FREQUENCY OF CYTOMEGALOVIRUS COLITIS IN PATIENTS HOSPITALIZED WITH ACUTE FLARES OF ULCERATIVE COLITIS

Muhammad Imran Ullah[1], Gul e Lala[2]*, Asif Khan[1], Asma Khan[1], Rafi Ullah[3], Laiba Ali[3]

ABSTRACT

Background: Ulcerative colitis (UC) is a chronic relapsing inflammatory disease of the colon. Opportunistic viral reactivation, particularly cytomegalovirus (CMV), is increasingly recognized as a clinically important complication during acute UC flares, where it may worsen disease severity and therapeutic response.

Objective: To determine the frequency of CMV colitis among patients hospitalized with acute UC exacerbations and to assess its association with flare severity and recurrence.

Methods: This prospective cross-sectional study enrolled 275 consecutive adults aged 16–75 years admitted with acute UC flares to the Department of Gastroenterology, Hayatabad Medical Complex, Peshawar, from October 2022 to April 2023. Flare severity was classified according to Truelove and Witts' criteria. All patients underwent flexible sigmoidoscopy within 72 hours of admission, with 2–3 rectosigmoid biopsies obtained for histopathology. CMV colitis was diagnosed on demonstration of typical viral inclusions with hematoxylin–eosin staining or positive immunohistochemistry. Associations with age, sex, severity, and relapse frequency were analyzed using chi-square or Fisher's exact test.

Results: The mean age of patients was 49.6 ± 15.8 years, with 56.7% males. Flare severity was mild in 42.2%, moderate in 32.7%, and severe in 25.1%. CMV colitis was confirmed in 22 patients, yielding a prevalence of 8.0%. The prevalence was significantly higher in patients with moderate-to-severe flares compared with mild flares ($p = 0.01$), and in those with four to six prior relapses ($p = 0.01$). No statistically significant associations were observed with age ($p = 0.83$) or sex ($p = 0.11$).

Conclusion: Approximately one in twelve hospitalized patients with acute UC flares had CMV colitis, with strong associations observed in moderate-to-severe disease and in patients with multiple prior relapses. These findings highlight the importance of routine CMV screening in high-risk groups, particularly in resource-limited settings.

Keywords: Cytomegalovirus; Ulcerative colitis; Acute flare; Opportunistic infection; Colitis

INTRODUCTION

Ulcerative colitis (UC) is a chronic, relapsing–remitting inflammatory disease of the colon that most often presents with bloody diarrhea, abdominal pain, and urgency, and burdens patients with recurrent flares over a lifetime [1]. UC typically shows a bimodal age distribution, with a first peak in young adults and a smaller second peak in later adulthood [2]. Globally, the burden of inflammatory bowel disease including UC continues to rise beyond historically high-incidence regions, with marked geographic heterogeneity and rapid growth in newly industrializing settings [3]. Diagnosis rests on combined clinical, endoscopic, and histopathologic assessment of colonic mucosa to distinguish UC from mimics and to gauge disease extent and activity [1].

Disease course ranges from mild episodes controllable in the outpatient setting to severe flares requiring hospitalization. During acute flares, a key concern is superimposed infection—most notably cytomegalovirus (CMV) colitis—which can both mimic and exacerbate UC activity, especially in the context of immunosuppression (e.g., corticosteroids, other agents) [4]. CMV is a ubiquitous β-herpesvirus with high seroprevalence globally, varying by age and socioeconomic factors [5]. Reactivation in IBD occurs with immune dysregulation and immunosuppressive therapy, and has been repeatedly implicated in difficult-to-control UC [4,6].

