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Impact of concurrent colonic CMV infection on clinical outcomes in immune checkpoint inhibitor–induced colitis☆

Hajir Ibraheim [a,b,1], Paolo Davide d'Arienzo [b,1], Nathan James Dean [b], William Duggleby [b], Ashish Singh [b], Thubeena Manickavasagar [b], Foteini Kalofonou [b], Mohamed Aboulela [b], Sree Vadera [b], Kirsty Ellen Anderson [b], Michael Campbell [b], Jacob Lewis [b], Paula Muehlschlegel [b], Stephanie Mullings [b], Jake James Symington [b], Sabeera Dar [b], Irene Oommen [c], Jenna Saad Hafidh [d], Robert Goldin [a], James Alexander [a], Anna Clare Olsson-Brown [e], Kate Young [b], Nicholas Powell [a,b,*]

[a] Department of Metabolism, Digestion and Reproduction, Imperial College London, UK
[b] Department of Cancer Services, The Royal Marsden Hospital, UK
[c] Gastroenterology Unit, Imperial College Healthcare NHS Trust, UK
[d] West Hertfordshire Hospitals NHS Trust, UK
[e] Sussex Cancer Centre, University Hospitals Sussex NHS Foundation Trust, UK

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ABSTRACT

Background and aims: Immune checkpoint inhibitors (ICI) frequently trigger ICI-colitis, commonly leading to ICI discontinuation. With expanding ICI use, ICI-colitis is emerging as a significant clinical challenge. Cytomegalovirus (CMV) infection is known to occur in ICI-colitis, but its prevalence, risk factors and clinical impact are poorly defined. This study aimed to characterise the clinical trajectory of ICI-colitis patients with concurrent colonic CMV infection as compared to a CMV-negative colitis group.

Methods: We retrospectively analysed consecutive ICI-treated patients with endoscopically and/or histologically confirmed ICI-colitis at two UK hospitals between 2015 and 2024. Clinical, endoscopic (Mayo Endoscopic Score, MES), treatment and oncologic outcome data were collected. CMV was identified by immunohistochemistry (IHC) on colonic biopsies. CMV-positive colitis cases were compared with CMV-negative colitis using chi-squared, Mann–Whitney U, and multivariable regression analyses.

Results: Among 249 ICI-colitis patients, IHC proven CMV-positive colitis was detected in 21 (8.4%). CMV-positive colitis was associated with dual ICI therapy (OR 2.8, CI 1.06–7.15), prior infliximab exposure (OR 6.4, CI 2.56–16.7), bloody stool (OR 2.7, CI 1.05–6.69), and higher endoscopic severity (MES 2–3; OR 4.1, CI 1.60–10.38), despite similar CTCAE diarrhoea grades between groups. They also had a higher likelihood of requiring escalation to advanced therapy (80% vs 41.5%; OR 5.6, CI 1.96–15.74), with this association remaining significant after adjusting for endoscopic severity ($p = 0.049$).

Abbreviations: Anti-TNF-α, Anti–tumour necrosis factor-α; CTCAE, Common Terminology Criteria for Adverse Events; CD, Crohn's disease; CRP, C-reactive protein; CMV, Cytomegalovirus; EPRs, Electronic patient records; FC, Faecal calprotectin; GI, Gastrointestinal; ICI, Immune checkpoint inhibitor; IrAEs, Immune-related adverse events; IHC, Immunohistochemistry; IBD, Inflammatory bowel disease; IFX, Infliximab; MES, Mayo Endoscopic Score; OS, Overall survival; PCR, Polymerase chain reaction; PFS, Progression-free survival; UC, Ulcerative colitis; UK, United Kingdom.

☆ Produced by the ICONIC group (Immune CheckpOiNt Inhibitor Colitis outcomes):

* Correspondence to: Department of Metabolism, Digestion and Reproduction, Imperial College London, W12 0NN, UK.

E-mail addresses: h.ibraheim@nhs.net (H. Ibraheim), paolo.d'arienzo@nhs.net (P.D. d'Arienzo), nathan.dean@nhs.net (N.J. Dean), w.duggleby@nhs.net (W. Duggleby), ashish.singh@rmh.nhs.uk (A. Singh), thubeena.manickavasagar@rmh.nhs.uk (T. Manickavasagar), foteini.kalofonou@rmh.nhs.uk (F. Kalofonou), Mohamed.Aboulela@rmh.nhs.uk (M. Aboulela), sree.vadera@nhs.net (S. Vadera), kirstyellen.anderson@gstt.nhs.uk (K.E. Anderson), michael.campbell17@nhs.net (M. Campbell), jacob.lewis@nhs.net (J. Lewis), paula.muehlschlegel@nhs.net (P. Muehlschlegel), stephanie.mullings@rmh.nhs.uk (S. Mullings), jake.symington5@nhs.net (J.J. Symington), Sabeera.dar1@nhs.net (S. Dar), irene.oommen@nhs.net (I. Oommen), jenna.hafidh2@nhs.net (J.S. Hafidh), robert.goldin@nhs.net (R. Goldin), j.alexander@imperial.ac.uk (J. Alexander), a.olsson-brown@nhs.net (A.C. Olsson-Brown), kate.young@rmh.nhs.uk (K. Young), nicholas.powell@imperial.ac.uk (N. Powell).

[1] Joint first author.

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Colectomy rates were higher albeit low overall. Antiviral therapy did not significantly affect corticosteroid duration or recurrence, and CMV tissue status did not influence overall or progression-free survival.
Conclusion: Concurrent CMV-positive colitis occurs in a notable subset of ICI-colitis patients and may worsen disease severity, highlighting the importance of endoscopic biopsy, especially in steroid-refractory cases.

