Original Article

Prevalence and Risk Factors of Cytomegalovirus Colitis in Inflammatory Bowel Disease Patients in Riyadh, Saudi Arabia: A Tertiary Center Experience

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Abstract

Background: Patients with inflammatory bowel disease (IBD) are at a higher risk of cytomegalovirus (CMV) colitis because of their immunocompromised status. There are no studies from Saudi Arabia regarding the prevalence of CMV colitis in patients with IBD.

Objective: To determine the prevalence, characteristics, and risk factors of CMV colitis in patients with IBD in Riyadh, Saudi Arabia.

Materials and Methods: This retrospective study included patients with a confirmed diagnosis of IBD (aged 14–75 years) who were followed up at King Fahad Medical City, a referral care center in Riyadh, between January 2016 and December 2021; patients with indeterminate colitis or incomplete medical records were excluded.

Results: A total of 341 patients with IBD were included, of which 236 (72.2%) had Crohn's disease (CD) and 105 (27.8%) had ulcerative colitis (UC). Qualitative CMV PCR was done for 192 patients (60 UC and 132 CD patients), of which 14 patients were positive for CMV colitis (7.3%), and all positive CMV colitis cases were among UC patients (23.3%). However, the hematoxylin and eosin (H and E) stain and immunohistochemistry were negative for all patients. Most patients with CMV colitis were on steroids (71.4%), had at least one flare-up (64.3%), and were on biologic treatment (71.4%). Significant predictors of CMV colitis were hemoglobin (OR: 0.7; 95% CI: 0.51–0.96), albumin (OR: 0.88; 95% CI: 0.78–0.98), and C-reactive protein (OR: 1.03; 95% CI: 1.01–1.06) levels.

Conclusion: This study found that the prevalence of CMV colitis was 7.3% among patients with IBD, and no case was diagnosed in patients with CD. In addition, as all cases diagnosed using qualitative CMV PCR were negative on H and E stain and immunohistochemistry, there is need for large-scale studies to improve the diagnosis of CMV colitis.

Keywords: Crohn's disease, cytomegalovirus colitis, epidemiology, diagnosis, immunocompromised, inflammatory bowel disease, steroids, ulcerative colitis

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INTRODUCTION

Cytomegalovirus (CMV) is a widespread virus that is a member of the family *Herpesviridae*.[1,2] The viremic phase of primary CMV is short, and usually presents asymptomatically in healthy individuals or with mononucleosis-like symptoms such as fever, fatigue, and swollen glands.[2-4] The self-limiting viremic phase of CMV is followed by a lifelong latency phase.[5]

Inflammatory bowel disease (IBD) is a chronic inflammation of the gastrointestinal tract due to an abnormal immune response to the gut microflora.[6] Crohn's disease (CD) and ulcerative colitis (UC) are two types of IBD.[6-8] IBD patients have a compromised immune system due to the severity of the disease and the use of immunosuppressants, and this increases their risk of developing CMV colitis, which is characterized by inflammation of the stomach/intestine due to CMV infection.[5,6] Diagnostic strategies for CMV colitis in patients with IBD are yet nonconforming due to a lack of consensus regarding indications for testing and diagnosis.[9]

It is yet unclear if CMV increases the severity of IBD and induces a UC flare-up.[5,10] Several studies have reported an increase in the prevalence of toxic megacolon and the risks of surgical intervention in patients with IBD who were infected with CMV.[5,11,12] Further, a study from Egypt reported that 34.8% of patients with corticosteroid refractory IBD were positive for CMV.[13,14] However, there is limited literature available on the prevalence and characteristics of CMV infection in IBD patients, especially from Saudi Arabia. Therefore, this study aims to assess the prevalence of CMV colitis in patients with IBD at King Fahad Medical City (KFMC), a referral care center in Riyadh, Saudi Arabia.

MATERIALS AND METHODS

Study design, setting, and participants

This retrospective study included patients with a confirmed diagnosis of IBD (aged 14–75 years) who were followed up at KFMC between January 1, 2016, and December 31, 2021. A confirmed diagnosis of IBD was according to the European Crohn's and Colitis Organization guidelines.[15] Patients diagnosed with indeterminate colitis or incomplete medical records were excluded. KFMC is one of the largest medical complexes in the Middle East with a 1200-bed capacity. The study was conducted after obtaining ethical approval from the Institutional Review Board of KFMC.