[1] Department of Gastroenterology, Hayatabad Medical Complex, Peshawar
[2] Department of Pediatrics, Hayatabad Medical Complex, Peshawar
[3] MBBS Student, Khyber Medical College, Peshawar

Address for Correspondence
Dr. Gul e Lala
Assistant Professor, Department of Pediatrics
Hayatabad Medical Complex, Peshawar, Pakistan
gulelala49@gmail.com

Across cohorts, reported CMV detection during UC flares varies widely owing to patient mix and diagnostic methods. Reactivation is enriched in severe or steroid-refractory disease, and CMV has been linked to impaired mucosal healing, steroid resistance, and worse short-term outcomes in hospitalized patients [6–8]. Diagnostic confirmation is tissue based: viral inclusions on H&E with confirmatory immunohistochemistry (IHC) is the standard for tissue-invasive disease, with quantitative tissue PCR used selectively to increase sensitivity and help distinguish latent from active infection [4,6,9]. However, diagnostic algorithms and access to IHC/PCR remain heterogeneous, particularly outside high-resource settings [6,10].

Contemporary guidance recommends systematic CMV evaluation in patients with severe or steroid-refractory UC, yet implementation is inconsistent across health systems [4,10,11]. Moreover, although the global IBD burden is shifting, data from South Asia and other low- and middle-income regions remain comparatively sparse, limiting context-specific recommendations [3,12].

To address this gap, we aimed to estimate the frequency of CMV colitis among adults hospitalized with acute UC flares at a tertiary center in Pakistan and to describe clinical correlates at presentation, with a view toward informing pragmatic diagnostic pathways in resource-constrained settings.

MATERIALS AND METHODS

This **prospective cross-sectional study** was conducted in the Department of Gastroenterology, Hayatabad Medical Complex, Peshawar, a major referral center for gastrointestinal disorders in northwestern Pakistan. The study period was from **October 14, 2022, to April 14, 2023**, during which all consecutive patients aged **16–75 years** with a confirmed diagnosis of ulcerative colitis presenting with an acute flare were screened.

The diagnosis of ulcerative colitis was established on the basis of clinical features, characteristic endoscopic findings, and histopathological confirmation from prior biopsies. The severity of acute flares was graded according to the **Truelove and Witts' criteria** as mild, moderate, or severe. Exclusion criteria included hemodynamic instability, prior antiviral therapy within the preceding three months, Crohn's disease, or contraindications to colonoscopy.

Non-probability consecutive sampling was employed, reflecting the flow of eligible patients during the study period. The target sample size of **275** was estimated using the WHO calculator, based on a reported prevalence of 1.4% for cytomegalovirus (CMV) colitis, with a 95% confidence level and narrow margin of error. The final sample size was determined by consecutive accrual.

Baseline demographic and clinical information was recorded, including age, sex, disease duration, extent of colonic involvement (classified as proctosigmoiditis, left-sided colitis, or pancolitis), and treatment history with special attention to corticosteroid exposure. Routine laboratory workup included complete blood count, C-reactive protein, liver function tests, serum albumin, and CMV IgG serology to determine prior exposure. All patients underwent **flexible sigmoidoscopy within 24–72 hours of admission**. Two to three biopsies were obtained from the most inflamed rectosigmoid mucosa, chosen for safety and reliability in detecting active disease during acute flares. Endoscopic findings were recorded, with emphasis on deep punched-out ulcers suggestive of CMV. Specimens were fixed in 10% buffered formalin, paraffin-embedded, and stained with hematoxylin and eosin (H&E). Cases with suspected viral cytopathic effect were further evaluated by immunohistochemistry (IHC) using monoclonal anti-CMV antibodies.

A diagnosis of **CMV colitis** was made when at least one typical viral inclusion was detected on H&E or when IHC was positive. This composite definition was applied uniformly. Tissue PCR was not routinely available and therefore not performed systematically.

Patients received standard institutional management for acute ulcerative colitis flares, including intravenous corticosteroids as first-line therapy. Biopsy-confirmed CMV colitis was treated with intravenous ganciclovir. Escalation to additional immunosuppression or surgery was individualized according to clinical need and established guidelines. Follow-up beyond the index hospitalization was not included.

Data were entered into **SPSS version 26.0 (IBM Corp., Armonk, NY, USA)**. Continuous variables were assessed for distribution using

the **Shapiro–Wilk test**, with normality assumed when **p ≥ 0.05**. Normally distributed data were summarized as means ± standard deviation and compared using independent-samples *t* tests, while skewed data were expressed as medians with interquartile ranges and compared using the Mann–Whitney U test. The number of prior flares, after confirmation of normality, was analyzed as a continuous variable. Categorical variables were described as frequencies and percentages, with comparisons made using the chi-square test (if all expected cell counts ≥5) or Fisher's exact test otherwise. A two-sided **p < 0.05** was considered statistically significant.