1. Introduction

Immune checkpoint inhibitors (ICI) targeting co-inhibitory immune checkpoints on T-cells, such as CTLA-4 and PD-1/PD-L1, have transformed cancer outcomes and yielded durable responses. Initially limited to advanced cancers, the remarkable progress in the field has established ICI therapy as standard of care in both adjuvant and neoadjuvant settings for some tumours too[1–3]. However, ICI success is hampered by their collateral impact on the immune system, triggering autoimmune-like effects, termed immune-related adverse events (irAEs). ICI-colitis is the second most common irAE, occurring in up to 43% of patients receiving dual anti-CTLA-4/anti-PD-(L)1 [4]. Furthermore, ICI-colitis represents the most common cause of severe toxicity and ICI discontinuation [5,6], underscoring the importance of understanding this emerging mucosal disease. ICI-colitis frequently necessitates hospitalisation and prolonged immunosuppression with corticosteroids and escalation to infliximab (IFX) and anti-integrin antibodies (vedolizumab) in refractory cases [7].

ICI-colitis exhibits some similarities to inflammatory bowel disease (IBD), particularly ulcerative colitis (UC), with respect to the clinical, endoscopic and histological findings as well as some underlying immunopathophysiological mechanisms [8,9]. Indeed, IBD patients receiving ICI therapy have a three-fold increased risk of developing ICI-colitis, compared to their non-IBD counterparts, further supporting the notion of shared disease mechanisms [10]. Interestingly, a recent study indicated that polygenic risk scores for UC, but not Crohn's disease (CD), may predict development of ICI-colitis in cancer patients [11]. Exploring the distinct and overlapping features of these diseases can accelerate understanding of ICI-colitis pathophysiology and support the rationale for repurposing established IBD therapies in this disease.

One area that has received considerably less attention is the impact of concurrent cytomegalovirus (CMV) colonic infection on clinical outcomes in ICI-colitis. CMV is a DNA herpesvirus that is highly prevalent in the general population with a global seroprevalence between 66% and 90% [12]. In immunocompetent individuals, CMV infection is typically asymptomatic or presents as a self-limiting illness. However, in immunocompromised populations, CMV can lead to severe systemic disease, including organ-specific involvement and widespread viral dissemination. In addition to immunodeficiency conditions, one of the most frequent clinical settings for the development of CMV-positive colitis is IBD, particularly UC. CMV is present in the colonic tissue of approximately 10–30% of adult cases with moderate to severe UC, especially in those with steroid-refractory disease [13–15]. The diagnosis of CMV-positive colitis is established through immunohistochemistry (IHC), tissue polymerase chain reaction (PCR), or a combination of both methods [16].

The clinical significance of concurrent CMV infection in UC remains uncertain, with conflicting data on whether CMV exacerbates inflammation or simply serves as a marker of more severe disease. However, increasingly, the evidence indicates an association with adverse outcomes including an increased risk of disease flares, prolonged flare severity and duration, hospitalisation, toxic megacolon, colectomy, and corticosteroid resistance [17–20]. Accordingly, a systematic review and meta-analysis of UC patients with concurrent CMV-positive colitis, demonstrated that antiviral therapy may reduce colectomy rates in corticosteroid-refractory patients (odds ratio 0.20; 95% confidence interval 0.08–0.49), though this benefit was not observed in the overall population [21].

Data on the prevalence of concurrent CMV infection in ICI-colitis remain limited. Additionally, emerging evidence suggests that ICI's may increase the risk of infection, even in the absence of immunosuppressive therapy for irAEs [22,23]. This increased risk may be attributed to aberrant immune responses.

In one study, CMV was identified in 4% (1/28) of patients with histologically proven ICI-colitis (4%) [24]. Franklin et al. reported CMV-positive colitis confirmed by IHC or PCR in nearly 10% (4/41) of ICI-colitis patients, all of whom were refractory to corticosteroid and IFX [25].

Although several case reports and case series have described CMV-positive colitis in the context of ICI-colitis [25], most lacked comparator groups, had small patient numbers and used inconsistent or non-robust definitions of CMV-positive colitis and ICI-colitis. Consequently, short and medium-term outcomes remain poorly defined. A summary of these studies are provided in Supplementary Table 1. Further work is needed to determine risk stratification and guide management.

The present study sought to characterise colonic CMV infection in ICI-colitis, including its prevalence, associated risk factors and clinical outcomes utilising stringent diagnostic criteria for both colitis and CMV infection.

2. Materials and methods

2.1. Study design

A retrospective analysis of consecutive patients treated for ICI colitis at two hospitals in London, UK, between January 2015 and March 2024 was conducted as part of the Immune CheckpOint Inhibitor Colitis Outcomes (ICONIC) collaboration. Electronic patient records (EPRs) were reviewed to identify patients who developed diarrhoea after receiving at least one cycle of ICI therapy, and underwent lower gastrointestinal (GI) endoscopic evaluation with colonic biopsies for histological analysis. ICI-colitis cases were included if inflammation was confirmed endoscopically and/or histologically with a minimum of 6 months of follow-up data.

EPRs were reviewed to extract demographic characteristics, cancer diagnosis, and ICI regimen, gastrointestinal symptoms (CTCAE diarrhoea grade and presence of blood), endoscopic findings (graded using the Mayo Endoscopic Score (MES) and categorised as mild inflammation (MES 0–1) or moderate–severe inflammation (MES 2–3)), and histological findings. Inflammatory markers (peak faecal calprotectin and C-reactive protein during the colitis episode), details of colitis episodes and management, and the type and duration of immunosuppressive therapies were recorded. Oncologic outcomes included overall survival (OS) and progression-free survival (PFS).

Colonic CMV tissue status was determined using immunohistochemistry (IHC). Comparator groups were ICI-colitis cases that were CMV-positive versus CMV-negative. Serological CMV status (IgG) and CMV DNA levels were recorded where available.

