









Anal fissures in COVID-19 survivors: Incidence, risk factors, and outcomes

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ABSTRACT

Objective: In spite of COVID-19's typical presentation in the form of fever, cough, myalgia, and pneumonia, other gastrointestinal manifestations have been reported. Among the COVID-19 survivors, anal fissure has been documented. The aim of this study was to report the incidence of anal fissure among those patients, its possible risk factors and outcome.

Material and Methods: This is a retrospective cross-sectional study which was conducted on COVID-19 patients' who were diagnosed with anal fissure. Those who survived and were discharged home safely were contacted to pick up whether they suffered from any symptoms suggesting anal fissure, to identify the risk factors of anal fissure and their outcomes.

Results: A total of 176 COVID-19 patients were enrolled in this study. The incidence of anal fissure among all patients was 36.9%. Patients were categorized into two groups; fissure and non-fissure groups. No significant difference was noted in the demographic data apart from age, which was younger in the fissure group. The majority of anal fissures resolved spontaneously after patients recovered from the COVID-19 symptoms with no specific treatment (43.1%).

Conclusion: Anal fissure is quite a common problem in COVID-19 patients. Young and middle-aged patients are more vulnerable to develop anal fissure after COVID-19 infection.

Keywords: COVID-19, gastrointestinal symptoms, anal fissure, risk factors

INTRODUCTION

Anal fissure is one of the most common anorectal problems, which is a longitudinal tear or defect in the anal canal mucosa distal to the dentate line. It occurs more commonly in young adults with equal distribution in both sexes (1,2). It affects 15% of women after childbirth (3).

Anal fissure may be asymptomatic or may cause severe pain depending on the degree of anal sphincter spasm. Further, it may be associated with low volume rectal bleeding. Secondary constipation usually happens due to fear of pain during defecation. The fissure is usually located posteriorly in 85% of cases and anteriorly in 15% of cases (4).

After declaration of COVID-19 as a pandemic, nearly all countries were affected. Typical presentations included fever, cough, myalgia, fatigue and pneumonia (5,6). Gastrointestinal tract (GIT) symptoms such as diarrhea, nausea and vomiting were also reported (7-9). Interestingly, GIT symptoms were associated with severe form of COVID-19 infection with a higher rate of intensive care unit (ICU) admission when compared to those with respiratory symptoms only (10). Moreover, the COVID-19 virus was isolated from the stool sample of the infected people even after clearance of chest symptoms (11). As surgeons took part in the battle against COVID-19, we noticed many patients who developed anal fissures during or after recovery from COVID-19. The aim of this study was to report the incidence of anal fissure among COVID-19 patients, its possible risk factors, and outcome.

MATERIAL and METHODS

Study Design

This is a retrospective cross-sectional study which was conducted on patients diagnosed with COVID-19 infection who were admitted to a tertiary referral isolation hospital between September 2020 and November 2020.

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The study protocol was approved by the Institutional Review Board (IRB) (IRB No. R.21.07.1383) and was retrospectively registered in the clinical trials registry with registration number (NCT05736926). Consent has been taken from the participating patients in this study before the interview.

Eligibility Criteria

Our hospital is a tertiary referral center that admits COVID-19 patients who experienced any symptoms that suggests this infection and confirmed by polymerase chain reaction (PCR) positive nasal swab or with chest findings suggesting COVID-19 infection through computerized tomography (CT), according to the local protocol of the Egyptian Ministry of Health adapted from the World Health Organization (WHO) recommendation. Patients of both sexes aged between 20-70 years with or without associated co-morbidities who received treatment for COVID-19 infection who, were discharged home safely, and presented with anal fissure during the follow up were included. Patients who did not experience anal pain or anal fissure, and patients who died were excluded from this study.

Patient Interview

Patients were identified by checking the electronic medical records (EMR) during the study period, eligible patients were addressed and then contacted by telephone call to pick up whether they suffered from any symptoms of anal pain, difficulty in defecation suggesting anal fissure, to identify the risk factors for anal fissure development, their outcomes, and how they were managed. Three hundred and fifty patients deemed eligible, and 176 (50.3%) responded while 174 did not. We relied on the patients' history for the diagnosis of anal fissure due to the pandemic and limitations of clinical activities, as outpatient visits were not recommended at that time. Patients with symptoms suggested the diagnosis of anal fissure were further asked about the treatment they received and whether their symptoms improved or not (Figure 1).

