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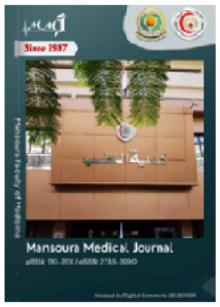

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Impact of COVID - 19 Pandemic on The Clinical Course of Inflammatory Bowel Disease in Egyptian Tertiary Centers

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ORIGINAL STUDY

Impact of Coronavirus Disease 2019 Pandemic on the Clinical Course of Inflammatory Bowel Disease in Egyptian Tertiary Centers

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Abstract

Background/aim: **The coronavirus disease 2019 (COVID-19) pandemic has a major impact on the clinical course of chronic diseases including inflammatory bowel disease (IBD). In the current study, we aimed to evaluate the clinical relapse and worsening of IBD activity during the COVID-19 pandemic.**

Patients and methods: **In this study 125 patients were included and were followed up for 1 year. Of them, 98 and 27 patients had inactive and active IBD before the study, respectively. The clinical activity of IBD was assessed by Crohn's disease activity index and simplified colitis clinical activity index. Severe acute respiratory distress syndrome coronavirus 2 infection was detected by real-time PCR.**

Results: **The mean age of included patients was 34.3 ± 11.2 years, of them 54 (43.2%) were males. Forty three (34.4%) and 82(65.6%) patients had Crohn's disease and ulcerative colitis, respectively. Forty-six (47%) patients developed a clinical relapse within 1 year. Of them, 22 (48%) patients were not adherent to treatment during the pandemic ($P \leq 0.05$); 33.3% of patients with active IBD before the study had worsened activity during the pandemic. The incidence of severe acute respiratory distress syndrome coronavirus 2 infection among the included patients was 8% ($n = 10$).**

Conclusion: **The majority of relapsed IBD patients were not adherent to treatment due to the fear of COVID-19 infection.**

Keywords: Coronavirus disease 2019, Crohn's disease, Inflammatory bowel disease, Relapse, Ulcerative colitis

1. Introduction

Globally, the prevalence of inflammatory bowel disease (IBD) increased substantially in many countries, which might pose a substantial social and economic burden on governments and health systems in the coming years. The age-standardized prevalence rate of IBD in Egypt increased from 17.9 to 26.7/100 000, between 1990 and 2017 with a 48.9% change (Alatab et al., 2020).

Since the start of 2020, the coronavirus disease 2019 (COVID-19) has become a pandemic, leading to disturbance in medical care and affecting patient−doctor communication. Patients with IBD have experienced substantial changes in the routine management of their conditions during the COVID-19 pandemic (Ricciuto et al., 2022; Wang et al., 2020).

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Indeed, a large anonymous web survey (conducted between March 30 and April 16, 2020) highlighted the presence of a communication gap between doctors and patients and suggested an urgent need to improve physician–patient communication to provide clear and specific recommendations for people with IBD (D'Amico et al., 2020).

IBD generally goes on with alternate courses of remission and reactivation, which could lead to increased complications. In addition, it requires long-term therapies (Kaplan, 2015) and regular contact with the IBD clinic (Mccombie et al., 2013). For these reasons, adherence to medical care is essential to maintain the disease in a remission phase and avoid relapse or worsening.

Promoting adherence to treatment among individuals affected by IBD was a challenge for healthcare providers, before the COVID-19 pandemic, where 43–60% of IBD adults were nonadherent to their prescribed oral medication regimen (Kane and Shaya, 2008; Kane et al., 2003). Indeed, nonadherent adults are 5.5 times more likely to experience disease reactivation than are their adherent counterparts (Kane et al., 2003).

2. Patients and methods

2.1. Setting

This prospective study was conducted on IBD patients, between April 1 2020 and April 1, 2021, at two IBD centers in Egypt and in two tertiary hospitals in Egypt; El Hussein University Hospital, Cairo, and Specialized Medical Hospital, Mansoura.