2.2. Statistical analyses

Statistical analyses were performed using GraphPad Prism version 10. Continuous variables are presented as medians and were compared using the Mann–Whitney *U* test or the Kruskal–Wallis test, as appropriate. Categorical variables are summarised as frequencies and percentages and were analysed using Fisher's exact test or the chi-squared test. Multivariable logistic regression was used to identify factors

independently associated with CMV-positive colitis, adjusting for potential confounders including age, sex, cancer type, ICI regimen, CTCAE diarrhoea grade, and MES.

Associations between CMV tissue status and OS and PFS were evaluated using survival analysis methods. Statistical significance was defined as a two-sided P value < 0.05.

Missing data were handled using complete-case analysis, and no data imputation was undertaken.

3. Results

Of 384 ICI-treated patients who underwent lower gastrointestinal endoscopy, 249 with endoscopically confirmed ICI-colitis and available histological biopsies were included (Fig. 1, Table 1). The median time from diarrhoea onset to last follow-up was 55.4 months (IQR 26.1–106).

CMV-positive colitis was identified by IHC in 21 patients (8.4%) (Fig. 2; Supplementary Table 2), tissue PCR confirmation was available in one case. The remaining 228 ICI-colitis patients were CMV-negative on colonic biopsy.

The median age was similar between groups (57 years [IQR 49.5–71.3] vs. 62 years [IQR 55–71]), as was the proportion of male patients (57.1% vs. 53.1%). Melanoma was the most common malignancy in both groups, occurring more frequently in CMV-positive than CMV-negative colitis (66.6% vs. 42.5%, respectively; $p = 0.03$). Accordingly, dual ICI regimens were more frequently observed in these cases (66.6% vs. 41.6%, $p = 0.03$) (Table 1).

Pre-colitis CMV serology was available for 13 patients with CMV-positive colitis, 9 (69.2%) of whom were seropositive. CMV blood PCR testing was performed during the colitis episode in 18 patients, with elevated viral titres identified in 8 cases. (see Supplementary Table 2). Pre-colitis CMV serology was available for 85 patients with CMV-negative colitis, of whom 42 (49.4%) were seropositive with elevated viral titres detected in 10 of 72 cases during the colitis episode. CMV seroprevalence did not differ significantly between patients with and without CMV-positive colitis (χ^2, $p = 0.18$). However CMV-positive colitis patients were five times more likely to have elevated viral titres (OR 5.0, 95% CI 1.65–13.9; $p = 0.004$).

3.1. Clinical features and endoscopic findings

The median time from initiation of ICI therapy to diarrhoea onset was numerically shorter in CMV-positive colitis compared with CMV-negative colitis (59 vs. 81 days, $p = 0.37$), potentially reflecting the higher use of anti–CTLA-4–containing regimens in this group.

There was no significant difference in the distribution of CTCAE diarrhoea grades between groups ($p = 0.42$) (Fig. 3a). Notably, tissue CMV-positivity was associated with 2.7-fold higher odds of bloody stool compared with CMV-negative patients (95% CI 1.06–6.6; $p = 0.038$) (Fig. 3B).

Median serum C-reactive protein levels were similar between the groups (34 vs. 37 mg/L, $p = 0.9$). While faecal calprotectin data were available for only four CMV-positive colitis cases, median levels were numerically higher compared to CMV-negative colitis patients (3237 vs. 500 μg/g, $p = 0.15$).

Most CMV-positive cases were identified at the initial endoscopy ($n = 15$), with 28.5% of cases ($n = 6$) detected on the second or third procedure. Among CMV-positive cases, patients who were CMV-negative on initial endoscopy underwent the procedure earlier than those who were CMV-positive at first endoscopy (median 3.5 vs. 23 days from symptom onset; $p = 0.054$). Repeat endoscopic assessment was also common in the CMV-negative colitis group (33.2%, $n = 76$).

CMV infection was identified in 1/81 (1.2%) patients with an MES of 0, 10/117 (8.5%) with an MES of 1, 4/32 (12.5%) with an MES of 2, and 6/19 (31.6%) with an MES of 3. Accordingly, CMV-positive colitis was associated with significantly higher MES ($p < 0.001$) with a 4.1-fold higher odds of moderate-to-severe inflammation (MES 2–3; 95% CI 1.6–10; χ^2, $p < 0.01$) (Fig. 3D). Notably, CTCAE grade diarrhoea did not correlate with endoscopic severity. However, bloody stool was associated with more severe endoscopic disease, occurring in 44.4% of patients with MES 2–3 compared with 12.1% of those with MES 0–1 (χ^2, $p < 0.0001$).

Histologically, most CMV-positive colitis cases ($n = 14$, 66.7%)

