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Impact of cytomegalovirus on outcomes in acute severe ulcerative colitis: a retrospective observational study

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Abstract

Background: Concomitant cytomegalovirus (CMV) is highly prevalent in acute severe ulcerative colitis (ASUC) but data for outcomes of CMV positivity in ASUC and the benefit of antiviral therapy remain unclear.

Objectives: We aim to determine the impact of CMV positivity, and antiviral therapy, on outcomes such as colectomy-free survival, length of hospital stay and readmission rate, among hospitalized patients with ASUC.

Design: This is a retrospective, multicentre study of patients admitted with ASUC.

Methods: CMV positivity was diagnosed from blood CMV DNA and inpatient colonic biopsies. Background demographics and disease characteristics, clinical characteristics and outcomes during admission and long-term outcomes were obtained from electronic medical records and compared according to the presence of CMV and the use of antiviral therapy.

Results: CMV was detected in 40 (24%) of 167 ASUC admissions. Previous steroid exposure was the only clinical predictor of CMV positivity on multivariate analysis. Outcomes of greater requirement for rescue therapy (60% *versus* 33%), longer hospital stay (14.3 *versus* 9.9 days) and higher readmission rates at 3 and 12 months were associated with CMV positivity. No difference was found in the rate of colectomy or colectomy-free survival. Antiviral therapy was not associated with a lower risk of colectomy but did extend the time to colectomy (126 *versus* 36 days).

Conclusion: CMV positivity was associated with worse outcomes of need for rescue therapy, hospital stay and readmissions. Antiviral therapy was not found to reduce the risk of colectomy but did extend the time to colectomy. Further prospective studies will be required to more clearly determine its benefit in patients with concomitant CMV and ASUC.

Plain language summary

Cytomegalovirus reactivation in acute severe ulcerative colitis

Cytomegalovirus (CMV) is a highly prevalent virus that may result in concominant reactivation in patients with acute severe ulcerative colitis and potentially worsen their outcomes. Our study aims to determine the impact of presence of CMV in patients with acute severe ulcerate colitis requiring hospitalisation and its association with outcomes including risk of surgical resection of colon, length of hospital stay, readmission rate, as well as effect of outcomes amongst those treated with antivirals for CMV. Our results did not find a significant association between detection of CMV on surgical risk, though outcomes including longer hospital stays, higher readmission rate were found. Antiviral

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use was not associated with lower risk of surgery but was found to prolong time to surgery. Given that our study was based on retrospective data, further prospective studies will be required to examine the benefit of antiviral use in outcomes for those with concominant CMV and acute severe ulcerative colitis. We conclude from our study that while having concomitant CMV with acute severe uclerative colitis may not necessarily increase risk for surgery, patients may still have worse outcomes in other areas therefore the detection of CMV should be considered a significant and clinically relevant result.

Keywords: ulcerative colitis, cytomegalovirus

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Introduction

Cytomegalovirus (CMV) is a highly prevalent virus of the herpes virus family. In immunocompetent adults, CMV typically is either asymptomatic or causes mild symptoms, followed by a lifelong latent phase.[1] However, patients with inflammatory bowel disease are at increased risk of CMV infection, with active ulcerative colitis (UC) imparting a 20-fold higher risk than individuals with normal colonic mucosa.[2,3] Concomitant CMV can occur in 16–43% of cases of severe, steroid-refractory UC and may worsen disease severity and clinical outcomes.[4,5] This is of particular concern in those with acute severe ulcerative colitis (ASUC), which can be life-threatening without urgent escalation of immunosuppressive therapy and may require colectomy in up to 30–40% of cases.[6,7] The European Crohn's and Colitis Organisation (ECCO) 2014 guidelines recommend colonic biopsies for the exclusion of CMV in all patients with ASUC. If concomitant CMV infection is diagnosed, antiviral therapy and consideration of temporary discontinuation of immunosuppressive treatments are recommended.[8]

The impact of concomitant detection of CMV on outcomes in UC varies between studies, due to significant heterogeneity in diagnostic criteria, study populations and the absence of the standardized antiviral treatment regimen.[9] A consensus has therefore not been established from existing literature on the clinical significance of CMV in ASUC, nor the benefit of antiviral therapy in improving outcomes.[10] Additionally, few studies have exclusively included patients with ASUC, who are at the highest risk for colectomy.

In our retrospective, multicentre observational study, we aim to determine the impact of CMV positivity, and the benefit of antiviral therapy, on outcomes such as colectomy-free survival, length of hospital stay and readmission rate, among hospitalized patients with ASUC.

Study population and method

This is a multicentre retrospective observational study. Patients admitted with ASUC to Blacktown, Westmead and Wollongong Hospitals between 2015 and 2021 were captured from International Classification of Disease coding and included in this study. Diagnosis of ASUC was made based on the fulfilment of Truelove and Witts Criteria[11] with the presence of $\geqslant$6 bloody stools/day and at least one of the following markers of systemic severity; fever $>$37.8°C, pulse rate $>$90 bpm, haemoglobin $<$105 g/L or C-reactive protein (CRP) $>$30 mg/L. Diagnosis of CMV positivity was made on the presence of detectable CMV DNA *via* blood or tissue polymerase chain reaction (PCR), or CMV viral inclusion bodies detected by immunohistochemistry (IHC) staining of colonic biopsies obtained during the same hospital admission. Those that did not meet Truelove and Witts criteria for ASUC diagnosis, those that did not undergo inpatient endoscopy and those with alternative diagnoses such as Crohn's or infectious colitis were excluded from the study. Individual admissions were included and examined separately for patients with multiple readmissions for ASUC to identify cases of the emergence of CMV positivity in subsequent admissions.

