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ABOUT COVER

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AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, *etc*. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus and Directory of Open Access Journals. The 2018 edition of Journal Citation Report® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

RESPONSIBLE EDITORS FOR THIS ISSUE

Retrospective Study

Two-year delay in ulcerative colitis diagnosis is associated with anti-tumor necrosis factor alpha use

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Abstract

BACKGROUND
Ulcerative colitis (UC) is an uncommon inflammatory bowel disease (IBD). However, its incidence has recently increased in South Korea. Moreover, UC diagnoses are frequently delayed, and the relationship between diagnostic delay and UC prognosis has not been extensively studied in South Korean patients.

AIM
To identify meaningful diagnostic delay affecting UC prognosis and to evaluate risk factors associated with diagnostic delay in South Korean patients.

METHODS
Medical records of 718 patients with UC who visited the outpatient clinic of six university hospitals in South Korea were reviewed; 167 cases were excluded because the first symptom date was unknown. We evaluated the relationship

between the prognosis and a diagnostic delay of 3, 6, 12, 18, and 24 mo by comparing the prognostic factors [anti-tumor necrosis factor (TNF)-α use, admission history due to acute flare-ups, frequent admission due to flare-ups, surgery associated with UC, and the clinical remission state at the latest follow-up] at each diagnostic interval.

RESULTS
The mean diagnostic interval was 223.3 ± 483.2 d (median, 69 d; 75th percentile, 195 d). Among the prognostic factors, anti-TNFα use was significantly increased after a diagnostic delay of 24 mo. Clinical risk factors predictive of a 24-mo diagnostic delay were age < 60 years at diagnosis [odd ratio (OR) = 14.778, 95% confidence interval (CI): 1.731-126.121], smoking history (OR = 2.688, 95%CI: 1.239-5.747, P = 0.012), and misdiagnosis of hemorrhoids (OR = 11.066, 95%CI: 3.596-34.053). Anti-TNFα use was associated with extensive UC at diagnosis (OR = 3.768, 95%CI: 1.860-7.632) and 24-mo diagnostic delay (OR = 2.599, 95%CI: 1.006-4.916).

CONCLUSION
A diagnostic delay > 24 mo was associated with increased anti-TNFα use. Age < 60 years at diagnosis, smoking history, and misdiagnosis of hemorrhoids were risk factors for delayed diagnosis.

Key words: Ulcerative colitis; Diagnostic delay; Anti-tumor necrosis factor alpha; Smoking

Core tip: We aimed to identify the diagnostic delay that affects the prognosis in Korean patients with ulcerative colitis. We found that the group with a ≥ 24-mo diagnostic delay had used anti-tumor necrosis factor alpha drugs more frequently than the group with a < 24-mo delay. We also found that additional risk factors for a 24-mo delay in diagnosis were age < 60 years, smoking history, and a misdiagnosis of hemorrhoids by a physician.

INTRODUCTION

Ulcerative colitis (UC) is an uncommon inflammatory bowel disease (IBD). However, its incidence has recently increased in South Korea. UC is diagnosed by clinical, endoscopic, and histologic findings because there is no definite diagnosis index. Therefore, differentiating it from other diseases of the intestines, such as acute gastroenteritis or irritable bowel syndrome (IBS) is often difficult, and its diagnosis is often delayed. It is unclear whether a diagnostic delay of IBD is clinically significant. Recent studies have shown that early control of IBD affects the quality of life and the disease course, including its prognosis[1-4].

Most studies of a diagnostic delay for IBD were focused on Crohn's disease (CD), and although the duration of the delay was different, the need for surgery was closely related to the diagnostic delay of CD in both Western and Asian populations[5-9]. There have been reports of clinical factors involved in the diagnostic delay of UC, but there is a lack of information regarding whether this delay affects the prognosis and treatment of UC for Asian patients[9]. Some patients have had symptoms for a long period, but the correct diagnosis was not made because UC was mild or had an insidious onset. A few studies have focused on how various durations of diagnostic delay can affect the future treatment and prognosis of these patients. Diagnostic delay and its impact on Western and Asian populations may be significantly different due to genetic or environmental factors; therefore, it is necessary to examine the results according to countries or regions.

Thus, we aimed to identify the period of delay in diagnosis (time from the first symptoms to UC diagnosis) that affected treatment and prognosis. We also evaluated the risk factors and clinical significance of a diagnostic delay for UC in South Korean patients.