The following clinical and demographic data were extracted from patients' electronic medical records by two physicians undergoing gastroenterology and hepatology fellowship: age, gender, smoking habits, duration of illness, levels of hemoglobin (HGB), albumin, and C-reactive protein (CRP), the extent of UC, and the locations of CD. The number of flare-ups was also recorded. Moreover, the endoscopic findings were recorded according to the Mayo Endoscopic Score (range: 0–3).[16]

Diagnosis and procedures

UC was diagnosed based on clinical history, examinations, and findings of a full ileo-colonoscopy. Histology was used to confirm the diagnosis and determine the extent and severity of the disease. Infectious etiologies were excluded using stool cultures and a *Clostridium difficile* toxin assay.[7,8] Additional biopsies from uninflamed regions and every colonic segment, including the rectum, especially in UC, were done as it can be helpful in the diagnostic process and in diagnosing microscopic pathology.[15] CD was diagnosed using a combination of investigative modalities, including, but not limited to, clinical history and physical examination, ileo-colonoscopy, and histology; histological evaluation usually shows focal or patchy inflammation and crypt distortion, with a tendency for granulomatous inflammation to worsen in the proximal colon.[7]

According to the Montreal classification, colitis was categorized as proctitis (E1), left-sided (E2), and extensive (E3) in UC.[14] As for CD, it was categorized as ileal (L1), colonic (L2), ileocolic (L3), and isolated upper (L4).[13] CMV colitis was defined by one of the following: positive tissue CMV polymerase chain reaction (PCR) (qualitative), positive histology (immunohistochemistry [IHC]), and hematoxylin and eosin (H and E) with or without cytopathic changes.[8,13,14,17] These tests were performed only in IBD patients clinically suspected of CMV colitis, mainly when they were steroid dependent, refractory, or on biological therapy with flare-ups.[9]

Statistical analysis

Continuous non-normally distributed variables are presented as a median and interquartile range, and categorical variables are presented as numbers and percentages. Statistical significance was evaluated using the Mann–Whitney *U* test for continuous variables and a Chi-square test or Fisher's exact test for categorical variables. The risk factors were tested using univariate and multiple logistic regression analyses. A *P* value of 0.05 was considered statistically significant. All statistical analyses were conducted using R for Windows, version 3.6.3.

RESULTS

Patients' characteristics

The data of 370 IBD patients were retrieved from the electronic medical records. However, 9 patients' data were incomplete or missing and 20 patients had been diagnosed with indeterminate colitis. Accordingly, the data of 341 patients with a confirmed diagnosis of IBD were included in the final analysis. Of these, 236 (69.2%) were diagnosed with CD.

In patients with UC, the median age was 30 years, and the mean (±SD) disease duration was 77.4 (±56.2) months (range: 12–348 months). In patients with CD, the median age was 36 years, and the mean disease duration was 69.1 (±39.9) months (range: 0–200 months). The prevalence of smoking was 77.8% and 53.4% among the UC and CD groups, respectively [Table 1].

Clinical, endoscopic, and laboratory characteristics

A significant difference in hemoglobin and albumin levels was detected in the CD and UC groups ($P < 0.05$). HBG was higher in the CD group (13 g/dL), while albumin was higher in the UC group (40 g/L). More than half (51.4%) of the UC patients were not on any biological agents compared with 11.8% of the CD patients. Infliximab was the most commonly used biological agent in both groups (62.3% in CD patients and 27.6% in UC patients). More than half of the patients in both groups were on azathioprine. Most CD patients were not on steroids (74.5%), while 40.0% of UC patients were on steroids [Table 2].

Prevalence of cytomegalovirus colitis

CMV qualitative PCR was done for 192 patients, of which 14 patients were positive for CMV colitis (7.3%), and all positive CMV colitis cases were among UC patients. Of these 14 patients, 8 (57.1%) were female, 2 (14.3%) were smokers, the median age was 36.5 years, and the median disease duration was about 71 months. The CRP median for CMV-positive patients was 8.50 mg/L. Most cases occurred in patients with extended colitis (85.7%), and none were found in ulcerative proctitis. Endoscopic findings showed that one patient (7.1%) had a Mayo score of 0, four (28.6%) had a Mayo score of 1, and nine (64.3%) had a Mayo score of 2–3 [Table 3].

