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ABOUT COVER

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Retrospective Study

Progress of ulcerative colitis patients during the COVID-19 pandemic

Toshikuni Suda, Morio Takahashi, Yasumi Katayama, Koichi Soga, Ikuhiro Kobori, Yumi Kusano, Masaya Tamano

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Abstract**BACKGROUND**

We have previously demonstrated that the first wave of the coronavirus disease 2019 (COVID-19) pandemic caused exacerbations in ulcerative colitis (UC) patients, probably through psychological and physical stress. However, successive waves of the COVID-19 pandemic continuously followed the first. The effects of this chronic stress on the disease condition in UC patients are of interest.

AIM

To clarify the effect of chronic stress from COVID-19 on disease condition in patients aggravated after the first wave.

METHODS

Our previous study investigated 289 consecutive UC outpatients treated in one center during March and April 2020, the period of the first wave of the COVID-19 pandemic. In this study, an identical group of 289 UC patients was evaluated using UC-disease activity index (UC-DAI), endoscopic mucosal appearance score, and Mats pathologic grade scoring.

RESULTS

Of the 289 UC patients included in the study in 2020, 10 patients dropped out as of 2021 and another 11 patients dropped out as of 2022, making three groups for 2020, 2021 and 2022. No significant differences in characteristics were found among the three groups. UC-DAI scores had aggravated during the period of the first wave of the COVID-19 pandemic, but significantly recovered in 2021 and remained stable in 2022. Mats grade scores significantly recovered in 2021 from those in 2020 and remained stable in 2022.

CONCLUSION

Disease activity of UC patients recovered in 2021 and remained stable in 2022, aggravated by the stress of the first wave of COVID-19 in 2020 despite persistence of the pandemic.

Key Words: Ulcerative colitis; COVID-19; Exacerbation; Stress; Ulcerative colitis disease activity index; Matts grade

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Core Tip: Previously, we demonstrated that the first wave of coronavirus disease 2019 (COVID-19) pandemic caused exacerbation in ulcerative colitis (UC) patients. Impact of the successive waves of the pandemic is of interest. We adopted the identical group of patients who were included in our previous study indicating the impact of the first wave in 2020. Disease activity of UC patients, aggravated by the stress of the first wave of COVID-19 in 2020, recovered significantly in 2021 and remained stable in 2022, despite persistence of the pandemic.

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INTRODUCTION

We have previously demonstrated that the first wave of the coronavirus disease 2019 (COVID-19) pandemic caused exacerbation of ulcerative colitis (UC) in patients, presumably through psychological and physical stress. Our findings also indicated that stress from COVID-19 did not directly influence the condition of UC patients, but provided a psychological background against which specific stress could act. Patients felt that everyday stress, such as the disease itself, work, or home life, directly induced exacerbation of the disease, which was probably enhanced by the background mood of anxiety about being sick and a sense of limitations on everyday activities in communications with others[1]. The pandemic continued throughout 2021, but the Japanese government ended the State of Emergency declaration and loosed restrictions on movement for people (including lock-downs) for economic and political reasons[2-4]. Inflammatory bowel disease (IBD) doctors would be able to implement preventive measures to avoid disease exacerbations if they become aware of the risks of exacerbation in advance. Preventive measures can include increasing 5-aminosalicylic acid (5-ASA) administration, providing topical formulations (5-ASA enema, prednisolone enema, budesonide form enema, *etc.*) and so on. IBD doctors are therefore concerned about the effects of successive waves of the COVID-19 pandemic on UC exacerbation. In this study, we followed-up the same group of UC patients included in the last study, in which these patients had shown significant exacerbation with the first wave of the COVID-19 pandemic[1]. Wintjens *et al*[5] indicated that fresh, acute stress in particular has a stronger influence than continuous stress on UC patients in the form of outcomes such as exacerbations.

We evaluated whether the condition of UC would stay aggravated during the second and subsequent waves of COVID-19 or whether recovery would be achieved and remain after some point. We therefore assessed patient conditions in 2021 and 2022, when the 2nd through 8th waves were experienced in Japan, using UC disease indices for symptoms, endoscopic mucosal appearance, and pathological scoring.