All data included in this study were obtained from electronic medical records. Background disease characteristics obtained included previous UC diagnosis, time from the initial diagnosis to first

documented admission with ASUC, previous endoscopic disease extent and severity and previous UC treatment. Clinical characteristics of admission including a daily number of bloody motions, pulse rate, fever and biochemical markers such as haemoglobin, albumin and CRP were obtained from initial assessment during each ASUC admission. Endoscopic disease severity during admission was assessed using the Mayo score. Inpatient treatment including steroids, anti-tumour necrosis factor (TNFα) drugs (i.e. infliximab) and cyclosporine as well as inpatient colectomy, use of antiviral treatment and length of stay were noted for each admission. Long-term outcomes such as readmissions, requirement for colectomy and time to colectomy were obtained from electronic documentation and outpatient clinical correspondence post-discharge.

Clinical outcomes of admissions with ASUC were compared according to the presence of CMV positivity and antiviral treatment. The primary study outcome is colectomy-free survival of patients with CMV positivity compared to patients without CMV. Secondary study outcomes include length of hospital stay, 30-day and 12-month readmission rate, total colectomy rate and time to colectomy. Subgroup analyses of outcomes were performed in those who had CMV inclusions seen on IHC compared to those who did not have CMV positivity, as well as those with CMV positivity by tissue PCR only without CMV inclusions seen on IHC.

Statistical analysis

Descriptive statistics were presented as mean ± standard deviation for normally distributed variables, the median and interquartile range for non-normally distributed variables and proportions (percentages) as appropriate. Power analysis was not performed. The sample size was determined based on the inclusion of all cases meeting inclusion criteria within the period in which electronic records at study sites were available. Independent samples *t*-test was used to analyse normally distributed numerical variables and Bayesian one-way analysis of variance was performed for analysis of multiple numerical variables. Wilcoxon rank-sum tests were similarly used for non-normal variables. Chi-squared tests were used to analyse categorical variables when observed frequencies in each cell were 5 or greater. Fisher's exact test was used for categorical variables when the observed frequency in at least one cell is less than 5.

Univariate analysis for identifying predictors of CMV was performed using Logistic regression. Factors with p values <0.1 were included in multivariate analysis. Cox regression was performed for the calculation of time to colectomy. The outcome for colectomy-free survival was analysed with the Kaplan–Meier method. All p values were tailed and results were considered statistically significant if $p < 0.05$. Analyses were conducted in STATA (Statacorp) and SPSS (IBM) statistical software version 28.

Results

A total of 167 admissions across three hospital sites met the inclusion criteria among 133 patients (Figure 1). Baseline demographics, disease characteristics and clinical characteristics during admission are summarized in Table 1. The mean age of total admissions was 36.1 years. 58% of admissions were male patients. 24.6% were the first presentation where a UC diagnosis was made. Among those with previous UC diagnoses, the mean time from diagnosis to ASUC admission was 61.4 months. 7.9% previously had proctitis, 46% left-sided disease and 31.9% pancolitis. 14.2% did not have documented previous endoscopic disease extent. 75.4% had prior steroid exposure, 43.1% were previously treated with immunomodulators and 29.9% biologics, of whom 43 (25.7%), 18 (10.8%) and 8 (4.8%) were previously treated with anti-TNFs, vedolizumab and tofacitinib, respectively.

In all, 40 patients with ASUC had CMV positivity. Blood CMV DNA level was tested *via* PCR in 45/167 (27%) of cases, of which 20/45 (44.4%) were positive. In total, 50% of positive blood CMV PCR results were below the quantifiable limit, while the median viral load for quantifiable PCR levels was 1138 copies/mL. Tissue CMV PCR was tested in 95/167 (56.9%) colonic biopsies, of which 34 (35.8%) were positive. IHC staining for CMV inclusion bodies was performed in 127/167 (76%) of colonic biopsies, of which 21/127 (16.5%) were positive. In all, 14 cases had detectable tissue PCR but no IHC staining viral inclusion bodies, while 5 with detectable tissue PCR did not have CMV IHC staining performed.