Diagnostic tests

All 14 patients with CMV colitis tested positive for CMV PCR (qualitative) in tissue samples. However, the H and E stain and IHC were negative for all patients. Therefore, PCR of the CMV tissue was the only parameter used for diagnosing CMV colitis in the present study. [Table 3].

Medications and management

Most CMV colitis patients (71.4%) were on steroids. Most (64.3%) had at least one flare-up episode before being diagnosed with CMV colitis. Biologic agents were the drug regimen in 10 of 14 patients (infliximab = 4; vedolizumab = 4; ustekinumab = 2). Azathioprine was part of the drug regimen in 50.0% (7/14) of CMV colitis patients. Methotrexate and 6-mercaptopurine were not prescribed for any patient diagnosed with CMV colitis. None of the CMV-positive patients underwent a colectomy [Table 3].

Risk factors

The univariate logistic regression analysis revealed that HGB, albumin, and CRP were significant predictors of CMV colitis. The odds ratios (ORs) for HGB and albumin laboratory findings were 0.7 (95% CI: 0.51–0.96) and 0.88 (95% CI: 0.78–0.98), respectively, thereby indicating that patients with higher HGB and albumin levels have a lower chance of developing CMV colitis. The OR for CRP was 1.03 (95% CI: 1.01–1.06), indicating that patients with a higher CRP have a higher chance of developing CMV colitis than those with a lower CRP. Adjusting factors using the multiple logistic regression model for HGB and albumin had no significant effect [Table 4].

Table 1: Comparison of demographic characteristics of the patients

Variable	Overall (*N*=341)	CD (*n*=236)	UC (*n*=105)	*P*
Age (years), median (IQR)	31.00 (25.00–40.00)	30.00 (24.00–38.00)	36.00 (26.00–41.00)	0.003*
Gender, *n* (%)				
Female	156 (47.7)	96 (40.9)	60 (65.2)	<0.001*
Male	171 (52.3)	139 (59.1)	32 (34.8)	
Smoking, *n* (%)				
No	49 (40.2)	41 (46.6)	8 (23.5)	0.034*
Yes	73 (59.8)	47 (53.4)	26 (76.5)	
Disease duration (months)				
Median (IQR)	60.00 (40.00–100.00)	60.00 (44.00–100.00)	60.00 (36.00–100.00)	0.784
Mean±SD	71.65±45.61	69.08±39.87	77.41±56.21	
Minimum–maximum	0–348	0–200	12–348	

*Significant at $P<0.05$. IQR – Interquartile range; SD – Standard deviation; CD – Crohn's disease; UC – Ulcerative colitis

Table 2: Comparison of clinical, endoscopic, and laboratory characteristics of the patients