2.2. Study design

In the first week of April 2020, all patients at the IBD clinical registry were contacted, informed about the precautions that should be taken to avoid COVID-19 infection and our regulations during the pandemic, and were invited to the study. The clinical relapse or worsening of the IBD activity was evaluated and recorded. In addition, the incidence of COVID-19 infection during the study was estimated. Two IBD specialist physicians contacted patients to explain the study objectives and invited them to complete two handwritten questionnaires (at the end of the first and second wave of the pandemic) to assess adherence to regular IBD clinic visits, and adherence to IBD drugs. Clinical evaluation of IBD activity was conducted through direct contact at regular IBD clinic visits. We categorized our cohort into two categories, based on the Crohn's disease activity index (CDAI) and simplified colitis clinical activity index (SCCAI) before the study. (a) IBD remission group ($n = 98$): a group of patients enrolled during their disease remission and (b) IBD-active group ($n = 27$): a group of patients enrolled while they had disease activity.

2.3. Patient inclusion

Patients with established IBD diagnosis for at least 4 months before the start of the study were included. Patients with unavailable CDAI and SCCAI records and those who did not complete the two written questionnaires were excluded. In addition, patients with IBD relapse due to enteric infection, nonsevere acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2)-systemic infection, and due to the use of NSAIDs were excluded.

2.4. Diagnosis of severe acute respiratory distress syndrome coronavirus 2 infection

The diagnosis of SARS-CoV-2 infection is based on the detection of SARS-CoV-2 by real-time PCR. Nasopharyngeal swabs were collected for SARS-CoV-2 RT-PCR testing as described before (Abdelmoniem et al., 2021). Briefly, probes were annealed to three target sequences specific to COVID-19: ORF1ab, nucleocapsid (N), and spike (S) primers/probes for bacteriophage MS2. Two of the three genes and the MS2 (positive control) must be positive.

2.5. Relapse and worsening of inflammatory bowel disease activity

IBD relapse and worsening were evaluated, during regular IBD clinic visits, between April 1, 2020, and April 1, 2021. The relapse or worsening of CD and ulcerative colitis (UC), during the study, was evaluated and recorded by IBD specialist physicians. IBD relapse is defined as CDAI more than 150 points and SCCAI more than one point, among CD and UC patients, who were on disease remission before the study. Worsening of IBD activity, defined as increased CDAI and SCCAI scores among patients with elevated CDAI (>150 points) and SCCAI (>1 point) before inclusion. The first episode of IBD relapse or worsening was only recorded and analyzed.

2.6. Adherence to inflammatory bowel disease management

During August 2020 and March 2021, all included patients were invited to complete two handwritten questionnaires to assess adherence to regular IBD clinic visits, and adherence to IBD drugs during the

first (April 1–August 31) and second (September 1–April 1) waves of COVID-19 pandemic.

2.7. Inflammatory bowel disease diagnosis

The initial diagnosis of IBD is based on clinical, endoscopic, laboratory, radiologic, and histologic data (Lamb et al., 2019).

2.8. Baseline inflammatory bowel disease histopathological activity

The baseline histological activity of CD and UC is based on Naini and Cortina (Naini and Cortina, 2012), and Nancy (Marchal-Bressenot et al., 2017) scores, respectively.

2.9. Inflammatory bowel disease activity before the study

The disease activity before the study period is based on the patient's records at the last visit (February–March 2020) before the beginning of the study. IBD remission was considered in patients with CDAI less than or equal to 150 points (Best et al., 1976) or SCCAI less than or equal to one point (Walmsley et al., 1998), within 2 months before the study. In contrast, active IBD is defined as CDAI more than 150 points and SCCAI more than one point, within 2 months before the study.

2.10. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage. The following tests were done: independent samples t test of significance was used when comparing between two means for parametric data, for nonparametric data, and Mann–Whitney Z test is used to compare the two groups. χ^2 test of significance was used to compare proportions between qualitative parameters.

