891 (9.1)	0.61
Adalimumab (%)	443 (2.6)	1800 (2.8)	0.14
Golimumab (%)	144 (0.84)	604 (0.94)	0.24
Vedolizumab (%)	29 (0.17)	156 (0.24)	0.086
Tacrolimus (%)	987 (5.8)	3683 (5.7)	0.84
Tofacitinib (%)	987 (5.8)	3683 (5.7)	0.84
Cytapheresis (%)	1243 (7.2)	4776 (7.4)	0.48
Surgery (%)	334 (2.0)	1270 (2.0)	0.88
In-hospital death (%)	462 (2.7)	125 (0.19)	**<0.0001**
Median days of hospital stay (IQR)	17 days (5–33)	16 days (6–28)	**<0.0001**

The bold value means statistical significance (< 0.05).
Abbrevation: IQR, interquartile range.

Table 3 Multivariate analysis of the association between clinical factors and surgery in elderly patients

Clinical factors	Number of patients n = 17 648	Surgery		
		Odds ratio	95% confidence interval	P value[†]
Sex	Male: 10 103	1		0.49
	Female: 7522	1.08	0.87–1.35	
Age categories	65–69 years: 5552	1		
	70–79 years: 7977	0.86	0.66–1.11	0.24
	Over 80 years: 4120	1.14	0.85–1.52	0.049
Body mass index categories	Overweight: 2944	0.99	0.71–1.37	0.90
	Normal range: 10 273	1		
	Underweight: 3940	**1.77**	**1.39–2.26**	**<0.0001**
Academic hospital	Yes: 4833	**2.84**	**2.27–3.54**	**<0.0001**
	No: 12 324	1		
Smoking	Yes: 5891	**1.51**	**1.21–1.90**	**0.0003**
	No: 11 266	1		
Two or more positive points of Charlson comorbidity index	Yes: 2394	0.99	0.70–1.40	0.95
	No: 15 254	1		
Usage of one or more molecular targeting drugs	Yes: 3036	**1.38**	**1.08–1.77**	**0.011**
	No: 14 121	1		
Systemic steroid injection	Yes: 2957	**3.57**	**2.83–4.49**	**<0.0001**
	No: 14 691	1		
Cytapheresis	Yes: 1243	1.05	0.73–1.50	0.80
	No: 16 405	1		

[†]Logistic regression analysis.
The bold value means statistical significance (< 0.05).

Table 4 Multivariate analysis of the association between clinical factors and in-hospital death in elderly patients

Clinical factors	Number of patients n = 17 648	In-hospital death		
		Odds ratio	95% confidence interval	P value[†]
Sex	Male: 10 103	1		**<0.0001**
	Female: 7522	**0.65**	**0.53–0.79**	
Age categories	65–69 years: 5552	1		
	70–79 years: 7977	**2.04**	**1.53–2.72**	**<0.0001**
	Over 80 years: 4120	**5.20**	**2.08–3.12**	**<0.0001**
Body mass index categories	Overweight: 2944	1.06	0.83–1.36	0.60
	Normal range: 10 273	1		
	Underweight: 3940	0.88	0.70–1.12	0.33
Academic hospital	Yes: 4833	0.95	0.77–1.17	0.65
	No: 12 324	1		
Smoking	Yes: 5891	1.03	0.85–1.26	0.75
	No: 11 266	1		
Two or more positive points of Charlson comorbidity index	Yes: 2394	0.91	0.68–1.20	0.50
	No: 15 254	1		
Usage of one or more molecular targeting drugs	Yes: 3036	1.22	0.96–1.55	0.092
	No: 14 121	1		
Systemic steroid injection	Yes: 2957	0.91	0.71–1.18	0.50
	No: 14 691	1		
Cytapheresis	Yes: 1243	0.98	0.67–1.42	0.90
	No: 16 405	1		
Surgery	Yes: 334	1.45	0.81–2.57	0.21
	No: 17 314	1		

[†]Logistic regression analysis.
The bold value means statistical significance (< 0.05).