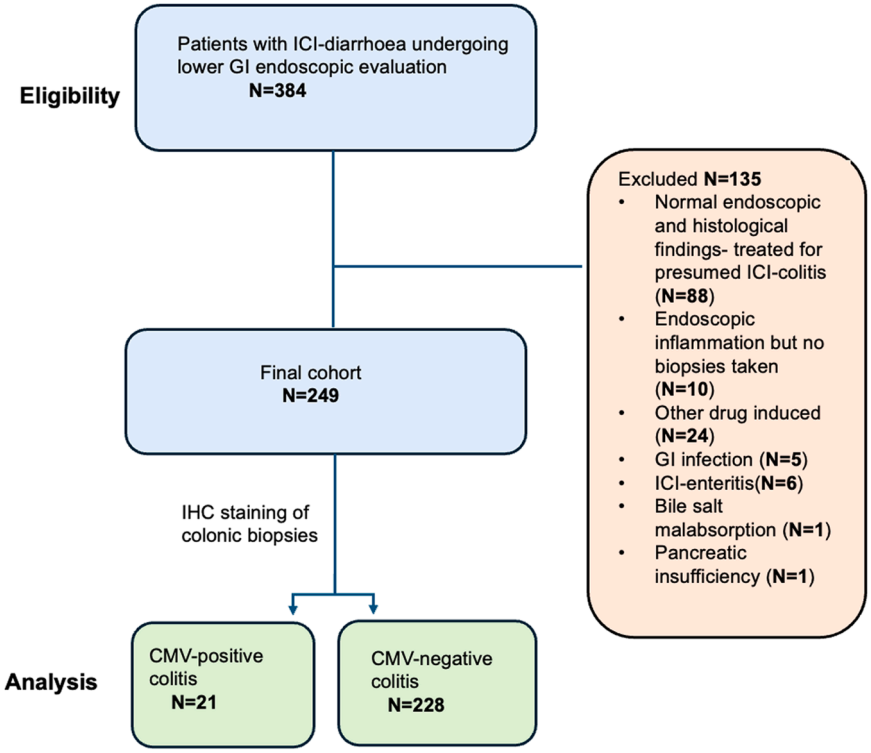


Fig. 1. CONSORT flow diagram.

Table 1
Cohort features.

Feature n (%)	CMV positive (n = 21)	CMV negative (n = 228)
Male sex	12 (57.1)	121 (53.1)
Age (median, IQR)	57 (49.5–71.3)	62 (55–71)
ICI regimen:		
Anti-CTLA-4 monotherapy	0 (0)	10 (4.4)
Anti-PD-(L)1 monotherapy	6 (28.5)	87 (38.1)
Dual anti-CTLA-4 + anti-PD-(L)1	14 (66.6)	95 (41.9)
Anti-PD-(L)1 + chemotherapy	1(4.8)	19(8.3)
Anti-PD-(L)1 + other	0	17(7.5)
Cancer type:		
Melanoma	14 (66.6)	97 (42.5)
Kidney	1 (4.8)	46 (20.2)
Lung	3 (14.3)	32 (14.0)
Bladder	1 (4.8)	11(4.8)
Mesothelioma	2 (9.5)	6 (2.6)
Oesophageal	0(0)	7(3.1)
Other*	0 (0)	29 (12.7)
ICI intent:		
Neoadjuvant	0(0)	3(1.3)
Adjuvant	3(14.2)	31 (13.6)
Palliative	18 (85.7)	194 (85.1)
Mayo Endoscopic Score		
0	1 (4.8)	80 (35.4)
1	10 (47.6)	107 (47.7)
2	4 (19)	28 (12.2)
3	6 (28.6)	13 (5.7)
CTCAE grade		
1	4 (19)	33 (15.2)
2	5 (23.8)	86 (38.5)
3	9 (42.9)	91 (40.8)
4	3 (14.3)	17 (7.6)
Proportion with bloody stool (%)	33.3	17.1
Median peak CRP (IQR)	37 (12–89)	34 (8–93)
Median peak faecal calprotectin µg/g (IQR)	3237 (606–4407)	500 (15–1177)
Median peak prednisolone dose (mg) pre-group defining endoscopy (IQR)	80 (50–98)	70 (40–80)

* 'Other' includes breast, colorectal, pancreatic, liver, uterine, ovarian and head and neck- each with n ≤ 5

displayed acute inflammation, with the remainder showing mixed acute and chronic inflammation (n = 5, 23.8%), chronic inflammation alone (n = 1), or 'other' patterns (n = 1). Although rates of acute and mixed inflammation were numerically higher in the CMV-positive colitis group, this was not statistically significant (Fisher's exact test, p = 0.30). Notably, microscopic colitis, including collagenous or lymphocytic patterns, was present in 9.2% of controls but in none of the CMV-positive cases.

3.2. Impact of immunosuppression exposure

Given reported associations between CMV reactivation and immunosuppression, exposure to immunosuppressive therapy for colitis prior to the group-defining endoscopy was evaluated. One CMV-positive patient had not yet received systemic immunosuppression. There were no significant differences between groups in corticosteroid duration (median 20 days [IQR 7–41.5] vs. 12 days [IQR 4–8]; p = 0.20) (Fig. 4A), peak prednisolone dose (80 mg vs. 70 mg; p = 0.08), or duration of intravenous methylprednisolone therapy (median 2 vs. 3 days; p = 0.12).

To minimise potential confounding from differences in timing of endoscopic assessment and therefore immunosuppressive exposure, a subgroup analysis was performed including only patients diagnosed with CMV-positive colitis at first endoscopy (n = 15). In this subgroup, time to first endoscopy was not significantly different between groups (median 23 vs 20 days; p = 0.21), as was corticosteroid exposure (median 19 vs 12 days; p = 0.30).

Assessment of immunosuppression with IFX (which was administered concurrently with systemic corticosteroids in all cases) showed that CMV-positive colitis was associated with 6.4-fold higher odds of prior IFX exposure (95% CI 2.56–16.65; p < 0.001). Specifically, 9 CMV-positive patients (42.9%) had received IFX compared with 24 with CMV-negative colitis (10.5%) (Fig. 4B).

Multivariable logistic regression to identify independent predictors of CMV-positive colitis could not be performed due to model instability related to collinearity and limited case numbers. Given this limitation, a secondary analysis was undertaken to explore the context of IFX exposure (pre-group defining endoscopy) across the cohort, irrespective of tissue CMV status. IFX-exposed patients were more likely to have received dual ICI therapy (68.8% vs. 40.1%; p = 0.002), and to present with CTCAE grade 3–4 diarrhoea (71.9% vs. 45.2%; p = 0.007).