Variable	Overall (*N*=341)	CD (*n*=236)	UC (*n*=105)	*P*
Hemoglobin, median (IQR) (g/dL)	13.00 (12.00–14.00)	13.00 (12.00–14.00)	12.00 (11.00–14.00)	0.001*
Albumin, median (IQR) (g/L)	39.00 (37.00–41.00)	39.00 (36.00–41.00)	40.00 (38.00–41.00)	0.012*
C-reactive protein, median (IQR) (mg/L)	4.00 (1.00–10.00)	4.00 (1.48–10.00)	3.00 (1.00–10.00)	0.067
Fecal calprotectin, median (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.159
Location of UC, *n* (%)				
E1: Ulcerative proctitis	33 (31.4)	0	33 (31.4)	NaN
E2: Left side colitis (distal to splenic flexure)	16 (15.2)	0	16 (15.2)	
E3: Extensive (proximal to splenic flexure)	56 (53.3)	0	56 (53.3)	
Location of CD, *n* (%)				
L1: Ileal	108 (45.8)	108 (45.8)	0	NaN
L2: Colonic	17 (7.2)	17 (7.2)	0	
L3: Ileocolonic	110 (46.6)	110 (46.6)	0	
L4: Isolated upper	1 (0.4)	1 (0.4)	0	
B1: Nonstricturing and nonpenetrating, *n* (%)				
No	144 (61.0)	144 (61.0)	0	NaN
Yes	92 (39.0)	92 (39.0)	0	
B2: Stricturing, *n* (%)				
No	159 (67.4)	159 (67.4)	0	NaN
Yes	77 (32.6)	77 (32.6)	0	
B3: Penetrating, *n* (%)				
No	171 (72.5)	171 (72.5)	0	NaN
Yes	65 (27.5)	65 (27.5)	0	
Perianal disease, *n* (%)				
No	175 (74.2)	175 (74.2)	0	NaN
Yes	61 (25.8)	61 (25.8)	0	
Use of biologics, *n* (%)				
Adalimumab	38 (11.4)	34 (14.9)	4 (3.8)	<0.001
Infliximab	166 (50.8)	141 (60.0)	25 (27.2)	
Not prescribed any biologics	81 (24.3)	27 (11.8)	54 (51.4)	
Ustekinumab	18 (5.5)	13 (5.5)	5 (5.4)	
Vedolizumab	19 (5.8)	12 (5.1)	7 (7.6)	
Infliximab, *n* (%)				
No	161 (49.2)	94 (40.0)	67 (72.8)	<0.001*
Yes	166 (50.8)	141 (60.0)	25 (27.2)	
Adalimumab, *n* (%)				
No	289 (88.4)	201 (85.5)	88 (95.7)	0.018*
Yes	38 (11.6)	34 (14.5)	4 (4.3)	
Vedolizumab, *n* (%)				
No	308 (94.2)	223 (94.9)	85 (92.4)	0.544
Yes	19 (5.8)	12 (5.1)	7 (7.6)	
Ustekinumab, *n* (%)				
No	309 (94.5)	222 (94.5)	87 (94.6)	1
Yes	18 (5.5)	13 (5.5)	5 (5.4)	
Small molecules, *n* (%)				
No	325 (99.4)	235 (100.0)	90 (97.8)	0.139
Tofacitinib	2 (0.6)	0	2 (2.2)	
Immunomodulators, *n* (%)				
6-mercaptopurine	1 (0.3)	0	1 (1.0)	0.006*
Azathioprine	196 (57.5)	134 (56.8)	62 (59.0)	
Methotrexate	21 (6.2)	21 (8.9)	0	
Not prescribed any immunomodulators	123 (36.1)	81 (34.3)	42 (40.0)	
Steroids, *n* (%)				
No	254 (74.5)	191 (80.9)	63 (60.0)	<0.001*
Yes	87 (25.5)	45 (19.1)	42 (40.0)	
Disease flares, *n* (%)				
None	132 (38.8)	90 (38.3)	42 (40.0)	<0.001*
One	124 (36.5)	72 (30.6)	52 (49.5)	
Two	70 (20.6)	63 (26.8)	7 (6.7)	
Three	13 (3.8)	10 (4.3)	3 (2.9)	
Eight	1 (0.3)	0	1 (1.0)	
Endoscopic findings, *n* (%)				
Mayo score: 0	17 (56.7)	12 (100.0)	5 (27.8)	<0.001*
Mayo score 1	4 (13.3)	0	4 (22.2)	
Mayo scores 2 and 3	9 (30.0)	0	9 (50.0)	
Qualitative PCR CMV tissue, *n* (%)				

Contd...

Table 2: Contd...

Variable	Overall (*n*=341)	CD (*n*=236)	UC (*n*=105)	*P*
No	178 (92.7)	132 (100.0)	46 (76.7)	<0.001*
Yes	14 (7.3)	0	14 (23.3)	
HE inclusion bodies, *n* (%)				
No	20 (95.2)	6 (85.7)	14 (100.0)	0.717
Yes	1 (4.8)	1 (14.3)	0	
IHC, *n* (%)				
No	14 (100.0)	0	14 (100.0)	NA
PCR blood, *n* (%)				
No	13 (92.9)	0	13 (92.9)	NaN
Yes	1 (7.1)	0	1 (7.1)	
IgG CMV, *n* (%)				
No	11 (78.6)	0	11 (78.6)	NaN
Yes	3 (21.4)	0	3 (21.4)	
Treatment was provided, *n* (%)				
No	7 (50.0)	0	7 (50.0)	NaN
Yes	7 (50.0)	0	7 (50.0)	