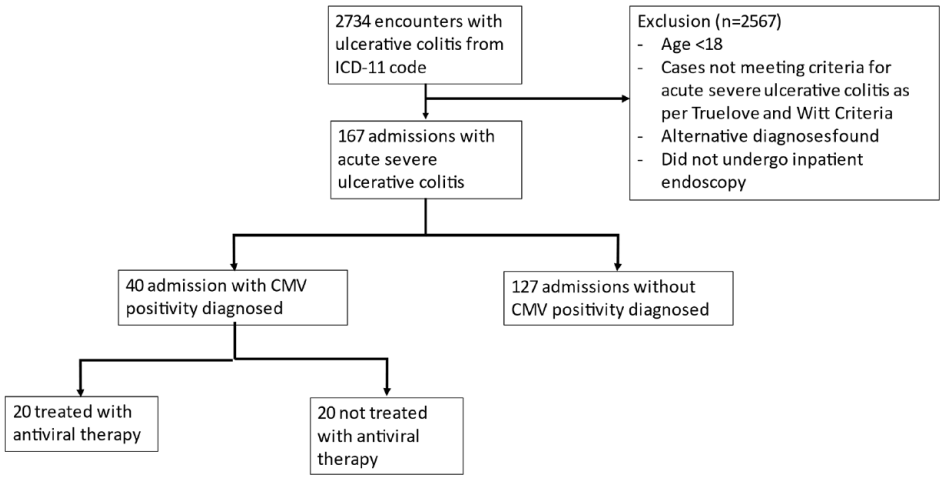

Figure 1. Flow diagram of all study patients identifying number with CMV positivity and those who received antiviral therapy.
CMV, cytomegalovirus.

CMV serology was tested in 71/167 (42.5%) of cases and CMV IgM was positive in 5/71 (7%).

Patients with CMV positivity were associated with a significantly lower proportion of first presentation with UC (10% *versus* 29.9%, $p=0.011$), a higher proportion of previous steroid exposure (87.5% *versus* 61.4%, $p=0.002$), immunomodulator (62.5% *versus* 37%, $p=0.004$) and biologic use (42.5% *versus* 26%, $p=0.047$). Among those with previous biologic use, only anti-TNF was associated with CMV positivity (26% *versus* 8.9%, $p=0.037$). Four patients had CMV positivity despite no previous UC diagnosis or immunosuppression exposure. Of these four, two had detectable blood CMV viral load, positive tissue PCR and CMV IHC staining inclusion bodies, while the other two had detectable tissue PCR only. No statistically significant differences were found in age, gender, previous disease extent and time from diagnosis to ASUC admission based on the presence of CMV.

Findings comparing initial clinical parameters of the Truelove and Witts Criteria during admission with ASUC between those with and without CMV are summarized in Table 1. At the initial assessment during admission, the mean daily number of bloody motions was 11.5. A total of 16.1% had a fever above 37.8°C. The mean pulse rate was 94 bpm, albumin 31.5 g/L, haemoglobin 124 g/L and CRP 61 mg/L. While there were trends towards lower mean albumin (29.4 *versus* 31.7 g/L, $p=0.062$) and CRP (47 *versus* 65.6 mg/L, $p=0.079$) among those with CMV positivity, no initial clinical characteristics of disease severity were found to be significantly worse with CMV positivity. The median time to endoscopy was 2 days. A total of 64.7% had Mayo 3 endoscopic severity. There were no statistically significant differences in endoscopic Mayo scores between those with and without CMV positivity. 92.5% received high-dose IV steroids. 39% required rescue therapy with either infliximab (38%), cyclosporine (8.3%) or both (4.8%).

Univariate analysis of predictors of CMV was performed *via* Logistic regression with findings summarized in Table 2. The first presentation of UC [odds ratio (OR): 0.27, $p=0.02$] carried a lower risk of CMV positivity, while previous steroid exposure (OR: 4.40, $p=0.02$), immunomodulator (OR: 2.84, $p=0.005$) and biologic use (OR: 2.11, $p=0.049$) carried a higher risk of CMV detection. Multivariate analysis of predictors with $p<0.1$ found only previous steroid exposure to remain significant (OR: 4.01, $p=0.007$).

Outcomes

A comparison of outcomes based on the presence of CMV is summarized in Table 3. Among all cases, the total colectomy rate was 35/167 (21%)

Table 1. Comparison of baseline demographics and disease characteristics prior to and during admission with ASUC.

Variable	Total ($n=167$)	ASUC with CMV positivity ($n=40$)	ASUC without CMV positivity ($n=127$)	p
Mean age	36.1	38.5	36.2	0.358
Male	58%	52.5%	59.8%	0.464
First presentation with UC	24.6%	10%	29.9%	0.011
The previous extent of colitis				
Unknown	14.2%	11.1%	14.9%	0.543
Proctitis	7.9%	11.1%	6.7%	0.735
Left sided	46%	52.8%	43.4%	0.336
Pancolitis	31.9%	25%	34.4%	0.303
Mean time from diagnosis to admission with ASUC (months)	61.4	48.6	66.6	0.241
Previous treatment				
Steroids	75.4%	87.5%	61.4%	0.002
Immunomodulators	43.1%	62.5%	37%	0.004
Biologics	29.9%	42.5%	26%	0.047
Daily bloody motions	11.5	11.15	11.6	0.629
Fever >37.8	16.1%	12.5%	17.3%	0.624
Mean pulse rate (bpm)	94	95	94.5	0.908
Mean albumin (g/L)	31.5	29.4	31.7	0.062
Mean haemoglobin (g/L)	124	120	125.5	0.151
Mean CRP	61	47	65.6	0.079
Endoscopic Mayo score				
Mayo 1	4.2%	0	5.5%	0.321
Mayo 2	31.1%	37.5%	29.1%	0.762
Mayo 3	64.7%	62.5%	65.4%	0.886
Inpatient high-dose steroids	155 (92.5%)	90%	93.7%	0.826
Inpatient rescue therapy	66 (39%)	60%	33.1%	0.002
Inpatient colectomy	12 (7.2%)	7.5%	7.1%	0.558