2.11. Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Faculty of Medicine, Al-Azhar University (Med._147Med.Research. COVID-19 Screening before Gastrointestinal procedures._00000175). All participants provided written informed consent before inclusion into the study.

3. Results

Among 125 patients included, the mean age was 34.3 ± 11.2 years, of them 54 (43.2%) were males; 43 (34.4%) patients had CD and 82 (65.6%) had UC. The mean duration of IBD was 3.7 ± 3.47 years. Primary sclerosing cholangitis is associated with IBD in three (4.1%) patients (Table 1).

3.1. Baseline histopathological activity

The majority of included patients had severe histopathological activity at IBD diagnosis. Indeed nine (7.2%), 42 (33.6%) and 74 (59.2%) patients had mild, moderate, and severe IBD activity, respectively (Table 1).

Table 1. Clinical characteristics of included patients.

	n = 125
Age	34.3 ± 11.2
Sex	
Male	54 (43.2%)
Female	71 (56.8%)
IBD category n (%)	
CD	44 (35.2%)
UC	81 (64.8%)
Duration of IBD	
Mean	3.7 ± 3.47
Associated comorbidities n (%)	
Diabetes mellitus	2 (1.6%)
Hypertension	3 (2.4%)
Aortic valve replacement	1 (0.8%)
Rheumatoid arthritis	1 (0.8%)
Ankylosing spondylitis	1 (0.8%)
autoimmune hepatitis	1 (0.8%)
SS thrombosis	1 (0.8%)
Nephrotic syndrome	1 (0.8%)
Sclerosing cholangitis	3 (2.4%)
Behcet's disease	1 (0.8%)
Bronchial Asthma	1 (0.8%)
VSD	2 (1.6%)
HCV	1 (0.8%)
Histopathological activity at diagnosis n (%)	
Mild	9 (7.2%)
Moderate	42 (33.6%)
Severe	74 (59.2%)
Clinical disease activity before the pandemic n (%)	
Active	27 (21.6%)
On remission	98 (78.4%)
IBD medications before the pandemic n (%)	
Steroids	31 (24.8%)
Thiopurines	104 (83.2%)
5 ASA	109 (87.2%)
TNF-alpha antagonists	14 (11.2%)
Cyclosporin	1 (0.8%)

5 ASA, 5-aminosalicylic acid; CD,CD, Crohn's disease; HCV, hepatitis C virus; IBD, inflammatory bowel disease; SS thrombosis, sagittal sinus thrombosis; UC, ulcerative colitis; VSD, ventricular septal defect.

3.2. Inflammatory bowel disease clinical activity before the study

While 98 (78.4%) patients were on clinical remission, before the beginning of the study, 27 (21.6%) patients had active IBD. Among CD patients, 34 (77.3%) had CDAI less than or equal to 150 and 10 (22.7%) had CDAI more than 150. However, 64 (73.8%) UC patients had SCCAI less than or equal to 1 and 17 (26.2%) had SCCAI more than 1.

3.3. The outcome of included patients during the pandemic

Among patients in clinical remission, 46 (47%) patients developed disease relapse during the study period. Of them, 22 (47.8%) patients during the first wave and 24 (52.2%) during the second wave. However, nine (33.3%) patients with active IBD before the study exhibited worsening of disease activity. Among the included patients, 10 (8%) get COVID-19 infection during the study. Of them, four developed infections during the first wave and six during the second wave. Fourteen IBD patients were admitted to the hospital during the study, nine admissions due to IBD-related causes and five due to COVID-19-related causes. Eleven (8.8%) patients underwent scalation of IBD treatment (Table 2).

Table 2. Outcome of included patients during the pandemic.