MATERIALS AND METHODS

Patients

This retrospective study was based on patient data collected from six university-affiliated hospitals located in metropolitan areas (Incheon-si, Ansan-si, Anyang-si, Suwon-si, Sungnam-si and Dongtan-si) near Seoul, South Korea, from January 2006 to December 2016. We analyzed the medical records of 718 patients who visited the outpatient clinic in 2016, had a definite diagnosis of UC, and were followed up for more than 6 mo. The diagnosis of UC was based on clinical, radiological, endoscopic, and pathologic findings. One hundred sixty-seven patients were excluded from the study because of incomplete medical record data regarding the first day of symptoms. Patients were not required to provide informed consent for inclusion in this retrospective study. We anonymized all clinical data to protect personal information. This study was conducted with the approval of the ethics committee of Hallym University Sacred Heart Hospital in Anyang, South Korea (IRB No. 2016-I607). The study was performed in accordance with the recommendations of the Declaration of Helsinki.

Data collection, definition, and assessment of clinical outcomes

Demographic characteristics of patients at the time of the first diagnosis were collected, including sex, age, body mass index (BMI), family history of UC, history of smoking, residence at the time of diagnosis (urban or rural), and education level (university education or less). Clinical medical records regarding the first symptoms and endoscopic and laboratory findings were also investigated, such as the day when the first symptom occurred, the day of the first physician visit, the day of first diagnosis, the type of symptoms (hematochezia, chronic diarrhea, abdominal pain), cases misdiagnosed as other diseases (hemorrhoids, IBS), Mayo score including endoscopic score[10-12], disease extension (proctitis, left side, extensive)[13], and C-reactive protein level (CRP, mg/dL). During data collection, to determine the Mayo endoscopic score and the extension of the disease, endoscopy findings were reviewed again by the endoscopist from each medical center. To reduce inter-observer variation, all endoscopist reviewers were trained using the same reference material[10-13] before the review. The use of prescribed medications [oral/intravenous (IV) steroids, azathioprine/6-mercaptopurine (AZA/6MP), or anti-tumor necrosis factor alpha (anti-TNFα)] and the first day of the prescribed medication were investigated. To determine the prognostic factors, the use of anti-TNFα, the hospital admission history due to acute flare-ups[14,15], frequent admission (more than two admissions due to UC flare-ups), surgery associated with UC, and the clinical remission state at the latest follow-up were obtained from the medical records. The diagnostic interval was defined as the time from the first symptom until UC diagnosis. We divided the patients into the early and delay groups according to several diagnostic interval criteria (3 mo, 6 mo, 12 mo, 18 mo and 24 mo). Then, we compared the two groups according to the aforementioned demographic and clinical characteristics to determine the diagnostic delay having a clinical impact.

Statistical analysis

Both categorical and continuous variables of baseline characteristics were analyzed. Continuous variables are shown as mean ± standard deviation or medians with ranges. To evaluate the criteria for a diagnostic delay having a clinical impact, the chi-square test, Fisher's exact test, and Kaplan-Meier method with the log-rank test were used to compare prognostic factors between the early group and delay group. After the meaningful diagnostic delay and prognosis factors were determined, they were compared to the clinical factors (sex, age, BMI, first symptom, cases misdiagnosed as hemorrhoids or IBS, Mayo score, disease extension, and CRP level) by univariate analysis. Multivariate logistic regression analyses including significant clinical factors from the univariate analysis were performed to evaluate risk factor-related diagnostic delay and prognosis. Odd ratios (OR) and 95% confidence intervals (CI) were calculated as measures of the correlation between the clinical variables and outcomes of interest. $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Baseline characteristics of patients

Clinical characteristics of the patients were as follows: male sex, 318 (55.7%); mean age at diagnosis, 40.56 ± 16.11 years; and BMI at diagnosis, 22.28 ± 3.19 kg/m^2 (Table 1). Seventy-seven of 443 (17.4%) had a history of smoking. Presenting first symptoms were hematochezia (388/548; 70.8%), diarrhea (164/548; 29.9%), and abdominal pain (39/548; 7.1%). The days from first symptoms to UC diagnosis were 223.28 ± 483.15 (median, 69); 75% of patients were diagnosed within 195 d. Time from the first symptoms to the first hospital visit was 154.22 ± 379.140 d (median, 40 d), and the time from the first hospital visit to diagnosis was 69.06 ± 295.04 d (median, 9 d). The Mayo score at diagnosis was examined in 399 patients; 179 (44.9%) had mild disease, 204 (51.1%) had moderate disease, and 220 (4.0%) had severe disease. Disease extension at diagnosis was examined in 547 patients; 253 (46.3%) had proctitis, 160 (29.3%) had left-side colitis, and 134 (24.5%) had extensive colitis. Prescribed medications used by all patients were as follows: oral/IV steroids, 250 (45.4%); AZA/6MP, 163 (29.8%); and anti-TNFα, 50 (9.1%).