3.3. Clinical outcomes of CMV-positive colitis

CMV-positive colitis patients were more likely to require escalation to advanced therapy (OR 5.6, 95% CI 1.96–15.74; p = 0.0016). Overall, 80% (n = 16) required escalation–11 to IFX, 4 to IFX and then vedolizumab, and 1 to vedolizumab – compared with 41.5% (n = 95) of CMV-negative colitis patients. Amongst those receiving IFX, 53.3% (n = 8) of CMV-positive patients required additional anti-inflammatory therapy, compared with 36.7% (n = 32) of CMV-negative patients (χ^2, p = 0.26). Colectomy rates were also numerically higher in CMV-positive cases compared with controls (10%, n = 2 vs. 0.4%, n = 1), although absolute numbers were small.

CMV-positive colitis was also associated with higher hospitalisation rates (80% vs 54.8%; p = 0.034), and a longer duration of hospital stay (14 days vs. 5 days; p = 0.009).

ICI-colitis recurrence rates after corticosteroid-free clinical remission

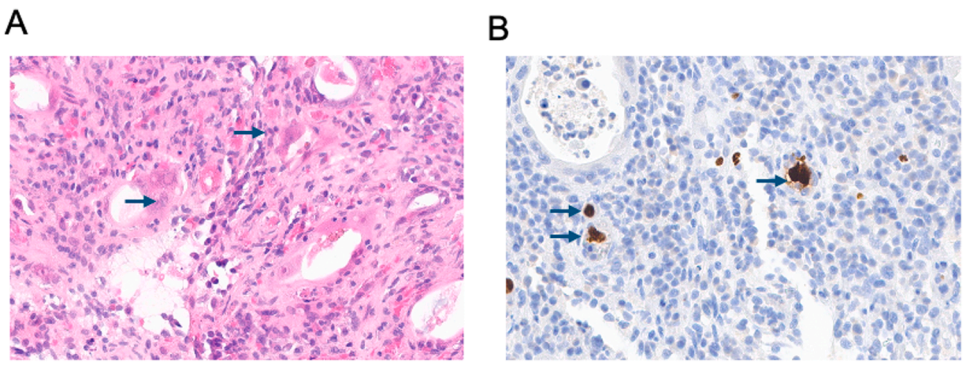


Fig. 2. Representative colonic biopsy from a patient with ICI–colitis demonstrating acute inflammation with crypt abscess, chronic inflammation and CMV infection on H&E staining (arrowheads) **(A)** with confirmation by CMV immunohistochemistry (arrowheads) **(B)** (magnification x400).