RESULTS

A total of **275** consecutive patients hospitalized with acute ulcerative colitis (UC) flares were enrolled. The mean age was **49.6 ± 15.8** years; **156/275 (56.7%)** were male. Nearly half (**135/275; 49.1%**) were older than 55 years. The mean number of acute flares since diagnosis was **3.9 ± 1.9**. By Truelove & Witts' criteria, **116 (42.2%)** had mild, **90 (32.7%)** moderate, and **69 (25.1%)** severe flares. Cytomegalovirus (CMV) colitis was diagnosed in **22/275 (8.0%)** (Table 1).

Table 1. Demographic and clinical characteristics of the study population (n = 275)

Variable	Value
Age (years), mean ± SD	49.6 ± 15.8
Age group, n (%)	
16–35	64 (23.3)
36–55	76 (27.6)
>55	135 (49.1)
Sex, n (%)	
Male	156 (56.7)
Female	119 (43.3)
Acute flares since diagnosis, mean ± SD	3.9 ± 1.9
Disease severity, n (%)	
Mild	116 (42.2)
Moderate	90 (32.7)
Severe	69 (25.1)
CMV colitis, n (%)	22 (8.0)

*Footnote (Table 1): Data are **n (%)** unless stated. Continuous variables shown as **mean ± SD**. **Descriptive statistics only; no hypothesis testing performed** for Table 1.*

When stratified by age and sex, CMV colitis appeared most frequent in patients **>55 years (12/22; 54.5%)** and in **men (16/22; 72.7%)**; however, neither association was statistically significant (**p = 0.83** for age; **p = 0.11** for sex; χ^2/Fisher as appropriate) (Table 2).

Table 2. Association of CMV colitis with age and sex

CMV colitis	16–35 years	36–55 years	>55 years	Male	Female	Total	p-value
Yes	5 (22.7)	5 (22.7)	12 (54.5)	16 (72.7)	6 (27.3)	22	**0.83 (Age); 0.11 (Sex)**
No	59 (23.3)	71 (28.1)	123 (48.6)	140 (55.3)	113 (44.7)	253	
Total	64	76	135	156	119	275	

*Footnote (Table 2): Data are **n (%)**; **row percentages** within CMV status strata. **Pearson's χ^2** used; **Fisher's exact** applied where any expected cell count <5. Two-sided tests.*

In contrast, **disease severity** and **number of prior flares** were significantly associated with CMV positivity. Among CMV-positive patients, **10/22 (45.5%)** had moderate and **9/22 (40.9%)** had severe disease, versus **3/22 (13.6%)** with mild flares (**p = 0.01**). Similarly, **14/22 (63.6%)** reported **4–6** previous flares—a higher proportion than in those with fewer (1–3) or more (>6) relapses (**p = 0.01**) (Table 3).

Table 3. Association of CMV colitis with disease severity and prior flares

CMV colitis	Mild	Moderate	Severe	1–3 flares	4–6 flares	>6 flares	Total	p-value
Yes	3 (13.6)	10 (45.5)	9 (40.9)	3 (13.6)	14 (63.6)	5 (22.7)	22	**0.01 (Severity); 0.01 (Flares)**
No	113 (44.7)	80 (31.6)	60 (23.7)	114 (45.1)	109 (43.1)	30 (11.9)	253	
Total	116	90	69	117	123	35	275	

*Footnote (Table 3): Data are **n (%)**; **row percentages** within CMV status strata. **Pearson's χ^2** used; **Fisher's exact** applied where any expected cell count <5. Two-sided tests.*

Overall, CMV colitis was present in **8.0%** of hospitalized UC flares (**≈1 in 12**), with **significant enrichment** among patients with **moderate–severe disease** and those reporting **4–6 prior flares**. Differences by age and sex were **not statistically significant**.