Basic demographic data extracted were age, sex, and associated comorbidities. Disease related parameters were collected including respiratory symptoms, fever, loss of smell and/or taste sensation, GIT symptoms, infection severity, and the need for oxygen therapy. Additionally, the investigations that were done either laboratory or radiological were extracted.

Outcomes

The primary outcome was the incidence of anal fissure in confirmed COVID-19 patients. Secondary outcomes were risk factors that could be associated with anal fissure in COVID-19 patients, how they were managed, and the prognosis.

Statistical Analysis

Data were analyzed by SPSS (version 23, UK, Bristol). Continuous data was expressed as mean \pm standard deviation (SD) or

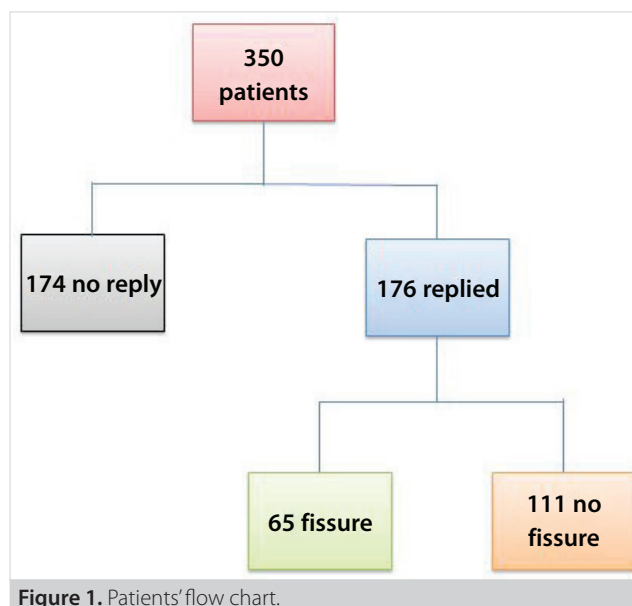


Figure 1. Patients' flow chart.

median and range based on normality. Categorical variables were expressed as number and percent. Student's t-test was used to process continuous data, whereas Fisher's exact test or Chi-square test were used for categorical variables. Risk factor analysis for anal fissure among COVID-19 survivors was assessed using binary logistic regression test. P values less than 0.05 were considered significant.

RESULTS

A total of 176 patients were enrolled in this study, among them 102 were males (58%) while 74 were females (42%). Median (IQR) age of patients was 53 (42-61).

As regard associated co-morbidities; 34.1% had hypertension, 29.6% had type II diabetes, 13.2% had chronic kidney disease, 11.9% had cardiac disease, and 6.8% had chronic liver disease. Regarding COVID-19 manifestations, the commonest symptoms were cough, fever and muscle fatigue, respectively. Median (IQR) oxygen (O_2) saturation was 90 (87-95). Based on route of O_2 supply, 39.2% received O_2 via mask with reservoir, 28.4% via O_2 mask, 6.3% via nasal cannula, while three patients (1.7%) via continuous positive air way pressure device (CPAP). Serum C reactive protein (CRP) was elevated with a median (IQR) of 30.8 (12-48). Median (IQR) hospital stay was 7 (2-12) days. The incidence of anal fissure was 36.9% among all admitted patients (Table 1).

In order to report possible risk factors, patients were further categorized into two groups; the first group included patients who developed anal fissure ($n= 65$) and the second group included patients who did not develop anal fissure ($n= 111$). The fissure group was significantly younger than the non-fissure group, with a median (IQR) age of [49 (41-59) versus 57 (44-65); $p= 0.004$]. No significant difference was noted between

Table 1 . Demographic data of all patients

Variables	Patients (n= 176)
Age (years) (Median + IQR)	53 (42-61)
Sex, n (%)	
Male	102 (57.9)
Female	74 (42.1)
Co-morbidities, n (%)	
Hypertension	60 (34.1)
Type II diabetes	52 (29.6)
Cardiac	21 (11.9)
Chronic liver disease	12 (6.8)
Chronic kidney disease	10 (13.2)
Neurological disease	9 (5.1)
Immunosuppressed	8 (4.6)
Taste loss, n (%)	20 (11.4)
Smell loss, n (%)	21 (11.9)
Muscle fatigue, n (%)	133 (75.6)
Cough, n (%)	156 (88.6)
Fever, n (%)	141 (80.1)
Diarrhea, n (%)	42 (23.9)
O ₂ saturation (Median + IQR)	90 (87-95)
O ₂ mask, n (%)	50 (28.4)
Nasal cannula, n (%)	11 (6.3)
Mask with reservoir, n (%)	69 (39.2)
CPAP, n (%)	3 (1.7)
Corticosteroids treatment, n (%)	130 (73.9)
Hospital stay (days) (Median + IQR)	7 (2-12)
Serum CRP (Median + IQR)	30.8 (12-48)
WBC count (Median + IQR)	9 (6.5-11.4)
Lymphocyte count (Median + IQR)	1.3 (1-1.8)
Anal fissure, n (%)	65 (36.9)
IQR: Interquartile range, CPAP: Continuous positive air way pressure, CRP: C-reactive protein, WBC: White blood cells.	