ASUC, acute severe ulcerative colitis; CMV, cytomegalovirus; CRP, C-reactive protein; UC, ulcerative colitis.

with a mean time to colectomy of 260 days (range: 6–1754) days. No difference was found with CMV in the rate of total colectomy (27.5% *versus* 18.9%, $p=0.351$). In all, 12 (7.2%) admissions with ASUC resulted in inpatient colectomy. The primary outcome of colectomy-free survival did

Table 2. Univariate and multivariate analyses for predictors of CMV positivity.

Variable	OR (univariate analysis)	95% CI	*p*	OR (multivariate analysis)	95% CI	*p*
Baseline demographics and disease characteristics						
Gender (male)	0.85	0.41–1.74	0.65			
Age	1.01	0.99–1.04	0.30			
First presentation	0.27	0.09–0.81	0.02	1.36	0.14–13.52	0.79
Disease extent	1.17	0.83–1.64	0.37			
Previous steroids	4.40	1.61–12.00	0.02	4.01	1.46–11.06	0.007
Previous immunomodulator	2.84	1.36–5.91	0.005	1.93	0.79–4.75	0.15
Previous biologic	2.11	1.00–4.42	0.049	0.96	0.36–2.53	0.93
Time from diagnosis to admission	1.00	0.99–1.00	0.51			
Clinical parameters during ASUC admission						
Number of bloody motions	1.00	0.93–1.06	0.72			
Fever ($T > 37.8$)	0.68	0.24–1.94	0.47			
Heart rate >90 bpm	1.00	0.99–1.02	0.76			
Albumin	0.95	0.89–1.01	0.09			
Haemoglobin <105	0.99	0.98–1.01	0.23			
CRP >30	0.99	0.98–1.00	0.05			
Disease extent	0.995	0.54–1.84	0.99			
Endoscopic Mayo score	1.087	0.576–2.05	0.797			

ASUC, acute severe ulcerative colitis; CI, confidence interval; CMV, cytomegalovirus; CRP, C-reactive protein; OR, odds ratio.

not differ based on CMV status as shown by the Kaplan–Meier Curve in Figure 2. No differences in colectomy rate were found based on endoscopic findings of Mayo 3 severity (62.5% *versus* 65.4%, $p = 0.886$), or rate of inpatient colectomy (7.5% *versus* 7.1%, $p = 0.558$) when comparing those with and without CMV. There was a trend towards earlier time to colectomy with CMV (85 *versus* 340 days, $p = 0.075$) but this did not reach statistical significance. Univariate analysis performed using logistic regression did not identify CMV positivity as a predictor of colectomy (OR: 1.36, $p = 0.472$) or 30-day colectomy rate (OR: 1.7, $p = 0.613$). In total, 33.5% required readmission post-discharge. CMV positivity was associated with a significantly higher rate of readmission, both at 30 days (25% *versus* 5.6%, $p = <0.001$) and 12 months (45% *versus* 15.7%, $p = 0.001$). The presence of CMV was associated with a greater requirement of rescue therapy (60% *versus* 33.1%, $p = 0.002$) and a longer mean hospital stay (14.3 *versus* 9.9 days, $p = 0.028$). No deaths occurred during the study period.

A separate sub-analysis was performed for comparison of outcomes in those with the presence of IHC staining inclusion bodies on colonic biopsy compared to cases without CMV positivity, as well as cases of CMV reactivation compared to cases with detectable tissue viral load on tissue biopsies. Outcomes are summarized in Table 4.

Table 3. Inpatient and long-term outcomes with CMV positivity.

Variable	Total ($n=167$)	ASUC with CMV positivity ($n=40$)	ASUC without CMV positivity ($n=127$)	p
Median length of hospital stay (days)	8	14.3	9.9	0.028
Total readmission rate	33.5%	53.8%	27.6%	0.038
Total colectomy rate	21%	27.5%	18.9%	0.351
30-Day colectomy rate	8.3%	10%	7.9%	0.674
30-Day readmission rate	10.3%	25%	5.6%	<0.001
Mean time to colectomy (days)	260	85	340	0.075

ASUC, acute severe ulcerative colitis; CMV, cytomegalovirus.