*Significant at $P<0.05$. NaN – Not a number; IQR – Interquartile range; CD – Crohn's disease; UC – Ulcerative colitis; PCR – Polymerase chain reaction; CMV – Cytomegalovirus; IHC – Immunohistochemistry; NA – Not applicable

DISCUSSION

The prevalence of CMV colitis in this study was 7.3% among IBD patients for whom qualitative CMV PCR was performed (14/192) and 23.3% among UC patients (14/60); no CMV colitis cases occurred in CD patients. The prevalence rates and the fact that CMV colitis is more common among patients with UC are in line with current data reported in the literature.[17,18]

The previously reported risk factors for CMV colitis were female gender, older age, an extended disease with active inflammation on histology, and being on azathioprine therapy.[19,20] A systematic review of CMV colitis showed that the prevalence of CMV colitis in UC was 19% versus 11% in CD. UC is more prevalent than CD for CMV colitis (14% versus 2.5%).[21] This aligns with our study that shows a prevalence of CMV colitis of 23.3% among UC patients.

Certain risk factors associated with positive CMV in tissue biopsies included using steroids, the extent of the disease, and the number of clinical flares. Similar findings were reported by Weng *et al.*,[5] where UC patients with CMV colitis presented as severe disease and left colon colitis (Montreal classification E2). As for CD with CMV colitis, colon involvement was most common. Most of our study's CMV colitis cases occurred in patients with extended colitis E3, proximal to the splenic flexure 12/14 (85.7%), followed by E2 left side colitis 2/14 (14.3%), and none were found in ulcerative proctitis.[5]

The current study found that steroids were the most commonly used medication among CMV colitis patients. In fact, steroid use was higher in CMV-positive cases (64%) than CMV-negative cases (22%). This finding is consistent with the findings of a meta-analysis, which showed that the risk of steroid resistance doubled in IBD patients with CMV colitis compared with IBD patients with no CMV infections.[22] Similarly, a retrospective study from Taiwan reported a high rate of steroid use among CMV-positive IBD patients, which is in agreement with our findings.[5]

Azer *et al.* state that half of the CMV-positive patients have punched-out ulcerations, a variability of mucosal defects, and a cobblestone-like appearance, which are diagnostic endoscopic features of CMV colitis.[10] A study suggested that a positive mucosal assay and the lack of extensive ulcerations in patients with UC indicates a latent CMV infection that does not require antiviral treatment.[23] However, our findings showed that 64.3% of cases had ulcerations (Mayo Score 2–3). In addition, the CRP mean for CMV-positive patients was 21.6 mg/L, which is higher than that of non-CMV patients (8.2 mg/L). Together, the ulcerations and the raised CRP level indicate that CMV colitis patients had an active inflammation due to the reactivation of CMV. However, future studies should quantitatively assess the PCR of the CMV tissue rather than qualitatively.

The prevalence of CMV varies significantly among UC patients when diagnosed with H and E and IHC, ranging from 0.5% in severe steroid-resistant colitis to 3% in severe colitis.[17] Further, a systematic review by Sager *et al.* reported that the histological prevalence (using H and E or IHC) ranges between 4.5% and 13.8%.[24] While another systematic review reported that the prevalence of positive H and E or IHC for CMV colitis results was between 2% and 29%.[21] However, in our study findings, all 14 CMV-positive patients tested negative with H and E

Table 3: Clinical, endoscopic, and laboratory characteristics of patients with and without cytomegalovirus (*N*=192)