both groups regarding sex. As regard associated comorbidities, no difference was detected apart from hypertension which was more prevalent in the non-fissure group (39.6% versus 24.6%; $p=0.042$).

Neither group showed any significant difference in COVID-19 related parameters. Surprisingly, all patients did not experience constipation symptom even in the fissure group. Furthermore, median O₂ saturation in both groups did not reveal any significant difference (89% versus 90%) respectively. The number of patients who required O₂ mask was higher in the fissure group than in the non-fissure group; however, this was not significant (36.9% versus 23.4%; $p=0.055$). There was no significant difference regarding the need of O₂ supply through nasal cannula, mask with reservoir or CPAP. Median (IQR) hospital stay for the fissure group was 6 (2-11) days, whereas in the non-fissure group was 8 (2-12) days. No significant difference was observed in serum CRP, white blood cell count or the differential lymphocytic count (Table 2).

Outcome of the Anal Fissure Group

Most of the patients' anal symptoms resolved spontaneously after they recovered from the COVID symptoms without receiving any treatment (43.1%). Four patients (6.2%) improved with medication and topical anal creams. Only one patient required surgery for chronic anal fissure. Five patients (7.7%) still have a tolerated anal pain; however, they refused further treatment. Five patients (7.7%) had anal fissure before COVID-19 infection and their symptoms became worsened after infection. Last, 22 patients (33.9%) did not respond to further questions on treatment outcome (Table 3).

DISCUSSION

In this retrospective cross-sectional study, the incidence of anal fissure was 36.9% among all admitted patients. The main presenting symptoms of COVID-19 disease were the usual respiratory symptoms in the form of dry cough with or without dyspnea (88.6%), fever (80.1%), and fatigue (75.6%) as most studies reported (6-9). Regarding GIT manifestation, the main presenting symptoms in our study were diarrhea (23.9%), anosmia (11.9%), and taste loss (11.4%). Some previous studies have found similar results to our study, that diarrhea was the commonest GIT presentation (3.8%-34%), followed by nausea or vomiting (3.9%-10.1%) and lastly abdominal pain (1.1%-2.2%) (12-14). In contrast to that, a study by Ungaro et al. have shown that anorexia was the commonest GIT manifestation (39.9%-50.2%) (15). In their study, Fang and his colleagues have attributed nearly half of their patients' symptoms of diarrhea to antiviral treatment (16). Additionally, Pan et al. have reported that GIT manifestations become worse with progression of the disease (17). Other rare GIT symptoms which have been reported were the GI bleeding and acute hemorrhagic colitis (18,19).

Mechanism of GIT Manifestation

Various reports have shown that COVID-19 virus uses the angiotensin converting enzyme II (ACE2) receptor as an entry to establish the infection. Moreover, ACE2 receptors are expressed by various tissues, including epithelial cells lining the GIT (20-24). Isolation of the RNA of the COVID-19 virus from the epithelial cells lining the GIT including the esophagus, stomach, duodenum and rectum has been reported. Moreover, presence of the virus itself in the intestinal cells can cause ileal and colonic dysfunction and hence the GIT manifestations (25,26). Another mechanism is that a host cell protein trans-membrane serine protease 2 which is present in the ileum and colon- helps in directing the virus to the host cells and so causing dysfunction (27,28). Thus, COVID-19 virus may cause digestive symptoms either by direct invasion into the target cells and/or immune-mediated tissue, or through inducing an end-organ injury (19,25). However, another theory suggested that the infection-induced respiratory complications, which lead to tissue hypoxia