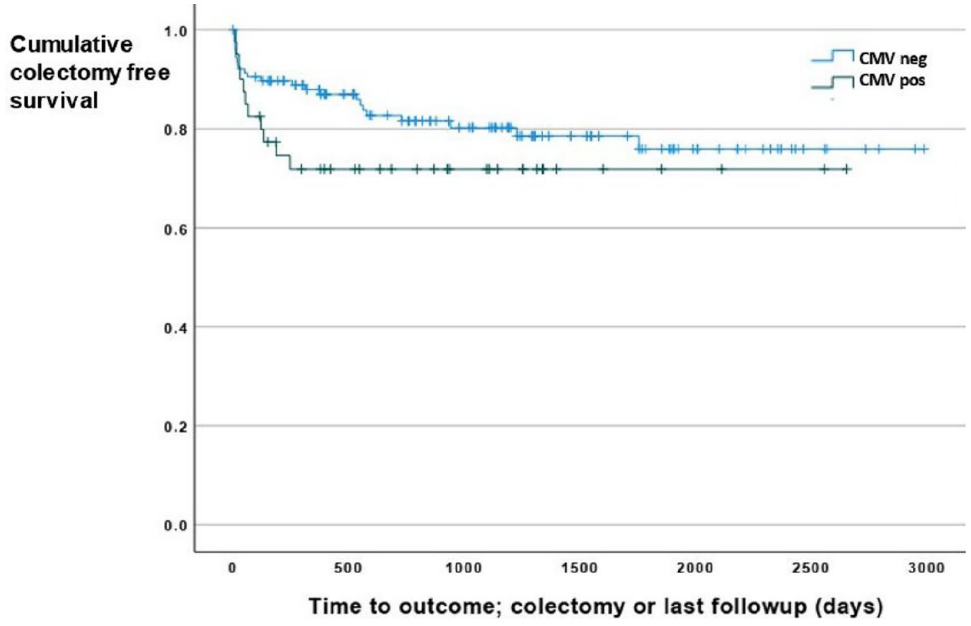

Figure 2. Colectomy-free survival based on CMV status in ASUC.
ASUC, acute severe ulcerative colitis; CMV, cytomegalovirus.

Similar to cases with CMV positivity, admission with the first diagnosis of UC (19% *versus* 43%, $p=0.046$) and requirement for rescue therapy (71.4% *versus* 33.1%, $p=0.001$) were the only clinical predictors for CMV reactivation, while the mean length of stay (17.8 *versus* 9.9 days, $p=<0.001$), 30-day readmission rate (23.8% *versus* 5.6%, $p=0.008$) and total readmission rate (52.3% *versus* 27.6%, $p=0.038$) were greater in CMV reactivation but no statistically significant differences in colectomy outcomes were identified. Outcomes were also compared between cases of CMV reactivation and cases with detectable tissue PCR on colonic biopsies but no CMV inclusion bodies on IHC stain (Table 4). No statistically significant differences were found for the length of hospital stay (17.8 *versus* 12.1 days, $p=0.154$), mean total readmission rate (52.3% *versus* 64%, $p=0.485$), 30-day readmission rate (23.8% *versus* 29%, $p=0.681$), total colectomy rate (29% *versus* 29%, $p=0.956$) and mean time to colectomy (102 *versus* 74 days, $p=0.514$). When compared to cases without CMV positivity, those with detectable CMV viral load on tissue PCR without detectable IHC-staining inclusion bodies had higher 30-day (29%

Table 4. Comparison of outcomes in CMV IHC-stain-positive cases *versus* CMV tissue PCR positive but IHC-stain-negative cases.

Variable	CMV IHC-stain positive for viral inclusion bodies ($n=21$)	CMV tissue PCR +ve, IHC-stain negative ($n=14$)	p
Length of hospital stay (days)	17.8	12.1	0.154
Mean readmission rate	52.3%	64%	0.485
30-Day readmission rate	23.8%	29%	0.681
Colectomy rate	29%	29%	0.956
Mean time to colectomy (days)	102	74	0.514

CMV, cytomegalovirus; IHC, immunohistochemistry; PCR, polymerase chain reaction.

versus 5.6%, $p=0.003$) and total readmission rate (52.6% *versus* 27.6%, $p=0.007$). Length of stay (12.1 *versus* 9.8 days), colectomy rate (29% *versus* 18.9%) and mean time to colectomy (74 *versus* 340 days) were numerically worse in those with detectable CMV on tissue PCR but differences did not reach statistical significance.

In total, 20/40 (50%) cases with CMV positivity were treated with antivirals. 14/21 cases with CMV IHC staining inclusion bodies received antivirals, while 6/19 cases with detectable tissue PCR without inclusion bodies received antivirals. In all, 14 received IV ganciclovir at a mean total daily dose of 700 mg (range: 520–1000 mg) for a mean duration of 6 days (range: 3–14). In all, 19 received valganciclovir for the mean duration of 21 days. All received the total daily dose of 1800 mg, and all but one received a treatment duration of a minimum of 14 days. Antiviral dose and duration were determined in conjunction with the involvement of the hospital infectious disease team, with patients with more severe or refractory disease receiving a longer duration of treatment. Those who received antiviral treatment and underwent colectomy were associated with a longer mean time to colectomy (126 *versus* 36 days, $p=0.028$) (Figure 3). Total colectomy rate and colectomy at 30 days and 12 months did not differ based on administration of antivirals (Figure 4). Antiviral treatment was not associated with the difference in length of hospital stay or readmissions.

Discussion

To our knowledge, this is one of the largest studies of CMV in ASUC. This study demonstrates that CMV positivity in ASUC is not associated with a significantly increased risk of colectomy, but may confer the risk of longer hospital stay, greater need for rescue therapy and higher rate of readmissions.