Diagnostic delay and prognosis

There were no statistically significant differences in the use of anti-TNFα, hospital admission history for acute flare-ups, frequent admission, surgery associated with UC, or clinical remission state at the latest follow-up between the early and delay groups with other diagnostic intervals (3, 6, 12 and 18 mo) (Table 2). In Figure 1, the use of anti-TNFα at the 3-mo diagnostic interval was insignificantly prevalent in the early group (34/322; 10.6%) and the delay group (16/229; 7.0%); however, the use of anti-TNFα by the early group and delay group began to decrease at the 18-mo diagnostic interval. Finally, at the 24-mo diagnostic interval, it was significantly higher in the delay group (8/42; 35.7%) than in the early group (42/509; 8.3%) (P = 0.019). Anti-TNFα free-survival rates between the early and delay groups according to the 24-mo diagnostic interval were significantly different (P = 0.034) (Figure 2). Therefore, it was determined that 24 mo was the diagnostic delay cutoff point for poor outcomes, and this delay was related to the use of anti-TNFα.

Risk factors associated with a 24-mo diagnostic delay

According to the univariate analysis (Table 3), sex, age, BMI, education level, residence at the time of diagnosis, family history of IBD, and the first symptom were not different between the early and delay groups. However, age < 60 years (P = 0.020), history of smoking (P = 0.008), and misdiagnosis of hemorrhoids (P = 0.000) were significantly increased in the delay group. According to the multivariate logistic regression analysis, independent risk factors predictive of 24 mo as the cutoff were age < 60 years (OR = 14.778, 95%CI: 1.731-126.121, P = 0.014), smoking history (OR = 2.688, 95%CI: 1.239-5.747, P = 0.012), and misdiagnosis of hemorrhoids (OR = 11.066, 95%CI: 3.596-34.053, P = 0.000) (Table 4).

Risk factors associated with the use of anti-TNFα

According to the univariate analysis (Table 5), sex, age, smoking history, BMI, CRP level at diagnosis, early steroid use within 2 mo of diagnosis, and early AZA/6MP use within 2 mo of diagnosis were not predictive factors for anti-TNFα use. However, moderate or severe Mayo score (P = 0.001), extensive disease (P = 0.000), and a diagnostic delay ≥ 24 mo (P = 0.019) were significantly increased in the delay group. According to the multivariate logistic regression analysis, independent risk factors predictive of anti-TNFα use were extensive disease (OR = 3.768, 95%CI: 1.860-7.632, P = 0.000) and a diagnostic delay of ≥ 24 mo (OR = 2.599, 95%CI: 1.006-4.916, P = 0.049) (Table 6).

DISCUSSION

We found that the ≥ 24-mo diagnostic delay group used anti-TNFα drugs more frequently than the < 24-mo delay group. We also found that risk factors for the 24-mo delay were age < 60 years, smoking history, and misdiagnosis of hemorrhoids by a physician.

In general, CD is known to have a longer diagnostic delay than UC[4,7,9,16,17]. This is because the main symptom of CD is abdominal pain, and it is necessary to differentiate it from IBS. Furthermore, those with UC seem to visit the hospital earlier because it is related to hematochezia. In three studies on delayed diagnosis in UC, the median delays were 1, 3.1 and 4 mo. These studies categorized patients at the 76th to 100th percentiles into the delay group, and according to this, a diagnosis of more than

Table 1 Baseline characteristics of patients (*n* = 551)	
Characteristics	**Value**
Male sex (%)	318/551 (55.7)
Age at diagnosis, yr	40.56 ± 16.11
BMI at diagnosis, kg/m^2	22.28 ± 3.19
Family history of IBD (%)	51/369 (13.8)
History of smoking (%)	77/443 (17.4)
First symptom	
Hematochezia	388/548 (70.8)
Diarrhea	164/548 (29.9)
Abdominal pain	39/548 (7.1)
Diagnostic interval, d (median)	223.28 ± 483.15 (69)
Time from first symptom to hospital visit, d (median)	154.22 ± 379.140 (40)
Time from first hospital visit to diagnosis, d (median)	69.06 ± 295.04 (9)
Mayo score at diagnosis (%)	
Mild	179/399 (44.9)
Moderate	204/399 (51.1)
Severe	220/399 (4.0)
Disease extent at diagnosis (%)	
Proctitis	253/547 (46.3)
Left side	160/547 (29.3)
Extensive	134/547 (24.5)
Steroid (oral or intravenous) use (%)	250/551 (45.4)
AZA/6MP use (%)	163/551 (29.6)
Anti-TNFα use (%)	50/551 (9.1)
Admission due to flare-up (%)	121/430 (22.0)
Frequent admission due to flare-up (%)	50/551 (9.1)
UC-related surgery (%)	7/551 (1.3)
Clinical remission at the latest follow-up (%)	333/467 (71.3)

BMI: Body mass index; IBD: Inflammatory bowel disease; AZA/6MP: Azathioprine or 6-mercaptopurine; Anti-TNFα: Anti-tumor necrosis factor alpha; UC: Ulcerative colitis.