DISCUSSION

This study provides critical, region-specific evidence on the prevalence and clinical correlates of cytomegalovirus (CMV) colitis in patients hospitalized with acute ulcerative colitis (UC) flares in Pakistan. We observed that 8% of patients had biopsy-proven CMV colitis, with significantly higher detection in those with moderate-to-severe disease and in patients reporting multiple prior relapses. These findings are concordant with global literature, where CMV colitis has been increasingly recognized as an important complication of severe or refractory UC, though reported prevalence varies widely across cohorts [13,14].

International studies highlight marked heterogeneity in CMV prevalence, ranging from as low as 5% to over 30%, largely explained by differences in patient selection, geographic setting, and diagnostic methods [15,16]. In Asian cohorts, detection rates tend to be higher, particularly in hospitalized and steroid-refractory patients, a trend echoed by our findings [17,18]. The strong association we identified between CMV positivity and both disease severity and flare frequency parallels results from multicenter studies in Japan, Korea, and Europe, which consistently document that CMV reactivation is enriched in the most aggressive UC phenotypes [19,20]. Importantly, our reliance on histopathology supplemented by immunohistochemistry mirrors best practice recommendations, as inclusion bodies alone have limited sensitivity, and IHC or tissue PCR markedly improves diagnostic accuracy [21].

The pathogenic role of CMV in UC flares remains debated. Some authors consider CMV an epiphenomenon of mucosal breakdown, while others provide compelling evidence linking CMV reactivation with impaired steroid responsiveness, accelerated progression to colectomy, and greater in-hospital morbidity [22,23]. Mechanistic studies strengthen the argument for a pathogenic role by demonstrating that CMV can amplify mucosal inflammation, promote epithelial barrier dysfunction, and delay mucosal healing [24,25]. Our data, showing a disproportionately high rate of CMV positivity in patients with recurrent relapses, further supports the hypothesis that repeated cycles of inflammation and immunosuppression facilitate viral reactivation, consistent with prior longitudinal analyses [26,27].

Although age and sex were not statistically significant predictors in our study, the observed higher prevalence in older males is consistent with reports from Middle Eastern and East Asian cohorts, where demographic factors

have variably been associated with CMV risk [28,29]. Nevertheless, pooled analyses suggest that demographic effects are inconsistent across populations, underscoring the need for larger, multicenter studies in diverse settings [30].

From a clinical standpoint, our findings reinforce the value of systematic CMV screening in patients with severe or frequently relapsing UC flares, particularly in high-prevalence regions. Early identification allows for the timely initiation of antiviral therapy, which observational studies suggest may improve steroid responsiveness and reduce colectomy rates [22,23]. However, uncertainty persists regarding the optimal diagnostic strategy, the precise role of antivirals in different subgroups, and the cost-effectiveness of routine screening, especially in resource-limited settings. The absence of standardized global protocols has contributed to inconsistent clinical practice, as highlighted in recent guideline updates [14,16]. For Pakistan and other low- and middle-income countries, the challenge is amplified by limited access to advanced diagnostics such as IHC or PCR, necessitating the development of pragmatic, resource-appropriate screening algorithms.

The limitations of our study must be acknowledged. As a single-center, cross-sectional analysis, generalizability is constrained, and long-term outcomes such as steroid responsiveness, colectomy, or mortality were not assessed. Additionally, although we used IHC to improve diagnostic yield, the lack of routine tissue PCR may have underestimated subclinical CMV reactivation. Despite these constraints, the prospective design, consecutive patient recruitment, and standardized diagnostic criteria represent key methodological strengths.

Overall, this study adds robust, region-specific data to a literature dominated by Western and East Asian cohorts, providing an essential foundation for local guideline development. In high-burden settings, integration of CMV screening into the management algorithm for severe UC may improve outcomes and reduce healthcare costs associated with prolonged hospitalization and surgery.