Table 5 Multivariate analysis of the association between clinical factors and surgery in non-elderly patients

Clinical factors	Number of patients *n* = 66 387	Surgery		
		Odds ratio	95% confidence interval	*P* value†
Sex	Male: 37 850	1		0.32
	Female: 28 837	1.06	0.95–1.19	
Age categories	Under 49 years: 49 906	1		
	50–59 years: 7977	1.00	0.86–1.17	1.00
	60–64 years: 4120	1.11	0.91–1.34	0.36
Body mass index categories	Overweight: 10 969	1.02	0.87–1.20	0.81
	Normal range: 38 998	1		
	Underweight: 14 510	**1.34**	**1.17–1.52**	**<0.0001**
Academic hospital	Yes: 4833	**3.24**	**2.89–3.63**	**<0.0001**
	No: 12 324	1		
Smoking	Yes: 21 694	**1.34**	**1.20–1.51**	**<0.0001**
	No: 42 783	1		
Two or more positive points of Charlson comorbidity index	Yes: 8774	**1.32**	**1.12–1.55**	**0.0008**
	No: 57 613	1		
Usage of one or more molecular targeting drugs	Yes: 11 404	**1.35**	**1.18–1.53**	**<0.0001**
	No: 53 073	1		
Systemic steroid injection	Yes: 11 562	**3.04**	**2.70–3.43**	**<0.0001**
	No: 54 825	1		
Cytapheresis	Yes: 4881	1.10	0.92–1.32	0.30
	No: 61 506	1		

†Logistic regression analysis.
The bold value means statistical significance (< 0.05).

(OR = 1.35, 95% CI: 1.18–1.53, $P < 0.0001$), and being treated with systemic steroid injection (OR = 3.04, 95% CI: 2.70–3.43, $P < 0.0001$) were identified as clinical factors affecting the risks of surgery.

The results of multivariate analysis of in-hospital death in non-elderly patients are summarized in Table 6. On multivariate analysis, being male and old-aged were identified as clinical factors affecting the risk of in-hospital death.

Table 6 Multivariate analysis of the association between clinical factors and in-hospital death in non-elderly patients

Clinical factors	Number of patients *n* = 66 387	In-hospital death		
		Odds ratio	95% confidence interval	*P* value†
Sex	Male: 37 850	1		**0.0025**
	Female: 28 837	**0.55**	**0.37–0.81**	
Age categories	Under 49 years: 49 906	1		
	50–59 years: 7977	**3.32**	**2.17–5.10**	**<0.0001**
	60–64 years: 4120	**6.34**	**4.16–9.66**	**<0.0001**
Body mass index categories	Overweight: 10 969	0.99	0.60–1.65	0.98
	Normal range: 38 998	1		
	Underweight: 14 510	1.25	0.83–1.88	0.29
Academic hospital	Yes: 4833	1.17	0.80–1.74	0.42
	No: 12 324	1		
Smoking	Yes: 21 694	0.72	0.48–1.08	0.12
	No: 42 783	1		
Two or more positive points of Charlson comorbidity index	Yes: 8774	0.70	0.37–1.31	0.26
	No: 57 613	1		
Usage of one or more molecular targeting drugs	Yes: 11 404	1.46	0.97–2.21	0.07
	No: 53 073	1		
Systemic steroid injection	Yes: 11 562	1.18	0.76–1.84	0.45
	No: 54 825	1		
Cytapheresis	Yes: 4881	1.33	0.74–2.38	0.33
	No: 61 506	1		
Surgery	Yes: 1318	1.05	0.33–3.34	0.94
	No: 65 069	1		

†Logistic regression analysis.
The bold value means statistical significance (< 0.05).

Discussion

Using a Japanese nationwide patient database, we investigated the clinical practice of treating elderly patients with UC compared to non-elderly patients, as well as the clinical factors affecting the course of treatment, surgical risks, and risk of in-hospital death. Our research showed that there were no differences in medication usage or surgery rate between the two groups; meanwhile, the elderly group showed worse results regarding the rate of in-hospital death and duration of hospital stay. Our study also showed that similar clinical factors affect surgery risk and in-hospital death in both elderly and non-elderly patients.

Elderly patients generally have a tendency to develop complications, worsening their clinical course. Therefore, it is important to clarify the clinical practice of treating elderly patients with UC so as to better manage these patients.

Only a few studies have reported on the realities of treating UC in elderly patients *versus* non-elderly patients. Despite two studies that reported on the treatment details for elderly patients in Japan,[12,13] the use of medication—especially molecular targeting drugs—has remained unclear, even after these drugs became available several years ago. Our results, however, showed the actual nationwide usage of molecular targeting drugs for elderly patients with UC. In addition, our study revealed that there were no differences in the rates of surgery between the elderly and non-elderly groups. These results indicate that the disease severity of those two groups might also not be different. This is compatible with a previous review that reported no difference in disease severity between the two groups.[9] This suggests that physicians should be able to select molecular targeting drugs without hesitation as a treatment approach to avoid surgery. However, clinicians have to select the appropriate therapeutic agents that take into account each patient's particular conditions, including age, disease severity, and complications.