3, 10 and 12 mo were classified as delayed diagnosis; non-steroidal anti-inflammatory drug (NSAID) use, male sex, and age < 40 years were suggested as factors related to delayed diagnosis[4,7,16]. In our study, the median delay was 3.3 mo; 75% of patients were diagnosed within 6.5 mo, and 7.6% of patients had a diagnostic delay of more than 24 mo. Therefore, the median delay and the delay for 75% of patients were not significantly different from that of other studies. In most previous studies, the definition of a diagnostic delay for IBD was defined as more than the 76th to 100th percentile of patients without a correct diagnosis[4,7,8,18]. Our initial hypothesis was that the diagnostic delay for 76th to 100th percentile of patients (> 6.5 mo in our study) would be correlated with prognostic factors; however, we did not find any significant results. Therefore, unlike previous studies, we did not predetermine the criteria for diagnostic delay; instead, we tried to determine the diagnostic delay that affects the prognostic factors. As a result, we found that a diagnostic delay of more than 24 mo was related to the use of anti-TNFα.

Age < 60 years at diagnosis, smoking history, and misdiagnosis of hemorrhoids were risk factors for the 24-mo diagnostic delay in our study. It is well known that smoking is related to UC[17]; however, a person who smokes may not be interested in health or may not be able to seek medical care because of economic reasons[19], which may have affected our results. Contrary to previous studies, we found that factors other than smoking were related to UC. Some studies showed that age older than 40 years was correlated with diagnostic delay, whereas others showed the opposite[7,16]. In our study, age of 40 years or younger and age of 40 years or older were not risk factors for diagnostic delay; however, age < 60 years was a risk factor for diagnostic delay. Additionally, misdiagnoses as hemorrhoids were risk factors, which was contradictory to the finding of a Western study that showed UC was sometimes found faster by hematochezia[4]. There were several reasons for these results. First, regarding
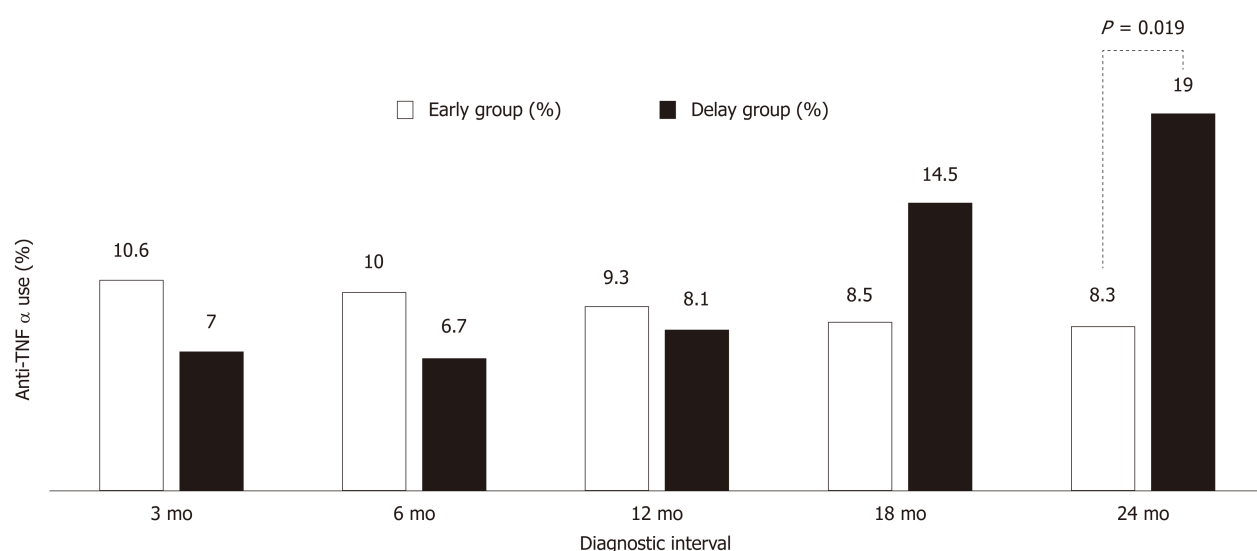
Figure 1 Difference in the anti-tumor necrosis factor alpha use rate (%) according to the diagnostic interval. Anti-TNFα: Anti-tumor necrosis factor alpha.

genetics, UC in Asian individuals, including South Koreans, may have a milder course than that in Western individuals, although the clinical features of both are similar[20-24]. Second, there are many regional differences in each country due to environmental factors such as medical accessibility and insurance status[25,26]. For example, in South Korea, colorectal cancer screening is performed after age 50 years, and hemorrhoids are common. Furthermore, recently, UC has been increasingly observed in Asian individuals compared to Western individuals. Therefore, because of environmental and genetic factors, our results may not be applicable to other populations. However, more research is necessary to determine whether our research represents the entire Asian population.