CONCLUSION

In conclusion, CMV colitis was identified in approximately one in twelve hospitalized patients with acute UC flares at our center, with prevalence significantly higher in those with severe disease and multiple relapses. These findings underscore the importance of CMV as a clinically relevant comorbidity in UC and highlight the need for routine screening in high-risk groups, particularly in resource-limited regions. While our data cannot resolve the ongoing debate regarding the causal role of CMV in UC pathogenesis, they strengthen the case for early recognition and targeted intervention to optimize patient outcomes.

REFERENCES

1. Rubin DT, Ananthakrishnan AN, Siegel CA, Barnes EL, Long MD. ACG clinical guideline update: ulcerative colitis in adults. **Am J Gastroenterol.** 2025;120(6):1187–1224. doi:10.14309/ajg.0000000000003463.
2. Lynch WD, Hsu R. Ulcerative colitis. In: **StatPearls** [Internet]. Treasure Island (FL): StatPearls Publishing; 2025–. Updated 2023 Jun 5. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459282/ (NCBI)
3. Caron B, et al. Epidemiology of inflammatory bowel disease across the ages in the era of advanced therapies. **J Crohns Colitis.** 2024;18(Suppl 2):ii3–ii15. doi:10.1093/ecco-jcc/jjae143.
4. Kucharzik T, Ellul P, Greuter T, Rahier JF, Verstockt B, Abreu C, et al. ECCO guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. **J Crohns Colitis.** 2021;15(6):879–913. doi:10.1093/ecco-jcc/jjab052.
5. Zuhair M, Smit GSA, Wallis G, Jabbar F, Smith C, Devleesschauwer B, Griffiths P. Estimation of the worldwide seroprevalence of cytomegalovirus: a systematic review and meta-analysis. **Rev Med Virol.** 2019;29(3):e2034. doi:10.1002/rmv.2034.
6. Goetgebuer RL, Allard T, Bossuyt P, Dulai PS, Nakase H, Peyrin-Biroulet L, et al. The diagnosis and management of CMV colitis in IBD: a practical review. **Scand J Gastroenterol.** 2022;57(9):1037–1049. doi:10.1080/00365521.2022.2088244.
7. Xiao L, Chen J, Li X, Huang M, Zhou Z. The impact of cytomegalovirus infection on ulcerative colitis: a review. **Infect Drug Resist.** 2024;17:4943–4958. doi:10.2147/IDR.S467322.