Table 2. Demographic data of both groups

	Non fissure (n= 111)	Fissure (n= 65)	p
Age (Years) (Median + IQR)	57 (44-65)	49 (41-59)	0.004
Sex ratio n (%)			0.917
Male	64 (57.7)	38 (58.5)	
Female	47 (42.3)	27 (41.5)	
Co-morbidities, n (%)			0.042
Hypertension	44 (39.6)	16 (24.6)	
Type II diabetes	35 (31.5)	17 (26.2)	0.450
Cardiac	10 (9)	11 (16.9)	0.118
Chronic liver disease	9 (8.1)	3 (4.6)	0.375
Chronic kidney disease	5 (4.5)	5 (7.7)	0.378
Neurological	3 (2.7)	6 (9.2)	0.058
Immunosuppressed	4 (3.7)	4 (6.4)	0.429
Taste loss, n (%)	12 (10.8)	8 (12.3)	0.736
Smell loss, n (%)	13 (11.7)	8 (12.3)	0.906
Muscle fatigue, n (%)	87 (78.4)	46 (70.8)	0.257
Cough, n (%)	98 (88.3)	58 (89.2)	0.849
Fever, n (%)	91 (82)	50 (76.9)	0.417
Diarrhea, n (%)	28 (25.2)	14 (21.5)	0.580
O ₂ saturation (Median + IQR)	90 (87-94)	89 (87-95)	0.973
O ₂ mask, n (%)	26 (23.4)	24 (36.9)	0.055
Nasal cannula, n (%)	8 (7.2)	3 (4.6)	0.493
Mask with reservoir, n (%)	49 (44.1)	20 (30.8)	0.079
CPAP, n (%)	2 (1.8)	2 (3.1)	0.584
Corticosteroids treatment, n (%)	86 (77.5)	44 (67.7)	0.154
Hospital stay (days) (Median + IQR)	8 (2-12)	6 (2-11)	0.324
Serum CRP (Median + IQR)	34.4 (12-56.1)	24.4 (12-48)	0.498
WBC count (Median + IQR)	9.15 (6.4-11.2)	8.6 (6.5-11.6)	0.981
Lymphocyte count (Median + IQR)	1.27 (0.95-1.6)	1.4 (1.1-2)	0.071

IQR: Interquartile range, CPAP: Continuous positive air way pressure, CRP: C-reactive protein, WBC: White blood cells.

Table 3. Outcomes of anal fissure patients

Outcomes	Results
Still having anal pain	5 (7.7)
Resolved spontaneously	28 (43.1)
Improved with medications	4 (6.2)
Improved with surgery	1 (1.5)
No reply	22 (33.9)
History of previous fissure	5 (7.7)

Values are n (%).

causing cell injury and death, is the main cause of digestive symptoms. In favor of this hypothesis is the common use of corticosteroids, antibiotics and non-steroidal anti-inflammatory drugs for the treatment of tissue hypoxia in critically ill patients. Nevertheless, patients may develop drug induced diarrhea and other GIT manifestations after hospitalization (29). Histologically, the epithelium of the GIT showed lymphocytic and plasma cells infiltration with interstitial edema which was seen in the

stomach, duodenum and rectum, while the esophagus showed patchy lymphocytic infiltration (29). Thus, presence of the virus in the rectum, or shedding of the viral RNA in stool of the infected people, its local inflammatory effect through tissue injury or ischemia can lead rectal or anal problems like anal fissure.

Median age of the people who suffered from anal fissure in our study was 49 years denoting that the middle age group is the commonest age of anal fissure presentation together with the young age people without any sex predominance (30). We also found that the fissure group needed more oxygen than the other group despite nearly equal O₂ saturation in both groups; however, this difference did not reach statistical significance. This may support the ischemic theory for anal fissure development. Another important notice was that the non-fissure group had a higher incidence of hypertension. This could explain that the use of antihypertensive medications in those patients could be protective against fissure.

We relied on the diagnosis of anal fissure among the studied group of patients on history via telephone calls because none of them visited our outpatient clinic to get examined to confirm the diagnosis due to limitation of clinical services during the pandemic. However, their main symptoms were severe anal pain and difficulty during defecation. Usually, anal fissure is diagnosed by inspection. It is considered acute if it has been present for less than six weeks, superficial, and having fresh clear mucosal edges, with little granulation tissue at its base. Whereas fissure is termed chronic if it has been present more than six weeks, having keratinized edges, skin tag, and if the fibers of the internal anal sphincter are visible (31,32).

Different treatment options are present for anal fissure. About 87% of acute anal fissures resolve with conservative treatment, while in chronic anal fissure, response to conservative management is reported in 50% of cases (33,34). Conservative management includes dietary habits modification, frequent sitz bath and local topical creams which cause relaxation of the internal sphincter, such as creams containing glyceryl trinitrate or calcium channel blockers together with local anesthetic (33,35). Several studies have reported the topical minoxidil cream in the treatment of anal fissure, which is a vasodilator agent, increases the blood supply to the fissure area hence promoting wound healing. It also causes smooth muscle hyperpolarization through activation of potassium channels and reduction of calcium influx through the calcium channels (36,37).