In the CD studies which examined the relation between diagnostic delay and prognosis, a delayed diagnosis of 13, 18, 25 and 34 mo was associated with CD-related surgery[5-8]. In a study of 1047 patients in South Korea, an 18-mo diagnostic delay was predictive of further development of intestinal stenosis, internal fistulas, and perianal fistulas[27]. Although the durations of the delays were different, the need for surgery was closely related to the diagnostic delay of CD in both Asian and Western populations. These studies indicated that as the duration of exposure to the disease increased, cumulative intestinal damage did not respond to medical treatment and the necessity for surgery increased. There are very few studies on the relationship between diagnostic delay and the prognosis of UC. A previous study performed in South Korea suggested that a diagnostic delay of 6.2 mo led to an increased risk for intestinal surgery[9]. Unfortunately, in our study, the number of surgeries (7/551; 1.3%) was too small, and the analysis was insufficient.

In our study, a 24-mo diagnostic delay was associated with the use of anti-TNFα drugs. In South Korea, certain factors regarding anti-TNFα use and surgery should be considered. First, a systemic analysis of IBD using population-based studies and randomized controlled trials suggested that anti-TNFα drugs had a protective effect against surgery in the biologic era, and that anti-TNFα drugs were used more frequently and earlier in South Korea[21,28]. Second, in Asia, the UC course is mild, patients resist surgery, and cases of colonic resection are rare[20-24]. In recent studies at an IBD specialized referral center in South Korea, the colectomy rate has decreased over the past 30 years for South Korean patients with UC[21]. In this study, 1119 patients were diagnosed between 2007 and 2013, the 7-year cumulative colectomy rate was 0.5% for patients diagnosed at this IBD referral hospital, and 4.7% for patients referred to this institution after diagnosis or treatment at another hospital. Therefore, because there is a possibility of a severe refractory cases in the referral population, the actual colectomy rate in South Korea is probably between 0.5% and 4.7% in biologic era, which is clearly lower than that of Western populations[29]. Third, practitioners in South Korea are unable to perform top-down treatment because of insurance problems; only patients who do not respond to steroids and AZT/6MP treatment can receive anti-TNFα treatment[30]. Thus, instead of surgery, the use of anti-TNFα drugs may be an important surrogate marker of the severity and prognosis of UC in South Korea.

The more extensive the disease, the longer the morbidity period; furthermore, primary sclerosing cholangitis and frequent admissions for flare-up were predictors

Table 2 Diagnostic delay and prognosis

Diagnostic interval	3 mo			6 mo			12 mo			18 mo			24 mo		
	Early group (%)	Delay group (%)	P value	Early group (%)	Delay group (%)	P value	Early group (%)	Delay group (%)	P value	Early group (%)	Delay group (%)	P value	Early group (%)	Delay group (%)	P value
	322	229		401	150		452	99		496	55		509	42	
	(58.4)	(41.6)		(72.8)	(27.2)		(82.0)	(18)		(90)	(10)		(92.4)	(7.6)	
Anti-TNFα use			0.150			0.249			0.847			0.137			0.019
No	288	213		361	140		410	91		454	47		467	34	
	(89.4)	(93.0)		(90.0)	(93.3)		(90.7)	(91.9)		(91.5)	(85.5)		(91.7)	(81.0)	
Yes	34	16		40	10		42	8		42	8		42	8	
	(10.6)	(7.0)		(10.0)	(6.7)		(9.3)	(8.1)		(8.5)	(14.5)		(8.3)	(19.0)	
Admission (flare-up)			0.269			0.203			1.000			0.509			0.703
No	246	184		307	123		353	77		389	41		398	32	
	(76.4)	(80.3)		(76.6)	(82.0)		(78.1)	(77.8)		(78.4)	(74.5)		(78.2)	(76.2)	
Yes	76	45		94	27		99	22		107	14		111	10	
	(23.6)	(19.7)		(23.4)	(18.0)		(21.9)	(22.2)		(21.8)	(25.5)		(21.8)	(23.8)	
Frequent admission			0.150			0.384			0.443			0.806			0.412
No	288	213		362	139		409	92		450	51		461	40	
	(89.4)	(93.0)		(90.3)	(92.7)		(90.5)	(92.9)		(90.7)	(92.7)		(90.6)	(95.2)	
Yes	34	16		39	11		43	7		46	4		48	2	
	(10.6)	(7.0)		(9.7)	(7.3)		(9.5)	(7.1)		(9.3)	(7.3)		(9.4)	(4.8)	
Surgery-related UC			0.457			0.092			0.114			0.523			0.428
No	319	225		398	146		448	96		490	54		503	41	
	(99.1)	(98.3)		(99.3)	(97.3)		(99.1)	(97.7)		(98.8)	(98.2)		(98.8)	(97.6)	
Yes	3	4		3	4		4	3		6	1		6	1	
	(0.9)	(1.7)		(0.7)	(2.7)		(0.9)	(3.0)		(1.2)	(1.8)		(1.2)	(2.4)	
Clinical remission			0.866			0.842			0.509			0.679			0.338
No	191	142		97	37		267	66		300	33		310	23	
	(71.0)	(71.7)		(29.0)	(28.0)		(70.6)	(74.2)		(71.6)	(68.8)		(71.9)	(63.9)	
Yes	78	56		238	95		111	23		119	15		121	13	
	(29.0)	(28.3)		(71.0)	(72.0)		(29.4)	(25.8)		(28.4)	(31.3)		(28.1)	(36.1)	