Previous data characterizing the impact of CMV on outcomes in ASUC, and the role of antiviral therapy, have been heterogeneous and conflicting. There is difficulty in differentiating the presence of CMV in steroid-refractory ASUC as being either pathogenic or an insignificant bystander.[12] As such there is disagreement on the clinical significance of CMV viremia and tissue CMV DNA *via* PCR in UC. Consensus statements published by Chen *et al.*[6] recommend diagnosis of CMV colitis based on colonic biopsy, histology and IHC supported by tissue and plasma PCR. The sensitivity of CMV viremia with tissue diagnosis of CMV ranges from 18% to 47%.[13,14] However, a high cut-off value for peripheral blood CMV PCR of 1150 copies/mL has been shown to increase the specificity for CMV colitis to 78.9%.[15] The significance of detectable tissue viral load *via* PCR has also not been clearly elucidated, especially in the absence of viral inclusion bodies. Other studies have suggested it likely represents low-level reactivation or latent CMV infection.[16] In our data, a comparison of outcomes in those with tissue PCR positivity that did not have viral inclusion bodies on histopathology nevertheless demonstrated similar outcomes compared to those with positive CMV PCR and viral inclusions. Other clinical and biochemical measures of disease severity outlined in this study and endoscopic extent and severity did not differ based on the presence of CMV. This suggests that CMV positivity, either *via* detectable CMV PCR and/or inclusion bodies, is not always a

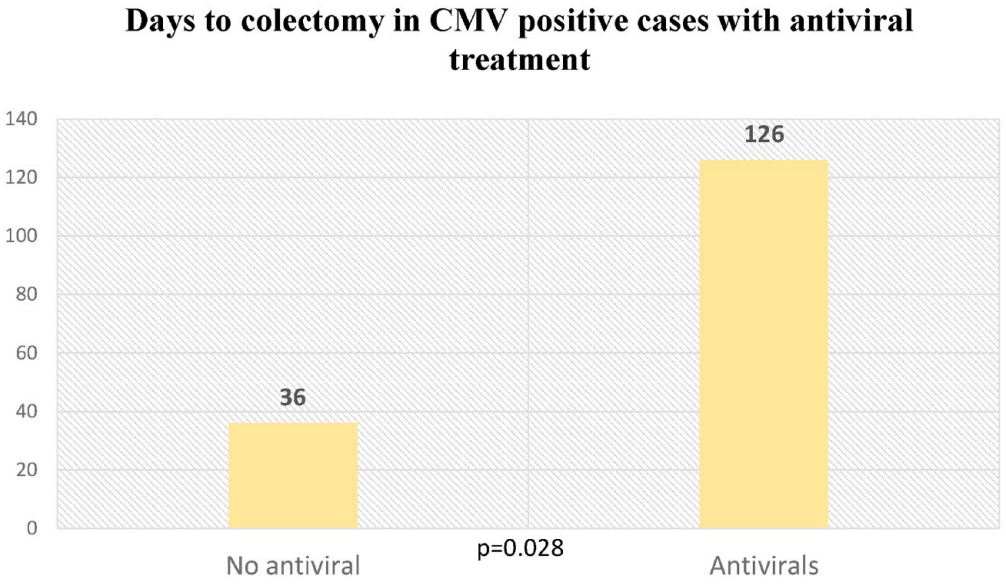

Figure 3. Time to colectomy (days) in CMV with antiviral treatment ($n = 40$).
CMV, cytomegalovirus.

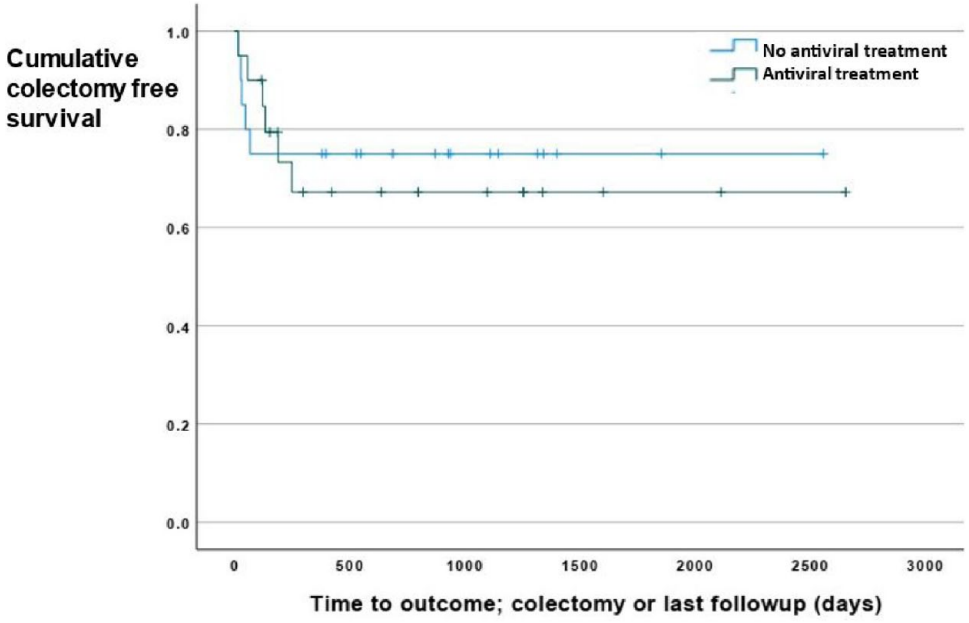

Figure 4. Colectomy-free survival with antiviral treatment among CMV-positive ASUC patients.
ASUC, acute severe ulcerative colitis; CMV, cytomegalovirus.