MATERIALS AND METHODS

Patients

Our original study included a total of 289 consecutive UC outpatients from a single center during March and April 2020, representing the period of the first wave of the COVID-19 pandemic. This same group of 289 UC patients visiting the clinic regularly was included in the present study. Of the 289 UC patients included in the 2020 study, 10 patients dropped out as of 2021 and another 11 patients dropped out as of 2022, making three groups for 2020, 2021 and 2022. The UC activity of these patients continued to be evaluated in March and April of both 2021 and 2022. The UC activity of patients was scored using the UC disease activity index (UC-DAI), including endoscopic mucosal appearance, and Matts pathological grading, as described below.

UC-DAI

The UC-DAI is defined as the total of scores for stool frequency (normal, 0; 1-2 stools/day more than normal, + 1; 3-4 stools/day more than normal, + 2; and > 4 stools/day more than normal, + 3), rectal bleeding (none, 0; blood visible with stool less than half the time, + 1; blood visible with stool half the time or more, + 2; and passage of blood only, + 3), physician rating of disease activity (normal, 0; mild, + 1; moderate, + 2; and severe, + 3), and physician rating of mucosal appearance (normal, 0; mild friability, + 1; moderate friability, + 2; and exudation, spontaneous bleeding, + 3)[6].

Matts UC pathological grading

Biopsy samples were acquired during endoscopic examination of the cecum, ascending colon, transverse colon, sigmoid colon and rectum. Each sample was assessed using the following standard: Grade 1, normal appearance; grade 2, some infiltration of the mucosa or lamina propria by either round cells or polymorphs; grade 3, marked cellular infiltration of the mucosa, lamina propria, and submucosa; grade 4, presence of crypt abscesses, with marked infiltration of all layers of the mucosa; and grade 5, ulceration, erosion, or necrosis of the mucosa, with cellular infiltration of some or all layers of the mucosa[7].

This retrospective study was reviewed and approved by the Ethics Committee at Dokkyo Medical University Saitama Medical Center (approval No. 20100). Written, informed consent was obtained from all UC patients prior to enrolment. This study conformed to the ethical guidelines of the 2008 Declaration of Helsinki. All data were obtained from clinical records, which were written on the day each patient visited the facility.

Statistical analysis

Quantitative data are presented as mean \pm SD. Discrete variables are presented as median and range. For statistical comparisons of UC-DAI, including endoscopic appearance and Matts pathological grade score, between the years of 2020, 2021 and 2022, we used paired *t*-tests. Values of *P* < 0.05 were considered significant.

RESULTS

Characteristics

Of the 289 UC patients included in the 2020 study, 10 patients dropped out as of 2021 and another 11 patients dropped out as of 2022, making three groups for 2020, 2021 and 2022. For two years, a total of 21 patients dropped out from the original group of patients; otherwise, the groups were identical. **Table 1** shows the characteristics of the study participants (including age, weight, height, smoking rate, sex, pancolitis rate, and medication) in 2020 at entry, and in 2021 and 2022 during repeated waves of the COVID-19 pandemic (**Table 1**).

Pharmacotherapies

Table 2 shows the pharmacotherapies used by the patients included in 2020 at entry, as well as in 2021 and 2022 (**Table 2**).

UC-DAI

Mean UC-DAI (\pm SD) during the first wave of the pandemic was 1.07 ± 1.62 , compared to 0.63 ± 1.29 in March and April 2021, and 0.48 ± 1.05 in March and April 2022. UC-DAI scores thus showed a significant recovery in 2021 and remained stable in 2022.

Although patients suffered repeated waves of the COVID-19 pandemic, UC-DAI recovered quickly after the first wave (2020 *vs* 2021, *P* = 0.0003; 2020 *vs* 2022, *P* = 0.000; 2021 *vs* 2022, *P* = 0.1755) (**Figure 1A**).

Matts grade score

Mean Matts grade score during the first wave of the pandemic was 2.80 ± 0.86 , compared to 2.59 ± 0.90 in March and April 2021 and 2.47 ± 0.91 in March and April 2022. Matts grade scores significantly recovered in 2021 from that of 2020 and remained stable thereafter (2020 *vs* 2021, *P* = 0.0074; 2020 *vs* 2022, *P* = 0.0001; 2021 *vs* 2022, *P* = 0.1652) (**Figure 1B**).