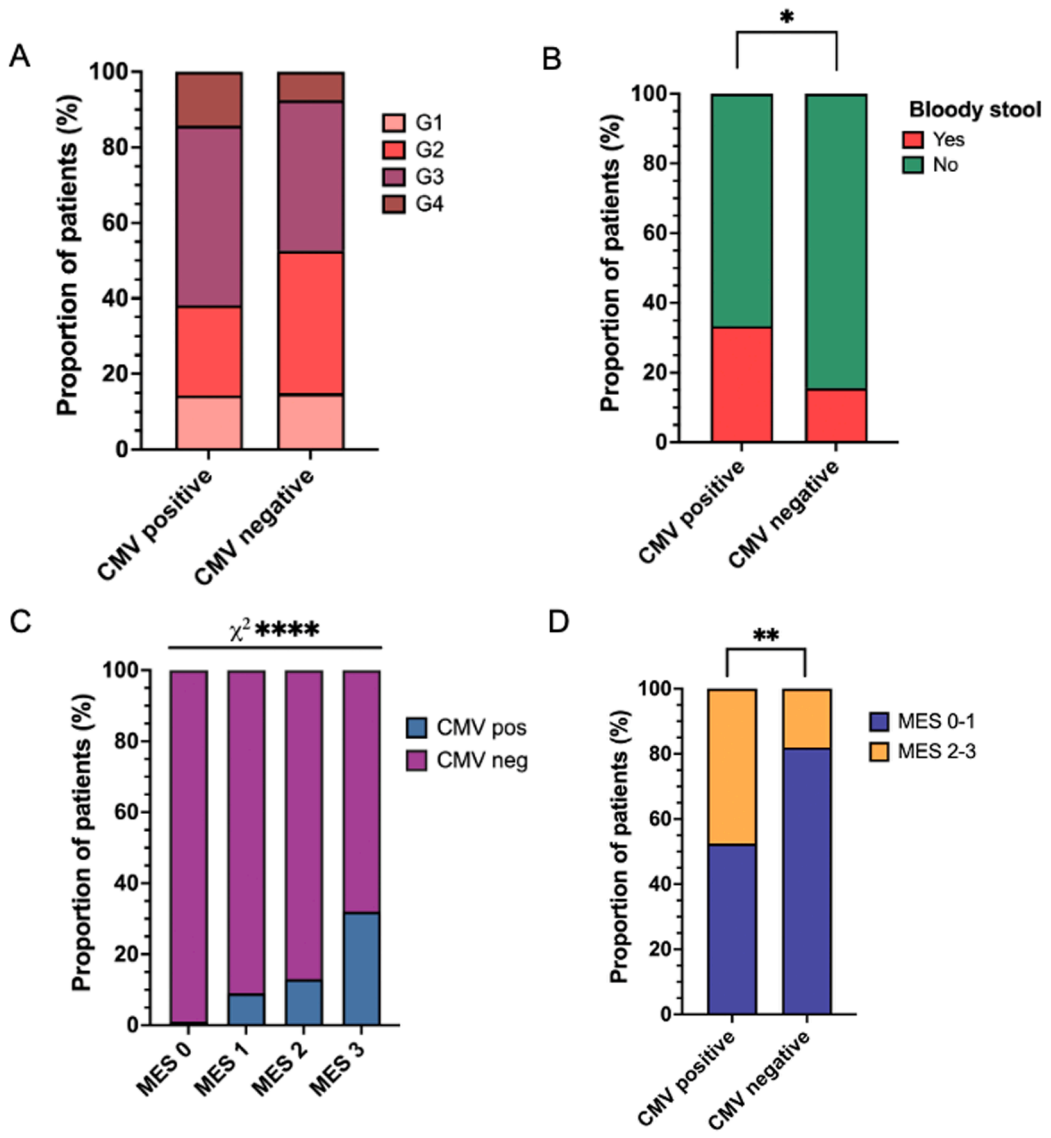


Fig. 3. (A) Distribution of CTCAE diarrhoea grades (G1–G4) in ICI-colitis, according to CMV-colitis status. (B) Proportion of ICI-colitis patients, with bloody stool, according to by CMV-colitis status. **P < 0.01; ****P<0.0001. (C) Distribution of Mayo endoscopic scores (MES) in ICI-colitis patients, according to CMV-colitis status. (D) Proportion of ICI-colitis patients with mild (MES 0-1) vs moderate to severe endoscopic inflammation (MES 2-3), according to CMV-colitis status.

were comparable in CMV-positive and CMV-negative colitis patients (20% vs 32.3%; χ^2, p = 0.32) (Fig. 4D).

To explore whether these associations reflected greater endoscopic severity rather than CMV colonic infection itself, further analyses adjusting for MES (0–1 vs 2–3) were performed. Among patients with mild inflammation (MES 0–1), CMV-positive cases remained more likely to require advanced therapy for corticosteroid-refractory disease (63.4% vs 32.6%; p = 0.049). Analyses within the MES 2–3 group showed a numerically higher proportion of CMV-positive patients requiring escalation compared with CMV-negative patients (90% vs. 63%, p = 0.19); however, interpretation is limited by smaller numbers in the MES 2-3 group overall. (Fig. 4C). After adjusting for MES score, CMV-positive colitis was not associated with hospitalisation.

3.4. Anti-viral therapy experience

Among the 21 CMV-positive colitis patients, antiviral therapy (ganciclovir or valganciclovir) was administered to 10 patients (Supplementary Table 2). The duration of antiviral therapy varied, ranging from 13 to 57 days. Antiviral therapy was used at clinician discretion, predominantly in treatment-refractory colitis. The duration of corticosteroid treatment was similar between treated and untreated CMV-positive colitis groups (median 75 days vs. 77 days, respectively; p = 0.59), as were rates of colitis recurrence following corticosteroid-free clinical remission (22.2% vs. 16.7%, respectively; Fisher's exact test, p > 0.99). Both patients who eventually required colectomy had also received antiviral therapy.

3.5. Cancer outcomes

The median follow-up duration from diarrhoea onset to last follow-up was numerically longer in the CMV-negative colitis group (22.2 months; IQR 10.6–41 vs 10.7 months; IQR 5.9–48, p = 0.4). By the end of the follow-up period, there were 12 deaths (57.1%) in the CMV-positive colitis group and 112 deaths (49.1%) in the CMV-negative colitis group, with the vast majority attributable to cancer progression. No deaths were directly related to CMV-positive colitis.

The median overall survival was 17 months (IQR 8.5–35.8) in patients with CMV-positive colitis compared with 28.6 months (IQR 14.2–49.9) in the CMV-negative colitis group, although this was not a