Variable	No CMV (*n*=178)	CMV (*n*=14)	*P*
Age (years), median (IQR)	31.00 (26.00–40.00)	36.50 (33.25–44.00)	0.059
Gender, *n* (%)			
Female	97 (54.5)	8 (57.1)	1
Male	81 (45.5)	6 (42.9)	
Smoking, *n* (%)			
No	27 (29.3)	1 (33.3)	1
Yes	65 (70.7)	2 (66.7)	
HGB, median (IQR) (g/dL)	13.00 (12.00–13.97)	11.35 (10.00–12.68)	0.014*
Albumin, median (IQR) (g/L)	38.00 (36.00–40.00)	37.00 (32.00–40.75)	0.398
CRP, median (IQR) (mg/L)	5.00 (2.00–10.00)	8.50 (2.42–28.50)	0.15
Fecal calprotectin, median (IQR)	0.00 (0.00–0.00)	0.00 (0.00–15.75)	0.001*
Type of IBD, *n* (%)			
CD	132 (74.2)	0	<0.001*
UC	46 (25.8)	14 (100.0)	
Duration (months), median (IQR)	50.00 (36.00–100.00)	71.00 (45.00–84.25)	0.351
Location UC, *n* (%)			
E1: Ulcerative proctitis	30 (65.2)	0	<0.001*
E2: Left side colitis (distal to splenic flexure)	6 (13.0)	2 (14.3)	
E3: Extensive (proximal to the splenic flexure)	10 (21.7)	12 (85.7)	
Location CD, *n* (%)			
L1: Ileal	86 (65.2)	0	NaN
L2 Colonic	8 (6.1)	0	
L3: Ileocolonic	37 (28.0)	0	
L4: Upper	1 (0.8)	0	
B1: Nonstricturing and nonpenetrating, *n* (%)			
No	69 (52.3)	0	NaN
Yes	63 (47.7)	0	
B2: Stricturing, *n* (%)			
No	111 (84.1)	0	NaN
Yes	21 (15.9)	0	
B3: Penetrating, *n* (%)			
No	103 (78.0)	0	NaN
Yes	29 (22.0)	0	
Perianal disease, *n* (%)			
No	109 (82.6)	0	NaN
Yes	23 (17.4)	0	
Biologics, *n* (%)			
Adalimumab	8 (4.7)	0	0.004*
Infliximab	104 (61.2)	4 (28.6)	
Not prescribed any biologics	42 (24.7)	4 (28.6)	
Ustekinumab	4 (2.4)	2 (14.3)	
Vedolizumab	12 (7.1)	4 (28.6)	
Infliximab, *n* (%)			
No	74 (41.6)	10 (71.4)	0.059
Yes	104 (58.4)	4 (28.6)	
Adalimumab, *n* (%)			
No	170 (95.5)	14 (100.0)	0.908
Yes	8 (4.5)	0	
Vedolizumab, *n* (%)			
No	166 (93.3)	10 (71.4)	0.019*
Yes	12 (6.7)	4 (28.6)	
Ustekinumab, *n* (%)			
No	174 (97.8)	12 (85.7)	0.003*
Yes	4 (2.2)	2 (14.3)	
Small molecules, *n* (%)			
No	178 (100.0)	12 (85.7)	<0.001*
Tofacitinib	0	2 (14.3)	
Immunomodulators, *n* (%)			
Azathioprine	124 (69.7)	7 (50.0)	0.032*
Methotrexate	17 (9.6)	0	
Not prescribed any immunomodulators	37 (20.8)	7 (50.0)	
Steroids, *n* (%)			
No	110 (61.8)	4 (28.6)	0.031*
Yes	68 (38.2)	10 (71.4)	
Disease flares, *n* (%)			

Contd...

Table 3: Contd...

Variable	No CMV (*n*=178)	CMV (*n*=14)	*P*
None	29 (16.3)	1 (7.1)	0.001*
One	75 (42.1)	9 (64.3)	
Two	63 (35.4)	1 (7.1)	
Three	11 (6.2)	2 (14.3)	
Eight	0	1 (7.1)	
Endoscopic findings, *n* (%)			
Mayo score 0	16 (100.0)	1 (7.1)	<0.001*
Mayo score 1	0	4 (28.6)	
Mayo score 2–3	0	9 (64.3)	
PCR CMV tissue, *n* (%)			
No	178 (100.0)	0	<0.001*
Yes	0	14 (100.0)	
HE inclusion bodies, *n* (%)			
No	6 (85.7)	14 (100.0)	0.717
Yes	1 (14.3)	0	
IHC, *n* (%)			
No	0	14 (100.0)	NA
PCR blood, *n* (%)			
No	0	13 (92.9)	NaN
Yes	0	1 (7.1)	
IgG CMV, *n* (%)			
No	0	11 (78.6)	NaN
Yes	0	3 (21.4)	
Treatment is given, *n* (%)			
No	0	7 (50.0)	NaN
Yes	0	7 (50.0)	
Colectomy, if done, *n* (%)			
No	1 (100.0)	14 (100.0)	NA