DISCUSSION

We have previously demonstrated that UC patients regularly visiting our clinic experienced exacerbation of UC after the first wave of the COVID-19 pandemic in 2020[1]. As of March 2021, Japan was experiencing its 8th wave of COVID-19[2]. The disease conditions of patients from the 2nd wave on are of interest. We retrospectively evaluated clinical conditions using the UC-DAI, as well as mucosal condition from endoscopic appearance and pathological Matts grading, which is reliably used worldwide to evaluate mucosal inflammation in UC patients[8,9]. Disease activity in UC patients worsened significantly with the first wave of the COVID-19 pandemic, but recovered significantly after the 2nd wave and remained stable thereafter up to the 7th wave (July and August 2022)[2]. Our previous report indicated that the condition of UC patients exacerbated with the first wave of COVID-19 largely through economic and social limitations on daily life, as well as uncertainty over when the pandemic would be over[1]. The pandemic remains ongoing in Japan, but disease exacerbation did not continue. Conversely, patients recovered soon after the second wave. The possibilities include either that the pandemic ceased to represent a major stressor or patient sensitivity to the stress became dulled. Robillard *et al*[10] reported that people expressed strong stress at the beginning of the pandemic, but this stress decreased over time and recovered to pre-pandemic levels by 2 mo after the declaration of a State of Emergency. This was considered to represent formation of a kind of self-defense. The majority of IBD patients may remain in remission thanks to new pharmacological agents such as biologics and JAK inhibitors. This enables medical practitioners to treat IBD patients in outpatient-based facilities. More attention is therefore being given to maintaining remission rather than treating severe cases[11]. To keep patients in remission, the present study indicated that IBD doctors should be aware of the stress situation of patients, and should anticipate the effects of stress on near-future disease activities to control and prevent flares. Upgrading remission

Table 1 Characteristics of study participants from the 2020, 2021, and 2022 groups

	2020 (n = 289)	2021 (n = 279)	2022 (n = 268)
Age (yr)	45.0 ± 15.8	45.13 ± 15.60	45.28 ± 15.40
Sex (M/F)	147/141	140/139	136/135
Height (cm)	163.6 ± 8.6	163.6 ± 8.6	163.7 ± 8.7
Weight (kg)	60.1 ± 11.3	60.1 ± 11.3	60.3 ± 11.1
Disease duration (years)	11.6 ± 8.5	11.50 ± 8.61	11.44 ± 8.40
Smokers	69 (23.8%)	66 (23.6%)	65 (24.2%)
Disease extent			
Total colitis	136 (47.0%)	113 (40.5%)	128 (47.7%)

Originally, 289 consecutive patients visiting the clinic were included into the study in March and April 2020, representing the first wave of the coronavirus disease 2019 pandemic. Ten patients dropped out from the original study group in 2021 and additional 11 patients dropped out in 2022. However, no significant differences were seen among the three groups for weight, height, disease duration, smoker rate, sex, disease extent or total colitis rate.

Table 2 Pharmacotherapies used for the 2020, 2021, and 2022 groups, n (%)