surrogate marker of more severe UC and should be considered a clinically significant factor that may result in worse outcomes. However, differences in outcomes between those with detectable tissue PCR only compared to those with detectable CMV-IHC staining inclusions are skewed by a higher proportion of antiviral use among the latter group; therefore, it is difficult to make firm conclusions without controlling for this variable.

Emerging data have identified quantitative viral load in colonic tissue as a more reliable indicator of the pathogenicity of CMV in UC. This may explain the conflicting results in previous studies.

A lower viral load is less likely to affect the disease course, while a higher viral load in colonic tissue may induce a greater mucosal inflammatory burden, leading to a lower response to conventional treatment and worse outcomes. Roblin *et al.*[17] reported a favourable response to immunosuppression in patients with tissue viral load <250 copies/mg, while viral load >250 copies/mg was predictive of resistance to three successive lines of treatment. Zagorowicz *et al.*[18] found no significant difference in risk of colectomy or colectomy-free survival based on the presence of CMV diagnosed in all patients *via* IHC, but on subgroup analysis, those with >5 IHC-positive cells had a higher rate of colectomy (33.3% *versus* 11.8%) and lower colectomy-free survival. However, tissue quantitative CMV PCR and quantification of IHC-positive cells are not widely performed outside of research settings, including in our centres. This may therefore affect the reliability of CMV positivity as a clinically significant finding in our study necessitating the use of clinical and qualitative results to guide clinical decision-making on when to treat positive cases.

In our study, the prevalence of CMV positivity in ASUC was 24%, though this may be under-representative as only 27% of patients with ASUC had testing for blood CMV PCR, 56.9% had testing for tissue CMV PCR and 76% had IHC staining on colonic biopsies. This may reflect a lack of compliance to, or insufficient awareness of guidelines recommending the exclusion of CMV in ASUC,[8] and the diagnostic modalities required to do so, among physicians in our study centres. Among colonic biopsies that had IHC staining for CMV performed, 16.5% had viral inclusion bodies detected. This is consistent with a reported prevalence of 16–36% from previous studies across patients with UC of varying severity.[5,19,13] Previous studies have significant variation in findings for predictors of CMV positivity in UC. Kojima *et al.*[20] found, in a study of 126 colectomy specimens, age at the time of operation to be the only risk factor for CMV positivity. Maher *et al.*[21] and Kishore *et al.*[22] reported female gender, pancolitis and active inflammation on histology as independent risk factors. In our study, we found prior steroid, immunomodulator and biologic exposure on univariate analysis to be associated with a higher risk of CMV positivity, while the first presentation of UC carried a lower risk. However, the multivariate analysis only found previous steroid exposure to remain a significant predictor. These findings are likely suggestive of the association between CMV positivity and previous immunosuppression exposure. Other studies have found steroid exposure to be associated with greater CMV colitis risk, particularly exposure equal to or greater than 3 months at a dose equal to or greater than 10 mg/day.[23,24] Criscuoli identified CMV *via* colonic biopsies in 33% of patients admitted with flares of steroid-resistant UC, compared to 10% in patients with steroid-responsive UC. A meta-analysis by Lv *et al.*[25] also found a greater association between steroid-resistant UC among CMV-positive patients (52.9%) compared to CMV-negative patients (30.2%). Unfortunately, given the retrospective nature of our study, data on the exact duration of treatment was incomplete and not available for analysis.

Nowacki *et al.*[26] developed a novel risk prediction score for CMV positivity based on risk factors of clinical disease activity, disease extent, disease duration, use of steroids and use of anti-TNF agents. However, this score has not yet been validated for routine clinical practice, and the heterogeneity of risk factors identified in previous studies indicates that these cannot be reliably used to screen for which patients require colonic biopsies for CMV. Indeed, our study identified four patients with CMV positivity in the absence of prior UC diagnosis or immunosuppressive therapy. This therefore supports current ECCO guidelines for obtaining colonic biopsies in all patients hospitalized with ASUC for exclusion of CMV.[8]

During the inpatient stay, CMV positivity in our study was associated with a higher need for rescue therapy with either infliximab and/or cyclosporine, greater length of hospital stay and higher number of readmissions. However, no difference in overall risk of colectomy or colectomy-free survival was found. A retrospective study of 149 patients with ASUC by Lee *et al.*[27] also found a greater requirement for rescue therapy (OR 2.28) with CMV but not a significant difference in inpatient colectomy rate. Oh *et al.*[28] similarly found a higher rate of readmission among hospitalized patients with UC flares with CMV (39% *versus* 16.3%). Other studies such as Delvincourt *et al.*[29] have shown no significant impact of CMV on disease severity, colectomy rate or length of

hospital stay. By contrast, studies such as Yoshino *et al.*[30] and Schenk *et al.*[31] found the risk of colectomy and colectomy-free survival to be worse in patients with concomitant CMV.