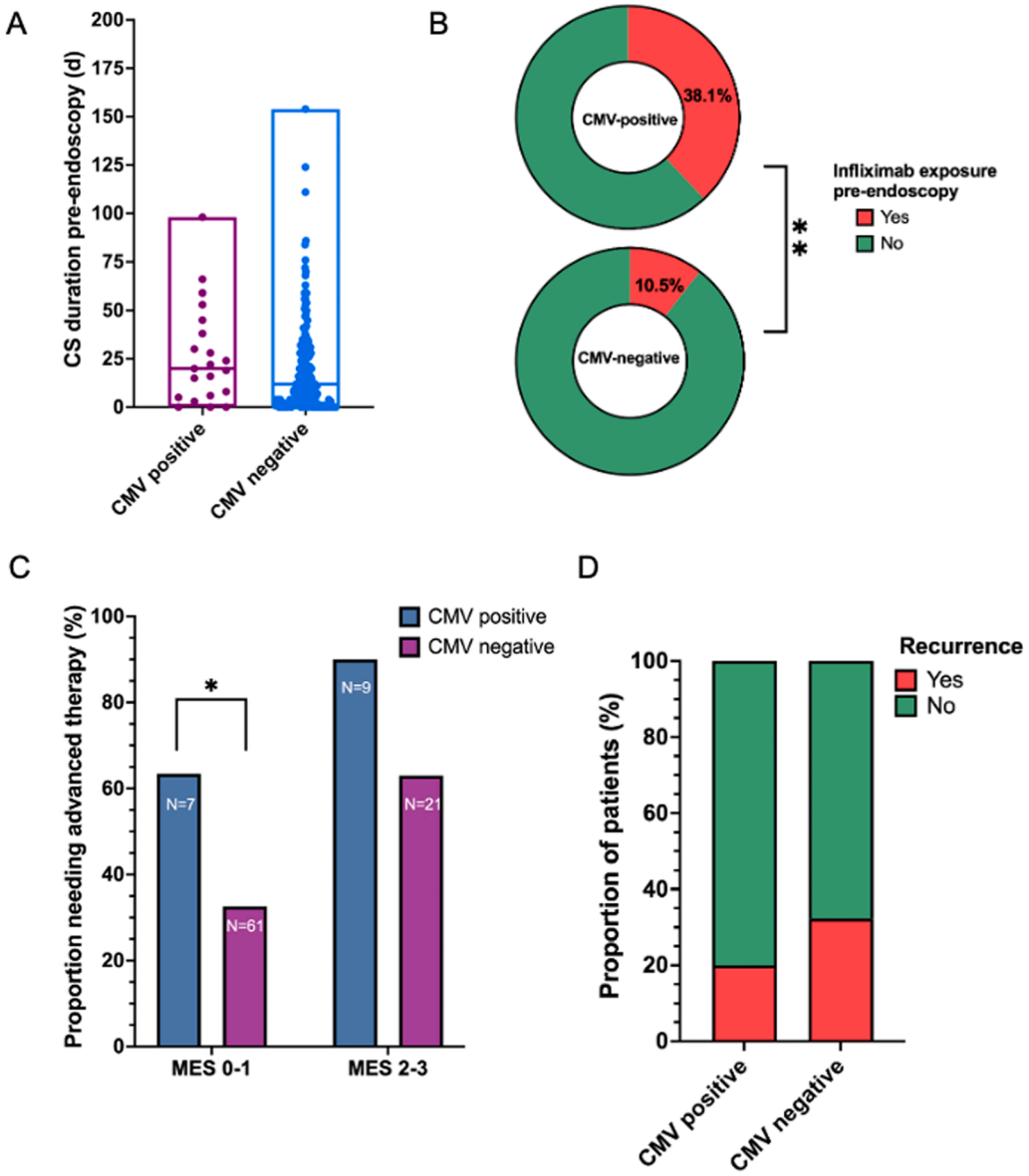


Fig. 4. **A**- Duration of corticosteroid (cs) therapy in ICI-colitis patients prior to endoscopy, according to CMV-positive colitis status. **B**- Proportion of ICI-colitis patients requiring escalation to infliximab, according to CMV-positive colitis status. **C**-Proportion of ICI-colitis patients requiring infliximab, according to CMV-positive colitis status and Mayo Endoscopic Score (MES). **D**- Proportion of ICI-colitis patients experiencing colitis recurrence after corticosteroid-free clinical remission, by CMV-positive colitis status. *P < 0.05; **P < 0.01.

statistically significant difference (p = 0.20). Multivariable Cox regression analysis indicated that CMV tissue status was not independently associated with overall survival (HR 1.35, 95% CI 0.68–2.49; p = 0.32). Factors associated with poorer survival included increasing age (HR 1.03, 95% CI 1.01–1.05; p = 0.0002) and stage 4 cancer (vs 1–3) (HR 2.14, 95% CI 1.32–3.67; p = 0.002) (Supplementary Table 3). To account for heterogeneity in cancer type and stage a subgroup analysis was performed in patients with stage 4 melanoma (n = 13 vs 73). CMV tissue status was not associated with OS (HR 1.43, 95% CI 0.59–2.99; p = 0.4) in this group.

Progression-free survival was not significantly different between CMV-positive and CMV-negative colitis groups, with medians of 13.4 months (IQR 4.1–32.4) and 15.6 months (IQR 7.8–33.8), respectively (HR 1.25, 95% CI 0.66–2.39; p = 0.50). A subgroup analysis of stage 4 melanoma patients also showed no significant difference (HR 0.78, 95% CI 0.34–1.83; p = 0.58).

4. Discussion

With the rapid expansion of ICI use, ICI-colitis - the most common cause of ICI discontinuation - is becoming increasingly prevalent and represents a growing clinical challenge. While concurrent colonic CMV infection has been reported in this context, evidence is limited to small case series. To date, this study represents the largest series describing the clinical features, management, and cancer outcomes of patients with ICI-associated CMV-positive colitis. A key strength was the inclusion of 228 CMV IHC–negative ICI-colitis controls, enabling comparative analysis, and the use of robust diagnostic criteria for both CMV infection (based on IHC) and ICI-associated colitis.

CMV-positive colitis was detected in 8.4% of patients evaluated for ICI-colitis, consistent with a previous smaller study [25] and comparable to rates reported in UC.

Although multivariable logistic regression to identify independent predictors of CMV-positive colitis was not feasible, an important finding was the association with prior IFX exposure. As all IFX treated patients

had also received corticosteroids, it is challenging to determine the effect of compound immunosuppression from those of IFX alone. Data examining the impact of IFX on CMV-positive colitis risk in IBD patients are limited. Two studies indicated no association, although both were constrained by small sample sizes, comprising only 29 [26] and 11 [27] patients in total. Interestingly, one patient in our cohort developed CMV-positive colitis without prior exposure to immunosuppressive therapy, suggesting that CMV-positive colitis can occur in the absence of iatrogenic immunosuppression.

Dual ICI therapy was also associated with a 2.8-fold increased odds of CMV-positive colitis compared to other regimens, reflecting the greater severity of ICI-colitis associated with dual ICI therapy.

CMV-positive colitis was not associated with CTCAE diarrhoea grade. However, it was linked to severe endoscopic disease, with nearly one-third of ICI- colitis patients with MES 3 testing positive for CMV. In line with previous studies, this discrepancy also underscores the limitation of symptom-based grading alone, reinforcing the importance of endoscopic assessment [28,29].

CMV-positive colitis was associated with corticosteroid refractory disease and increased escalation to advanced therapy, even after adjusting for endoscopic severity. This indicates that concurrent CMV infection may contribute to treatment resistance rather than simply reflecting disease severity. Accordingly, prompt endoscopic evaluation with biopsy to assess for CMV should be considered in patients with corticosteroid-refractory disease.

In the context of IBD, CMV infection has been associated with increased risk of severe colitis, colectomy, and prolonged hospitalisation [17–20]. Although the limited number of colectomies in our cohort precluded formal analysis, it is noteworthy that colectomy rates were higher among CMV-positive cases mirroring findings in the IBD population.