In the present study, 6.2% of our patients improved on conservative treatment, while 7.6% still have anal pain and are advised to seek medical advice at least to have some local medications. Nevertheless, 43.1% of our patients improved spontaneously without any treatment immediately after they recovered from COVID infection. Botulinum toxin injection in the internal anal sphincter has an important role as a chemical sphincterotomy and many studies have shown its efficacy in pain reduction with minor side effects (38). The last option which is reserved for chronic anal fissure is surgical treatment which entails lateral internal sphincterotomy, which is the gold standard treatment option for chronic anal fissure in comparison to non-surgical management (30). Only one patient in our study required surgical intervention because his pain became worse, and his fissure turned chronic without any response to medical treatment. He improved after surgery without any complications.

In relation to our study, Nakamura et al. have reported a case presented with restless, deep anal discomfort which worsens with rest, in spite of exclusion of anal fissure. They have reported it as restless anal syndrome which improved by clonazepam (39).

Anal Fissure Among COVID-19 Survivors and General Population

In our study, the incidence was 36.9% among all admitted patients. Middle aged group patients were the risky group. In contrast, anal fissure among general population is quite a common anal problem. About 10% of new patients visiting the colorectal outpatient clinics have anal fissure (40).

Moreover, in a population-based cohort study, the authors found the incidence of anal fissure in the United States, about 342,000 anal fissure cases each year with an average lifetime risk of 7.8% (41). In addition, anal fissure in the general population is more commonly seen in middle and young aged patients with equal sex distribution, which is similar to our results.

Study Limitations

This study has the following limitations: it is a retrospective one, with small sample size, and small response rate, so that we can't make solid evidence. However, to the best of our knowledge, this is the first study to report anal fissure problem following COVID-19 infection. Further studies with large sample size and more proof are needed to confirm this issue.

CONCLUSION

We observed an association between COVID-19 survivors and anal fissure development during or after recovery from the disease. However, this association has not been proven with conclusive evidence. Young and middle-aged people are more vulnerable. Anal fissure among COVID-19 patients may improve with or without medical treatment and may require surgery in some chronic cases.

Ethics Committee Approval: This study was approved by Mansura University Mansura Faculty of Medicine Medical Research Ethics Committee Institutional Review Board (Decision no: R.21.07.1383, Date: 08.08.2021).

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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ORİJİNAL ÇALIŞMA-ÖZET

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COVID-19'dan sağ kurtulanlarda anal fissürler: Görülme sıklığı, risk faktörleri ve sonuçlar

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ÖZET

Giriş ve Amaç: Ateş, öksürük, miyalji ve pnömoni gibi COVID-19'un tipik belirtileri yanında diğer gastrointestinal belirtiler de rapor edilmiştir. COVID-19'dan iyileşenler arasında anal fissür görülmektedir. Bu çalışmanın amacı bu hastalarda anal fissür görülme sıklığını, olası risk faktörlerini ve sonuçlarını bildirmektir.

Gereç ve Yöntemler: Bu, anal fissür tanısı alan COVID-19 hastaları üzerinde yapılmış, retrospektif kesitsel bir çalışmadır. Hayatta kalan ve güvenli bir şekilde evlerine taburcu edilen kişilerle temasa geçilerek anal fissürü düşündüren herhangi bir semptom olup olmadığı öğrenildi, anal fissürün risk faktörleri ve sonuçları belirlendi.

Bulgular: Bu çalışmaya toplam 176 COVID-19 hastası dahil edildi. Tüm hastalarda anal fissür görülme sıklığı %36,9 idi. Hastalar iki gruba ayrıldı; çatlak ve çatlak olmayan gruplar. Fissür grubunda yaşın daha küçük olması dışında demografik verilerde anlamlı bir farklılık görülmedi. Anal fissürlerin çoğunluğu, hastalar spesifik bir tedavi olmaksızın COVID-19 semptomlarından kurtulduktan sonra (%43,1) kendiliğinden düzeldi.

Sonuç: Anal fissür, COVID-19 hastalarında oldukça sık görülen bir sorundur. Genç ve orta yaşlı hastalar, COVID-19 enfeksiyonundan sonra anal fissür geliştirmeye daha yatkındır.

Anahtar Kelimeler: COVID-19, gastrointestinal semptomlar, anal fissür, risk faktörleri

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