8. Qin Y, Zhang Q, Chen H, et al. Risk factors of cytomegalovirus reactivation in ulcerative colitis: a systematic review. **Diagnostics (Basel).** 2021;11(11):1952. doi:10.3390/diagnostics11111952.
9. Esen S, Akpinar H, Turan E, et al. Diagnostic utility of cytomegalovirus DNA load for predicting outcomes in ulcerative colitis. **Infect Dis Ther.** 2024;13(3):803–819. doi:10.1007/s40121-024-00954-8.
10. Soni K, Puing A. Cytomegalovirus colitis in adult patients with inflammatory bowel disease. **Viruses.** 2025;17(6):752. doi:10.3390/v17060752.
11. Moran GW, de Silva PS, Irving PM, et al. British Society of Gastroenterology guidelines on acute severe ulcerative colitis (ASUC). **Gut.** 2025;74(Suppl 2):s1–s101. doi:10.1136/gutjnl-2024-334395.
12. Sanat ZM, Vahedi H, Malekzadeh R, Fanni Z. Epidemiologic profile of inflammatory bowel disease in WHO-EMRO countries: a systematic review and meta-analysis. **BMC Public Health.** 2024;24:1732. doi:10.1186/s12889-024-18816-z.
13. Lawlor G, Moss AC. Cytomegalovirus in inflammatory bowel disease: pathogen or innocent bystander? **Inflamm Bowel Dis.** 2010;16(9):1620–1627. doi:10.1002/ibd.21265.
14. Magro F, Magalhães J, Macedo GN. Cytomegalovirus and ulcerative colitis: place for a personalized approach. **Ther Adv Gastroenterol.** 2021;14:17562848211004827. doi:10.1177/17562848211004827.
15. Pillet S, Pozzetto B, Roblin X. Cytomegalovirus and ulcerative colitis: place of antiviral therapy. **World J Gastroenterol.** 2016;22(6):2030–2045. doi:10.3748/wjg.v22.i6.2030.
16. Bert F, Lambert J, Lortholary O, Guillemot D. Cytomegalovirus infection in inflammatory bowel disease: an update on diagnosis and management. **Clin Microbiol Infect.** 2016;22(10):857–863. doi:10.1016/j.cmi.2016.07.011.
17. Kim YS, Kim YH, Kim JS, et al. Cytomegalovirus infection in patients with active ulcerative colitis: a prospective study in Korea. **Intest Res.** 2014;12(4):277–284. doi:10.5217/ir.2014.12.4.277.
18. Yoshino T, Nakase H, Ueno S, et al. Frequency of cytomegalovirus reactivation in patients with ulcerative colitis in Japan. **J Gastroenterol.** 2013;48(11):1259–1266. doi:10.1007/s00535-013-0750-3.
19. Roblin X, Pillet S, Oussalah A, et al. Cytomegalovirus load in inflamed colonic mucosa is predictive of resistance to immunosuppressive therapy in ulcerative colitis. **Am J Gastroenterol.** 2011;106(11):2001–2008. doi:10.1038/ajg.2011.207.
20. Lee HS, Kim YH, Kim JS, et al. Clinical impact of cytomegalovirus infection in patients with ulcerative colitis: a multicenter study. **Inflamm Bowel Dis.** 2016;22(4):762–768. doi:10.1097/MIB.0000000000000722.
21. Kishore J, Ghoshal UC, Ayyagari A. Infection with cytomegalovirus in patients with inflammatory bowel disease: diagnostic utility of immunohistochemistry. **Indian J Gastroenterol.** 2004;23(5):168–170. PMID: 15587294.
22. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. **J Crohns Colitis.** 2014;8(6):443–468. doi:10.1016/j.crohns.2013.12.013.
23. Shukla T, Singh S, Loftus EV Jr, Bruining DH, McCurdy JD. Antiviral therapy in steroid-refractory ulcerative colitis with cytomegalovirus: systematic review and meta-analysis. *Inflamm Bowel Dis.* 2015;21(11):2718–2725. doi:10.1097/MIB.0000000000000489.
24. Ciccocioppo R, Racca F, Paolucci S, et al. Cytomegalovirus infection in inflammatory bowel disease: interplay with the immune system and therapeutic implications. **World J Gastroenterol.** 2014;20(35):12414–12425. doi:10.3748/wjg.v20.i35.12414.
25. Griffiths P, Reeves M. Pathogenesis of human cytomegalovirus in the gastrointestinal tract. **J Infect Dis.** 2021;223(Suppl 1):S48–S56. doi:10.1093/infdis/jiaa646.
26. Park SC, Jeen YT, Kim WH. Clinical characteristics and treatment outcomes of cytomegalovirus colitis in patients with ulcerative colitis in Korea. **Korean J Intern Med.** 2017;32(1):82–89. doi:10.3904/kjim.2014.354.

27. Al-Zafiri R, Abou Saleh M, Abdul-Wahab A, et al. Prevalence and outcomes of cytomegalovirus colitis in ulcerative colitis: a Saudi tertiary-center experience. **Saudi J Gastroenterol.** 2020;26(5):263–269. doi:10.4103/sjg.SJG_112_20.
28. Lavagna A, Bergallo M, Daperno M, et al. CMV DNA detection in colonic biopsies: relationship with age and clinical outcome in ulcerative colitis. **Dig Liver Dis.** 2004;36(11):818–823. doi:10.1016/j.dld.2004.06.007.
29. Pardi DS, Tremaine WJ, Sandborn WJ. Cytomegalovirus infection in ulcerative colitis: risk factors and outcomes. **Inflamm Bowel Dis.** 2002;8(6):551–556. doi:10.1097/00054725-200211000-00005.
30. Ko JH, Peck KR, Lee WJ, Lee JY, Cho SY, Ha YE, et al. Clinical presentation and risk factors for cytomegalovirus colitis in immunocompetent adult patients. **Clin Infect Dis.** 2015;60(6):e20–e26. doi:10.1093/cid/ciu969.