The early group was defined as receiving a diagnosis earlier than the diagnostic interval, and the delay group was defined as receiving a later diagnosis. Clinical remission was investigated in 467 patients. And the proportion of the delay group in 467 patients was similar to that of 551 patients: 3 mo (42.3%), 6 mo (28.2%), 12 mo (19%), 18 mo (9.6%) and 24 mo (7.7%). Anti-TNFα: Anti-tumor necrosis factor alpha; UC: Ulcerative colitis.

of colonic resection of UC[31-33]. In addition, in a study of step-up treatment for UC, risk factors for anti-TNFα use were female sex, age > 40 years, extra-intestinal manifestation, and extensive disease[34]. In another study, extensive disease was also associated with anti-TNFα and AZA/6MP for UC[35]. Therefore, if the use of anti-TNFα replaces UC-related surgery as a prognostic factor, then extensive disease is an important factor in the prognosis of UC with a diagnostic delay, as indicated by our multivariate analysis. Unfortunately, several clinical factors such as early use of steroids, use of azathioprine, and Mayo scores were not associated with anti-TNFα use in our study.

There were some limitations to our study. First, it was a retrospective study; therefore, important clinical information, the first day of UC-related symptoms, may have been inaccurate because of recall bias. In addition, nearly one-fourth of patients were excluded from the study because of incomplete medical record data regarding the first day of symptoms. Second, NSAID use, oral contraceptive use, socioeconomic status, and EIM were not investigated. Third, the use of anti-TNFα drugs was greater in the early group than in the delay group when the diagnostic interval was 3 mo. This was presumably owing to the inclusion of patients with acute flare-ups; however, in our study, the diagnostic criteria for the acute flare-up group were not clear, hence this condition could not be ruled out. Nevertheless, this was the first multicenter study of the average diagnostic delay period for UC in the South Korean
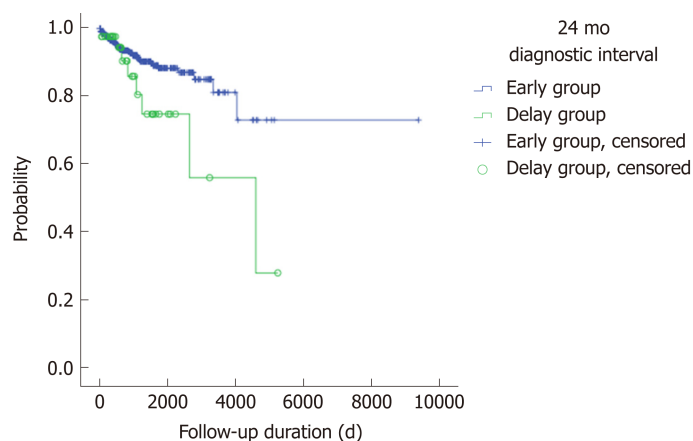
Figure 2 Anti-tumor necrosis factor alpha-free survival between the early and delay groups according to the 24-mo diagnostic interval (P = 0.034).

population. The prognosis was assessed according to the use of anti-TNFα in Asians avoiding surgery, and it was assumed that these patients could represent the Asian population with mild UC.

Our study suggested that a 24-mo diagnostic delay should be avoided in UC patients even those with mild UC symptoms. Care should be taken not to overlook UC in young patients with hemorrhoids who smoke.