*Significant at $P<0.05$. NaN – Not a number; IQR – Interquartile range; HGB – Hemoglobin; CRP – C-reactive protein; CD – Crohn's disease; UC – Ulcerative colitis; PCR – Polymerase chain reaction; CMV – Cytomegalovirus; IHC – Immunohistochemistry; NA – Not applicable

Table 4: Risk factors of cytomegalovirus colitis in inflammatory bowel disease patients using univariate and multiple logistic regression

Factors	Univariate logistic regression			Multiple logistic regression		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)	1.04	0.99–1.08	0.094			
Gender						
Female	-	-				
Male	0.9	0.29–2.69	0.8			
Smoking						
No	-	-				
Yes	0.83	0.08–18.3	0.9			
Duration (months)	1	0.99–1.02	0.6			
Hemoglobin	0.7	0.51–0.96	0.024*	0.78	0.56–1.10	0.14
Albumin	0.88	0.78–0.98	0.02*	0.93	0.82–1.06	0.3
C-reactive protein	1.03	1.01–1.06	0.007*	1.03	1.00–1.06	0.018*
Fecal calprotectin	1.01	1.00–1.03	0.3			
Type of IBD						
CD	-	-				
UC	260,076,000	0.00–NA	>0.9			
Steroids						
No	-	-		-	-	
Yes	4.04	1.30–15.2	0.022*	4.21	1.19–18.8	0.035*
IgG CMV						
No	-	-				
Yes	1	0.00, infinity	>0.9			

*Significant at $P<0.05$. OR – Odds ratio; CD – Crohn's disease; UC – Ulcerative colitis; CMV – Cytomegalovirus; IBD – Inflammatory bowel disease; CI – Confidence interval; NA – Not available; IgG – Immunoglobulin G

and IHC. This finding might be due to conventional H and E stains having low sensitivity (ranging from 10% to 87%), the detection of inclusion bodies being difficult, or false-negative biopsies being common.[25,26] Compared with H and E and IHC staining, tissue PCR has the highest detection rates.[27,28] The high sensitivity of the qualitative tissue PCR is reflected in the findings of this study, where all 14 CMV-positive patients tested positive for it. This

result substantiates the findings of Bontà *et al*., who showed that tissue PCR was positive for all seven patients with CMV colitis.[17] Selection bias and the heterogeneity of the diagnostic methods used may explain the variation in the results of each study, as the gold standard for detecting CMV colitis has yet to be established.[22]

CMV colitis is extremely rare in healthy individuals, suggesting that it needs a certain degree of immunosuppression to be reactivated.[29] In our study, 71% of the patients with CMV colitis were on biological immunosuppressive agents. Therefore, in IBD, both therapy and disease aid in the reactivation of CMV.

Limitations

This is a retrospective study and has the inherent limitations of this study design. Further, the study design may have led to missing clinical details. In addition, the data were gathered from a relatively small sample size and only from one tertiary care center in Riyadh, and thus may have limited generalizability. Another limitation was that CMV was only tested in symptomatic patients. Lastly, future studies should be conducted with a quantitative analysis of CMV PCR.

CONCLUSION

This study revealed a prevalence of 7.3% for CMV colitis among patients with IBD. Further, all cases of CMV colitis were in patients with UC. In addition, as all cases diagnosed using qualitative CMV PCR were negative on H and E stain and IHC, there is need for large-scale studies to improve the diagnosis of CMV colitis.

Ethical considerations

The study was approved by the Institutional Review Board (Ref. No: 21-477; date: November 15, 2021) of KFMC, Riyadh, Saudi Arabia. The requirement for patient consent was waived owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: Y.A.O, A.A.L, AA, NAO, A.A.G; Methodology: S.A.R, A.A.Q, A.A.E, A.A.A, B.A.I; Data analysis: M.A.A, H.A, S.A, F.A.M; Writing–original draft preparation: Y.A.O, A.A.L, Y.A.T, A.A.G, S.A.R; Writing – review and editing: Y.A.O, A.A.L, Y.A.T, A.A.G, S.A.R.

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Conflicts of interest

There are no conflicts of interest.

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