	125
Relapse	
Overall	46/98 (47%)
1st wave	22
2nd wave	24
Worsening	
Overall	9/27 (33.3%)
1st wave	9
2nd wave	9
COVID-19 infection	
Overall	10/125 (8%)
1st wave	4
2nd wave	6
Hospital admission	14
IBD related	9
COVID-19-related admission	5
Scalation of treatment	11 (8.8%)
Increase steroids	5
Increased thiopurine dose	1
Change TNF-alpha antagonist to another biologic	3
Add biologic	2
Death	2/125 (1.6%)
Brain tumor	1
Bone marrow suppression due to cyclosporine	1

COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; TNF-alpha, tumor necrosis factor-alpha.

Among the included patients, two (1.6%) died during the study period due to brain tumor ($n = 1$) and cyclosporine-induced bone marrow suppression ($n = 1$).

3.4. Inflammatory bowel disease relapse during the pandemic

Among 98 patients with IBD remission before the study, 46 (47%) developed clinical relapse between April 1, 2020 and April 1, 2021 (Table 2). Their mean age was 33.9 ± 9.7 years; there were 18 (39.1%) males and 28 (60.9%) females. Of them, 13 (28.3%) patients had CD and 33 (71.17%) had UC. The mean duration of IBD among patients with clinical relapse was 3.8 ± 3.6 years. Twenty-five (54.3%) patients with clinical relapse had severe histopathological IBD activity at diagnosis. A significant number ($n = 22$; 47.8%) of patients with clinical relapse had missed one or more IBD medications during the study ($P \leq 0.05$) (Table 3). Of them, 45.5% ($n = 10$) missed IBD medications because of the fear of immune suppression and increased susceptibility to SARS-CoV-2 infection. Using steroids, immunosuppressive drugs and biologics were not related to IBD clinical relapse (Table 3). The frequency of SARS-CoV-2 infection among patients with clinical relapse and those without clinical relapse was 6.5% ($n = 3$) and 7.7% ($n = 4$), respectively.

3.5. Inflammatory bowel disease worsening during the pandemic

Among 27 patients with clinically active IBD before the study, nine (33.3%) patients experienced increased CDAI ($n = 4$) and SCCAI ($n = 5$), between April 1, 2020 and April 1, 2021 (Table 2). Their mean age (32 ± 7.58 years) was significantly younger than those without IBD worsening (Table 4). The frequency of male sex was significantly higher among patients with IBD worsening ($P \leq 0.05$). Four (44.4%) patients with IBD worsening had CD and five (55.5%) had UC. The mean duration of IBD among patients with clinical disease worsening was 2.66 ± 1.78 years. All patients with IBD worsening had severe histopathological activity at IBD diagnosis. Neither missed regular outpatient clinic visits nor missed IBD medications were related to IBD worsening. Using steroids, immunosuppressive drugs, and biologics before the study was not related to IBD clinical disease worsening (Table 3). The rate of SARS-CoV-2 infection was significantly higher among patients with IBD worsening (Table 4).

Table 3. Characteristics of patients with inflammatory bowel disease relapse during the pandemic.