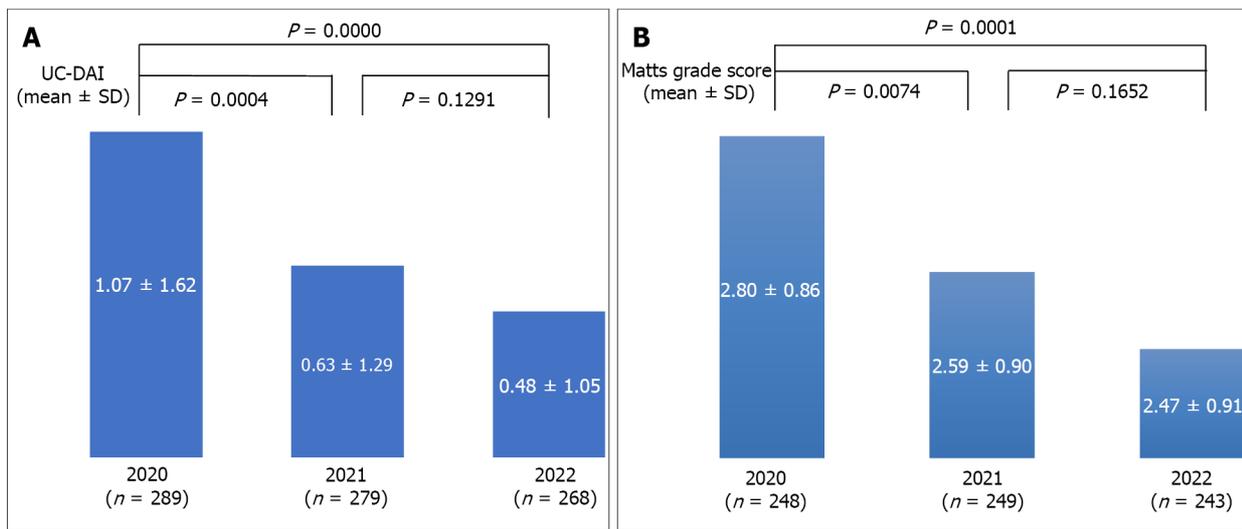
	2020 (n = 289)	2021 (n = 279)	2022 (n = 268)
5-ASA	165 (57.0)	158 (56.6)	151 (56.3)
AZA or 6-MP	35 (12.1)	32 (11.4)	33 (12.3)
IFX	36 (12.4)	35 (12.5)	33(12.3)
ADA	26 (8.9)	26 (9.3)	26 (9.7)
GLM	9 (3.1)	9 (3.2)	7 (2.6)
VDZ	0 (0)	1 (0.3)	1 (0.3)
UST	0 (0)	1 (0.3)	1 (0.3)
TFN	2 (0.6)	2 (0.7)	3 (1.1)
TF	8 (2.7)	8 (2.8)	7 (2.6)
IR	5 (1.7)	5 (1.7)	4 (1.0)
PSL	1 (0.3)	0 (0)	1 (0.3)
CHM	1 (0.3)	1 (0.3)	1 (0.3)
ND	1 (0.3)	1 (0.3)	0 (0)

5-ASA: Aminosalicic acid; AZA: Azathioprine; 6-MP: Mercapton; IFX: Infliximab; ADA: Adalimumab; GLM: Golimumab; UST: Ustekinumab; TFN: Tofacitinib; VDZ: Vedolizumab; TF: Topical formulation; IR: Intestinal regulator; PSL: Prednisolone; CHM: Chinese herbal medicine; ND: No drug.

treatments involves measures such as increasing doses of 5-ASA, adding extra topical therapy, and using systemic administration of steroid and biological agents as necessary. Of course, the additional risks should always be taken into consideration. IBD doctors must always strive to balance the benefits and risks.

CONCLUSION

We have demonstrated that the disease activity of UC patients as assessed by UC-DAI, endoscopy and pathology (Matts grading), which was exacerbated in 2020 with the first wave of the COVID-19 pandemic, recovered significantly in 2021 and remained stable in 2022, despite the persistence of the pandemic. In order to keep patients in remission, IBD doctors should anticipate the risk of flares according to these findings and upgrade treatments in advance.



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Figure 1 Score. A: Ulcerative colitis disease index score was exacerbated by the first wave of the coronavirus disease 2019 (COVID-19) pandemic as compared with those 1 and 2 years later. Ulcerative colitis disease activity index score exacerbated by the first wave of COVID-19 was significantly recovered a year later and remained or tended to be improved 2 years later despite pandemic persistence; B: Matts grade score, representing the pathological severity of colonic mucosa during the first wave of COVID-19 as compared with those 1 and 2 years later. Matts grade score was significantly recovered a year later and remained or tended to be improved 2 years later, despite pandemic persistence. UC-DAI: Ulcerative colitis disease activity index.

ARTICLE HIGHLIGHTS

Research background

Previously, we reported that patients with ulcerative colitis (UC) had the worst symptoms during the coronavirus disease 2019 (COVID-19) pandemic.

Research motivation

The COVID-19 pandemic continued in 2021 and 2022.

Research objectives

We investigated whether people with UC had changes in symptoms in 2021 and 2022.

Research methods

Patients with UC included in previous studies were compared using UC-disease activity index (UC-DAI) and the Matts grade score.

Research results

Both UC-DAI and Matts grade scores fell from 2020 to 2021 and did not rise in 2022.

Research conclusions

Patients with UC experienced stress and worsened their symptoms in 2020 during the COVID-19 pandemic. The virus epidemic continued in 2021 and 2022, but the symptoms did not worsen.

Research perspectives

Since the symptoms of patients with UC are significantly worsened by stress, doctors need to pay attention to the worsening of symptoms of patients with ulcerative colitis when a major disaster occurs in the future.

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FOOTNOTES

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