Table 3 Comparisons of clinical characteristics between the early and delay groups according to the 24-mo diagnostic interval for patients with ulcerative colitis

		Total	Early group (< 24 mo)	Delay group (≥ 24 mo)	*P* value
Sex (%)					0.872
	Male	318 (57.7)	293 (57.6)	25 (59.5)	
	Female	233 (42.3)	216 (42.4)	17 (40.5)	
Age (%)		40.56 ± 16.11	40.93 ± 16.20	41.21 ± 14.47	0.903
					0.020
	≥ 60 yr	80 (14.5)	79 (15.5)	1 (2.4)	
	< 60 yr	471 (85.5)	430 (84.5)	41 (97.6)	
BMI (%)					0.306
	< 25 kg/m^2	295 (83.3)	268 (82.7)	27 (90.0)	
	≥ 25 kg/m^2	59 (16.7)	56 (17.3)	3 (10.0)	
Education (%)					0.561
	< University	170 (56.5)	152 (55.9)	18 (62.1)	
	≥ University	131 (43.5)	120 (44.1)	11 (37.9)	
Residence at diagnosis (%)					0.498
	Rural	503 (94.2)	466 (94.3)	37 (92.5)	
	Urban	31 (5.8)	28 (5.7)	3 (7.5)	
Family history of IBD (%)					0.782
	No	318 (86.2)	291 (85.8)	27 (90.0)	
	Yes	51 (13.8)	48 (14.2)	3 (10.0)	
Smoking (%)					0.008
	No	366 (82.6)	339 (84.1)	27 (67.5)	
	Yes	77 (17.4)	64 (15.9)	13 (32.5)	
First symptom (%)					
					0.540
Hematochezia	No	160 (29.2)	146 (28.9)	14 (33.3)	
	Yes	388 (70.8)	360 (71.1)	28 (66.7)	
					0.229
Chronic diarrhea	No	384 (70.1)	358 (70.8)	26 (61.9)	
	Yes	164 (29.9)	148 (29.2)	16 (38.1)	
Diagnosis before UC					
					0.000
Hemorrhoids (%)	No	487 (94.7)	453 (95.8)	34 (82.9)	
	Yes	27 (5.3)	20 (4.2)	7 (17.1)	
					0.066
IBS (%)	No	494 (96.1)	457 (96.6)	37 (90.2)	
	Yes	20 (3.9)	16 (3.4)	4 (9.8)	
Mayo score at diagnosis (%)					0.958
	Mild	179 (44.9)	163 (44.9)	16 (44.4)	
	Moderate + Severe	220 (55.1)	200 (55.1)	20 (55.6)	
Disease extent at diagnosis (%)					0.914
	Proctitis + left side	413 (75.5))	381 (75.4)	32 (76.2)	
	Extensive	134 (24.5)	124 (24.6)	10 (23.8)	

BMI: Body mass index; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; IBS: Irritable bowel syndrome.

Table 4 Risk factors predictive of 24-mo diagnostic delay according to the univariate and multivariate analyses

	Univariate		Multivariate	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (≥ 60 yr *vs* < 60 yr)	7.533 (1.021-55.557)	0.020	14.778 (1.731-126.121)	0.014

Smoking history (no *vs* yes)		2.550 (1.249-5.206)	0.008	2.688 (1.239-5.747)	0.012
Misdiagnosed as hemorrhoids (no *vs* yes)		4.663 (1.842-11.803)	0.000	11.066 (3.596-34.053)	0.000

OR: Odd ratio; CI: Confidence interval.

Table 5 Risk factors related to anti-tumor necrosis factor alpha use

		Total	Anti-TNFα No	Anti-TNFα Yes	*P* value
Sex (%)					0.731
	Male	318 (57.7)	288 (57.5)	30 (60.0)	
	Female	233 (42.3)	213 (42.5)	20 (40.0)	
Age (%)		40.56 ± 16.11	41.10 ± 16.76	38.36 ± 16.05	0.268
					0.913
	< 60 yr	278 (50.5)	428 (85.4)	43 (86.0)	
	≥ 60 yr	273 (49.5)	73 (14.6)	7 (14.0)	
Smoking (%)					0.422
	No	366 (82.6)	329 (83.1)	37 (78.7)	
	Yes	77 (17.4)	67 (16.9)	10 (21.3)	
BMI (%)					0.667
	< 25 kg/m^2	295 (83.3)	260 (83.6)	35 (81.4)	
	≥ 25 kg/m^2	59 (16.7)	51 (16.4)	8 (18.6)	
Mayo score at diagnosis (%)					0.001
	Mild	179 (44.9)	170 (47.6)	9 (21.4)	
	Moderate + severe	220 (55.1)	187 (52.4)	33 (78.6)	
Disease extent at diagnosis (%)					0.000
	Proctitis + left side	413 (75.5)	394 (79.3)	19 (38.0)	
	Extensive	134 (24.5)	103 (20.7)	31 (62.0)	
CRP level at diagnosis (%)					0.536
	< 5 mg/dL	265 (79.3)	17 (73.9)	282 (79.0)	
	≥ 5 mg/dL	69 (20.7)	6 (26.1)	75 (21.0)	
Steroid use after diagnosis					0.269
	< 2 mo		116 (57.1)	31 (66.0)	
	≥ 2 mo		87 (42.9)	16 (34.0)	
AZA/6MP use after diagnosis					0.741
	< 2 mo	47 (29.2)	37 (29.8)	10 (27.0)	
	≥ 2 mo	114 (70.8)	87 (70.2)	27 (73.0)	
Diagnostic delay (%)					0.019
	< 24 mo	509 (92.4)	467 (93.2)	42 (84.0)	
	≥ 24 mo	42 (7.6)	34 (6.8)	8 (16.0)	

Anti-TNFα: Anti-tumor necrosis factor alpha; BMI: Body mass index; AZA/6MP: Azathioprine or 6-mercaptopurine.