	Relapsed ($N = 46$)		Not relapsed ($N = 52$)		$t/\chi^2/F$	P
Age	33.9 ± 9.7		33.13 ± 12.2		$t = 0.34$	0.732 NS
Sex [*n* (%)]						
Males	18	39.1	22	42.3	$\chi^2 = 0.1$	0.749 NS
Females	28	60.9	30	57.7		
IBD category [*n* (%)]						
CD	13	28.3	20	38.5	$\chi^2 = 1.13$	0.286 NS
UC	33	71.17	32	61.5		
Duration of IBD	3.8 ± 3.6		3.35 ± 2.37		$t = 0.74$	0.457 NS
Bassline histopathological activity [*n* (%)]						
Mild	4	8.7	4	7.7	$\chi^2 = 0.53$	0.765 NS
Moderate	17	37	23	44.2		
Severe	25	54.3	25	48.1		
Treatment before the pandemic [*n* (%)]						
Steroids						
Yes	16	34.8	10	19.2	$\chi^2 = 3.02$	0.081 NS
No	30	62.2	42	80.8		
Immunosuppressives						
Yes	40	87	45	86.5	$\chi^2 = 0.003$	0.915 NS
No	6	13	7	13.5%		
Biologics [*n* (%)]						
Yes	5	10.9	3	5.8	$\chi^2 = 0.84$	0.357 NS
No	41	89.1	49	94.2		
Get instructions [*n* (%)]						
Yes	25	54.3	30	57.7	$\chi^2 = 0.11$	0.739 NS
No	21	45.7	22	42.3		
Missed outpatient clinic visits [*n* (%)]						
Yes	31	67.3	32	61.5	$\chi^2 = 0.36$	0.546 NS
No	15	32.6	20	38.5		
The cause of the missed visit [*n* (%)]						
COVID-19-related cause	25	80.6	29	90.6	$\chi^2 = 1.28$	0.257 NS
COVID-19 not related	6	19.4	3	9.4		
Missed drugs [*n* (%)]						
Yes	22	47.8	14	26.9	$\chi^2 = 4.5$	0.032 S
No	24	52.2	38	73.1		
The missed drugs						
Steroids	9		5			
5ASA	12		4		$\chi^2 = 6.2$	0.1 NS
AZT	11		12			
Biologics	5		0			
The cause of missed drug [*n* (%)]						
COVID-19-related cause	10	45.5	5	35.7	$\chi^2 = 0.33$	0.563 NS
COVID-19 not related	12	55.5	9	64.3		
COVID-19 infection [*n* (%)]						
Yes	3	6.5	4	7.7	$\chi^2 = 0.05$	0.822 NS
No	43	93.5	48	92.3		

CD, Crohn's disease; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; UC, ulcerative colitis.

4. Discussion

In the current study, we found that the incidence of IBD relapse during the COVID-19 pandemic is 47%. Missed IBD medication was significantly higher among relapsed patients; 33.3% of active IBD patients had worsened activity during the pandemic. The incidence of SARS-CoV-2 infection among IBD patients was 8%. Patients with worsened IBD activity were more vulnerable to SARS-CoV-2 infection.

4.1. Inflammatory bowel disease remission group

During the COVID-19 pandemic, with lockdown and social distancing, patients with IBD may have difficulty in medical consultation, endoscopic examination, and monitoring of treatment. Moreover, patients with IBD are at an increased risk of relapse due to noncompliance to treatment, stress, and infection. The relapse rate (47%) among our IBD cohort was comparable with the reported relapse

Table 4. Inflammatory bowel disease worsening during the pandemic.

	Worsening activity ($N = 9$)		Not worsened ($N = 18$)		$t/\chi^2/F$	P
Age	32 ± 7.58		39.83 ± 12.16		$t = 1.75$	0.092 NS
Sex [*n* (%)]						
Males	7	77.8	7	38.9	$\chi^2 = 3.6$	0.056 NS
Females	2	22.2	11	61.1		
IBD category [*n* (%)]						
CD	4	44.4	6	33.3	$\chi^2 = 0.31$	0.673 NS
UC	5	55.6	12	66.7		
Duration of IBD	2.66 ± 1.78		4.97 ± 5.87		$t = 0.27$	0.787 NS
Baseline histopathological activity [*n* (%)]	9	100	15	83.3	$\chi^2 = 2.2$	0.137 NS
Severe [*n* (%)]	0	0	3	16.7%		
Treatment before the pandemic [*n* (%)]						
Steroids						
Yes	2	22.2	4	22.2	$\chi^2 = 0.0$	1.0 NS
No	7	77.8	14	77.8		
Immunosuppressives						
Yes	7	77.8	15	83.3	$\chi^2 = 0.004$	0.943 NS
No	2	22.2	3	16.7		
Biologics [*n* (%)]						
Yes	2	22.2	3	16.7	$\chi^2 = 0.12$	0.726 NS
No	7	77.8	15	83.3		
Get instructions [*n* (%)]						
Yes	6	66.7	12	66.7	$\chi^2 = 0.0$	1.0 NS
No	3	33.3	6	33.3		
Missed outpatient clinic visits [*n* (%)]						
Yes	4	44.4	10	55.6	$\chi^2 = 0.29$	0.586 NS
No	5	55.6	8	44.4		
The cause of the missed visit [*n* (%)]						
COVID-19-related cause	3	75	7	70	$\chi^2 = 0.03$	0.851 NS
COVID-19 not related	1	25	3	30		
Missed drugs [*n* (%)]						
Yes	3	33.3	4	22.2	$\chi^2 = 0.38$	0.534 NS
No	6	66.7	14	77.8		
The missed drugs						
Steroids	1		1			
5ASA	1		1		$\chi^2 = 0.11$	0.990 NS
AZT	2		3			
Biologics	1		1			
The cause of the missed drug [*n* (%)]						
COVID-19-related cause	2	66.7	2	50	$\chi^2 = 0.19$	0.659 NS
COVID-19 not related	1	33.3	2	50		
COVID-19 infection [*n* (%)]						
Yes	3	33.3	0	0	$\chi^2 = 6.7$	0.009 S
No	6	66.7	18	100		