The clinical factors that affect surgery in elderly and non-elderly patients were similar—namely, being underweight, treatment in an academic hospital, history of smoking, usage of one or more molecular targeting drugs, and treatment by systemic steroid injection. Lower BMI, treatment in an academic hospital, usage of molecular targeting drugs, and treatment by systemic steroid injection are thought to reflect severe disease activity, which contributes to a higher risk of surgery. Furthermore, treatment in an academic hospital might be related to the referral bias for more patients who need surgery. However, there are several reports about the association between smoking and UC-related surgery, and their conclusions are contradictory.[23–27] A meta-analysis showed an increased risk of surgery in ex-smokers with UC compared to nonsmokers (hazard ratio = 1.38).[24] Our present analysis also showed a negative impact of smoking on risk of surgery in both elderly and non-elderly patients. However, the DPC database cannot distinguish between current smokers and ex-smokers—only the Brinkman Index can perform this distinction. A prospective observational study should be conducted to clarify the true influence of current smoking on disease course. In any case, although there is one study that reported that smoking reduces the risk of developing UC,[28] physicians should consider recommending that patients quit smoking after UC diagnosis.

On the contrary, the rate of in-hospital death in the elderly group was higher than that in non-elderly group, even though the rates of surgery were not different. Furthermore, multivariate analysis revealed that only male and older age affected in-hospital death in both groups; CCI was not a clinical factor that affected in-hospital death in the multivariate analysis. These results reflect that another clinical factor other than disease severity may be impacting the rate of in-hospital death. As described above, elderly age is one of those factors. A prospective multicenter cohort study revealed that the rates of in-hospital death and severe infections in elderly patients with UC treated with anti-tumor necrosis factor (anti-TNF)-α antibodies had increased by 9% and 8.4%, respectively.[29] Another study reported that elderly patients treated with anti-TNFα antibodies were likely to develop severe infections compared to non-elderly patients.[30] These studies indicate that infections might impact the rate of in-hospital death in elderly UC patients. Another single-center retrospective study showed that the rate of in-hospital death in elderly patients who underwent urgent surgery was higher than in patients who underwent elective surgery (26.7% *vs*. 0.88%, respectively).[31] That study also reported that complications after urgent surgery—including respiratory infection and mycotic infection—were common causes of in-hospital death.[31] Their results demonstrate that complications after surgery may also affect the rate of in-hospital death in elderly patients. In any case, it is necessary to pay significant attention to the presence of infection whether clinicians treat elderly patients with medical treatment or surgery. There is a study reporting five lifestyle factors such as never-smoking, normal BMI, vigorous physical activity, alternate Mediterranean diet, and light drinking are associated with reduced mortality rate in patients with IBDs.[32] Although we could investigate the former two factors, the DPC database does not contain the data of the latter three factors. Further investigations are warranted to clarify the full range of clinical factors that affect the rate of in-hospital death in elderly UC patients.

This study had several limitations. First, the DPC database does not record the onset and disease duration of UC. Several studies have reported the difference in disease severity between elderly-onset and non-elderly-onset patients with UC, but their conclusions are inconsistent. A nationwide survey in Japan reported that the disease severity of elderly-onset patients was higher than that of non-elderly-onset patients[12]; meanwhile, several studies have reported that non-elderly-onset patients showed either worse disease severity[10,11,33] or no difference[6] at all. As described above, the impact of disease-onset age on the clinical course remains unclear. Second, the DPC database does not contain data on a patient's condition, such as disease extension, endoscopic and pathological findings, laboratory data, and computed tomography findings. Therefore, we evaluated disease severity by investigating therapeutic agents and surgery rates. Third, DPC-participating hospitals were typically acute-care and relatively large-volume hospitals. Therefore, DPC data do not necessarily reflect all patients nationwide. Our study focused only on patients who required admission, not outpatients. Despite these limitations, the DPC database allowed us to collect and analyze data from a large number of patients, which is useful for establishing hypotheses for future study designs.

Conclusion

In Japan, the clinical practice of treating elderly patients with UC is not different from treating non-elderly patients with UC. Although the disease severity of elderly UC patients may not be different from that of non-elderly patients, the rate of in-hospital death of elderly patients is higher. We should thus pay significant attention when treating elderly UC patients with medical treatment or surgery.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Multivariate analysis* of the association between clinical factors and surgery in all patients.
Table S2. Multivariate analysis* of the association between clinical factors and in-hospital death in all patients.