Table 6 Risk factors predictive of anti-tumor necrosis factor alpha use according to the univariate and multivariate analyses

	Univariate		Multivariate	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Mayo score (mild *vs* moderate + severe).	3.333 (1.550-7.169)	0.002	2.168 (0.956-4.916)	0.064
Disease extent (proctitis + left side *vs* extensive)	6.241 (3.388-11.496)	0.000	3.768 (1.860-7.632)	0.000
Diagnostic delay (< 24 mo *vs* ≥ 24 mo)	2.616 (1.138-6.014)	0.019	2.599 (1.006-4.916)	0.049

OR: Odd ratio; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Ulcerative colitis (UC) is diagnosed by clinical, endoscopic, and histologic findings because there is no definite diagnosis index. Therefore, differentiating it from other diseases of the intestines, such as acute gastroenteritis or irritable bowel syndrome is often difficult, and its diagnosis is often delayed. Recent studies have shown that early control of inflammatory bowel disease (IBD) affects the quality of life and the disease course, including its prognosis.

Research motivation

Most studies of a diagnostic delay for IBD were focused on Crohn's disease. There have been reports of clinical factors involved in the diagnostic delay of UC, but there is a lack of information regarding whether this delay affects the prognosis and treatment of UC. Diagnostic delay and its impact on Western and Asian populations may be significantly different owing to genetic or environmental factors; therefore, it is necessary to examine the results according to countries or regions.

Research objectives

We aimed to identify the delay in diagnosis (time from the first symptoms to UC diagnosis) that affected treatment and prognosis. We also evaluated the risk factors and clinical significance of a diagnostic delay for UC in South Korean patients.

Research methods

This retrospective study was based on patient data collected from six university-affiliated hospitals located in South Korea from January 2006 to December 2016. We analyzed the medical records of 718 patients who visited the outpatient clinic in 2016, had a definite diagnosis of UC, and were available for follow-up for more than 6 mo. One hundred sixty-seven patients were excluded from the study because of incomplete medical record data regarding the first day of symptoms. To determine the prognostic factors, the use of anti-tumor necrosis factor alpha (TNFα) drugs, the hospital admission history due to acute flare-ups, frequent admission, surgery associated with UC, and the clinical remission state at the latest follow-up were obtained from the medical records. The diagnostic interval was defined as the time from the first symptom until UC diagnosis. We divided the patients into the early and delay groups according to several diagnostic interval criteria (3 mo, 6 mo, 12 mo, 18 mo and 24 mo. Then, we compared the two groups according to the demographic and clinical characteristics to determine the diagnostic delay having a clinical impact.

Research results

The days from first symptoms to UC diagnosis were 223.28 ± 483.15 (median, 69); 75% of patients were diagnosed within 195 d. The use of anti-TNFα drugs at the 3-mo diagnostic interval was insignificantly prevalent in the early group (34/314; 10.6%) and the delay group (16/229; 7.0%); however, the use of anti-TNFα drugs by the early group and delay group started to decrease at the 18-mo diagnostic interval. Finally, at the 24-mo diagnostic interval, it was significantly higher in the delay group (8/42; 35.7%) than in the early group (42/509; 8.3%) ($P = 0.019$). Anti-TNFα free-survival rates between the early and delay groups according to the 24-mo diagnostic interval were significantly different ($P = 0.034$). Therefore, it was determined that 24 mo was the diagnostic delay cutoff point for poor outcomes. According to the multivariate logistic regression analysis, independent risk factors predictive of a diagnostic delay of 24 mo were age < 60 years [odd ratio (OR) = 14.778, 95% confidence interval (CI): 1.731-126.121, $P = 0.014$], smoking history (OR = 2.688, 95%CI: 1.239-5.747, $P = 0.012$), and misdiagnosis of hemorrhoids (OR = 11.066, 95%CI: 3.596-34.053, $P=0.000$).

Research conclusions

We found that the ≥ 24-mo diagnostic delay group more frequently used anti-TNFα compared to the < 24-mo delay group. We also found that risk factors for a 24-mo delay were age < 60 years, smoking history, and misdiagnosis of hemorrhoids by a physician.

Research perspectives

Prospective studies are needed to reduce recall bias for important clinical studies such as the first day of UC-related symptoms.

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