CD, Crohn's disease; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; UC, ulcerative colitis.

rate before the COVID-19 pandemic (Gubatan et al., 2020).

The risk of relapse was significantly associated with missed IBD medications. Indeed, lockdown measures were not risk factors for relapse among IBD patients. Interestingly, SARS-CoV-2 infection was not significantly associated with missed IBD medications among the remission group. Like our findings, several studies have reported an increased rate of relapse among IBD patients who stopped or delayed IBD medications (Gubatan et al., 2020; Allocca et al., 2020; Rizzello et al., 2021). These findings highlighted the importance of adherence to maintenance treatment, among patients with IBD remission, to avoid disease deterioration during the COVID-19 pandemic.

In total, the incidence of SARS-CoV-2 infection among the IBD remission group was 7% ($n = 7/98$). There was no significant difference between the incidence of SARS-CoV-2 infection among IBD patients with relapse (6.5%) and those patients without relapse (7.7%). In addition, the duration of IBD and type of medications were not associated with the risk of SARS-CoV-2 infection. Moreover, neither health education nor missed medication was a risk for COVID-19 infection (BogochII et al., 2020). These

data lent us support to speculate that the risk of SARS-CoV-2 infection, among patients with bassline IBD remission, is not related to disease characteristics.

4.2. Active inflammatory bowel disease group

Progressive worsening of IBD activity was reported among 33% of the active IBD group. Worsening of disease activity was significantly associated with SARS-CoV-2 infection ($P < 0.009$). Indeed, 11% of active IBD patients developed SARS-CoV-2 infection. We could not report any significant association between the duration of IBD, type of medication or missed medication, and risk of SARS-CoV-2 infection among the active IBD group. Entry of SARS-CoV-2 into enterocytes or colonocytes is through angiotensin-converting enzyme II receptors. Many studies (Nowak et al., 2020; Rubin et al., 2020) have reported overexpression of angiotensin-converting enzyme II receptors in the inflamed mucosa of the gastrointestinal tract. This may explain the increased risk of SARS-CoV-2 infection among active IBD patients. This increased risk of SARS-CoV-2 infection among active IBD patients infers that patients with IBD activity should be given priority during COVID-19 vaccination.

Notably, our SARS-CoV-2-infected patients recovered completely without hospitalization or intensive care admission. This data supports the previous report (Axelrad et al., 2021), indicating that IBD had no impact on the outcome of SARS-CoV-2 infection.

The limitation of our study may relate to the small sample size, which did not allow statistical analysis to predict the factors associated with IBD reactivation.

4.3. Conclusion

Patients with IBD had no increased incidence of relapse during the COVID-19 pandemic. Withdrawal of maintenance medications increased the risk of IBD relapse among patients with disease remission. Active IBD patients are at increased risk of SARS-CoV-2 infection and worsening of IBD symptoms.

Conflicts of interest

There are no conflicts of interest.

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