Another finding was the observation that some patients were seronegative prior to ICI-colitis onset, suggesting that both primary CMV infection and viral reactivation can occur in this context. Further research is needed to clarify the impact of primary infection versus reactivation on clinical outcomes and determine the clinical utility of serological screening pre-ICI therapy. While CMV-positive colitis was not associated with increased seropositivity, it was linked to a higher likelihood of viraemia, suggesting limited utility in measuring blood CMV DNA levels in CMV-negative colitis patients.

Experience with anti-viral therapy in this cohort was limited and heterogeneous, reflecting the absence of clear guidelines for CMV management in ICI-colitis. Anti-viral therapy was typically reserved for refractory cases, and no clear benefit was observed in terms of corticosteroid duration or recurrence rates. Both patients who eventually required colectomy had also received anti-viral therapy. While these findings should be interpreted cautiously given the small numbers, they highlight the uncertainty surrounding the role of anti-viral therapy in this context. Similarly, the role of anti-viral therapy in IBD-associated CMV-positive colitis remains unclear, although there is a suggestion it may reduce the colectomy rate in a subgroup of UC patients [21]. Prospective studies are needed to define which patients may benefit most from anti-viral treatment and the optimal timing of therapy.

Importantly, CMV-positive colitis was not associated with worse cancer outcomes in this study. OS and PFS were comparable between CMV-positive and CMV-negative patients, and CMV tissue status was not an independent predictor of mortality on multivariable analysis. While reassuring, these findings should again, be interpreted cautiously given the limited number of CMV cases and heterogeneity of cancer type.

Intriguingly, a recent study by Milotay et al. [30] found that CMV serostatus was associated with improved survival and reduced severity of toxicity in patients receiving anti-PD-1 checkpoint blockade therapy. Seropositive patients had increased T- cell clonality and cytotoxicity, and a distinct $CD8^+$ T cell transcriptomic profile, with upregulation of effector pathways including TCR and IFNγ-mediated signalling suggesting that CMV serostatus may play a role in modulating immune responses to immunotherapy. Additional studies with larger, more homogeneous cohorts are required to better understand the impact of CMV-positive colitis on clinical and cancer outcomes. Indeed, localized CMV reactivation has been associated with significant tissue damage in organs including the lungs, post-transplant grafts, gastrointestinal tract, and liver. These localised infections may have distinct immunological consequences compared to the more generalised immune modulation observed with systemic CMV seropositivity.

This study has several limitations including the lack of data on cumulative corticosteroid doses, as only therapy duration was captured. This restricts assessment of the true immunosuppressive burden, limiting interpretation of our findings. The retrospective design and limited number of number of CMV-positive colitis cases restricted the ability to perform more extensive multivariable analyses.

While preferential endoscopic evaluation in patients with more severe clinical symptoms cannot be entirely ruled out, local guidelines at both centres recommend endoscopic assessment for all ICI-associated diarrhoea cases, irrespective of CTCAE grade, which mitigates this potential bias. Moreover, as previously mentioned, published data indicates that endoscopic severity is independent of CTCAE grade diarrhoea [28,29].

Finally, heterogeneity in treatment approaches, including timing of antiviral therapy, limits firm conclusions regarding antiviral management efficacy.

In conclusion, CMV-positive colitis should be considered in patients with severe or steroid-refractory immune-mediated colitis, markers of which include exposure to compound immunosuppression and dual ICI therapy. Prompt endoscopic assessment with biopsy is essential, as CMV infection itself may contribute to worse outcomes and affected patients warrant closer monitoring. Larger, prospective studies are needed to validate these observations and guide optimal management strategies.

CRediT authorship contribution statement

Hajir Ibraheim: Writing – review & editing, Writing – original draft, Validation, Software, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Paolo Davide d'Arienzo:** Writing – review & editing, Validation, Software, Resources, Investigation, Data curation, Conceptualization. **Nathan James Dean:** Writing – review & editing, Validation, Software, Resources, Investigation, Data curation, Conceptualization. **William Duggleby:** Data curation. **Ashish Singh:** Data curation. **Thubeena Manickavasagar:** Data curation. **Foteini Kalofonou:** Data curation. **Mohamed Aboulela:** Data curation. **Sree Vadera:** Data curation. **Kirsty Ellen Anderson:** Data curation. **Michael Campbell:** Data curation. **Jacob Lewis:** Data curation. **Paula Muehlschlegel:** Data curation. **Stephanie Mullings:** Data curation. **Jake James Symington:** Data curation. **Sabeera Dar:** Data curation. **Irene Oommen:** Data curation. **Jenna Saad Hafidh:** Data curation. **Robert Goldin:** Data curation. **James Alexander:** Data curation. **Anna Clare Olsson-Brown:** Validation, Supervision, Data curation. **Kate Young:** Writing – review & editing, Validation, Supervision, Conceptualization. **Nicholas Powell:** Writing – review & editing, Validation, Supervision, Conceptualization.

Ethical approval

Study data were collected with approval from the Royal Marsden Hospital Committee for Clinical Research (SE1320) and the Imperial College Healthcare Trust (1030).

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors did not use any AI or AI-assisted technologies.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Disclosure of competing interests.** JLA has received conference fees from Celltrion, Tillots Pharma and Takeda with speaker fees from Abbvie and Johnson & Johnson. AOB has received travel support from Roche and MSD; receiving honoraria from BMS, Eiasi, Bohringer-Inglehiem, Ipsen, Regeneron, GSK, Merck, and Chugai; and receiving travel support and honoraria from AstraZeneca outside the submitted work. NP declares advisory and/or speaker fees from Abbvie, Allergan, Celgene, Debiopharm, Ferring and Vitor Pharma, and lecture fees from Allergan, Dr Falk Pharma, Janssen, Takeda and Tillotts Pharma.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116795.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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