Current ECCO guidelines recommend the use of antiviral therapy in cases of severe steroid-resistant UC with detectable CMV. Existing evidence supporting antiviral use generally is more robust for severe cases of UC,[32,33] but overall strength of evidence remains poor due to lack of randomized prospective studies. There are also no studies that validate a specific antiviral medication or treatment duration.

A meta-analysis from Shukla *et al.*[34] of 333 patients found no difference in risk of colectomy after antiviral therapy among all patients with CMV positivity in UC (OR: 0.92), but subgroup analysis of eight studies found significantly lower colectomy risk in those with steroid-refractory UC (OR: 0.2). Similarly, Kim *et al.*[35] found in a prospective multicentre study of 72 patients with CMV in UC, 79% of steroid-refractory UC cases clinically improved with ganciclovir. By contrast, Delvincourt *et al.*[29] found in a retrospective case–control study that antiviral treatment did not affect the 3-month colectomy rate (15% *versus* 10%, $p = 0.9$) or length of hospital stay, even in a subgroup analysis of patients with severe UC flare only. A study by Al-Zafiri *et al.*[36] of 31 hospitalized patients with IBD and UC also did not find antiviral therapy to reduce colectomy risk.

Viral burden in colonic tissue has similarly been found to correlate with the likelihood of response to antiviral therapy, though a viral load threshold to commence antiviral treatment has not been established. Nguyen *et al.*[37] found antiviral treatment in patients with a higher number of IHC-staining inclusion bodies resulted in a lower rate of colectomy (44%) compared to untreated patients (83%). Okahara *et al.*[38] found patients with high tissue CMV viral load (median 16,000 copies/μg) may respond to antiviral treatment without additional UC therapy, whereas patients with low viral load (<5500 copies/μg) would benefit from intensifying UC therapy only, but firm conclusions were limited by small sample size. In our study, we were also unable to make any appreciable conclusions on the benefit of antiviral therapy in tissue PCR positivity *versus* IHC stain positivity in reducing the risk of colectomy. We did interestingly find antiviral use in CMV positivity to be associated with a longer time to colectomy of nearly 90 days. This can allow for measures to optimize surgical outcomes such as controlling inflammation, improving nutrition and weaning steroids.[39] However, due to the limited patient numbers in our study receiving antiviral therapy and the absence of clear criteria for treatment or a standardized treatment protocol for antiviral administration, our findings as such are insufficient to justify the use of antiviral therapy in all cases of CMV positivity in ASUC, and further randomized studies that prospectively compare surgical outcomes with antiviral treatment are required.

Our study was limited by several factors. Our data were obtained retrospectively from electronic medical records of public hospitals. Lack of a centralized database may result in under-recognition of hospitalizations, colectomies and other outcomes outside of shared hospital networks. The retrospective nature of our study also means there is significant heterogeneity in available data affecting outcomes. Examples include differences in clinical practice, expertise and resources available across different centres for determining inpatient management of ASUC, appropriate diagnostic workup of CMV and determination of the need for colectomy, duration of hospital admission and readmission. As previously mentioned, a lack of consistent testing for blood and tissue PCR, and inconsistent IHC staining for viral inclusion bodies likely underestimated the incidence of CMV positivity in our ASUC cases. There was also no quantification of CMV viral load from colonic samples, limiting our ability to assess outcomes in a subgroup of patients with high tissue viral load. Determination of the benefit of antiviral therapy was also limited by the retrospective nature of the study as indications for antiviral therapy and regimens were not standardized, and antiviral use was often at the discretion of treating physicians. Larger protocolized prospective studies will be required to investigate this further.

Conclusion

In conclusion, CMV positivity did not significantly increase the need for colectomy in ASUC, but its presence may still have an impact on secondary outcomes such as greater length of stay,

more frequent readmissions and the need for inpatient rescue therapy. Given only one predictor was found for CMV positivity (prior steroid exposure) in this study, all patients with ASUC should still undergo endoscopy and colonic biopsies for CMV detection. The role of antiviral use for CMV positivity in ASUC remains unclear, but our finding of longer time to colectomy in those who received antiviral use may reflect an important benefit in its use. Further research *via* prospective studies is required to more clearly determine the benefits of anti-virals among UC patients with concomitant CMV infection.

Declarations

Ethics approval and consent to participate

This study was approved by the Western Sydney Local Health District Human Research Ethics Committee (2022/ETH01216). Consent for patient participation/data collection in this study was not required given its retrospective nature and negligible risk pathway for ethics approval; no direct patient contact was sought during the collection of data.

Consent for publication

Not applicable.

Author contributions

Dazhong Huang: Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Validation; Writing – original draft; Writing – review & editing.

Michael Rennie: Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Alicia Krasovec: Data curation; Investigation.

Shyam Nagubandi: Data curation; Investigation.

Sichang Liu: Data curation; Investigation.

Edward Ge: Data curation; Investigation.

Barinder Khehra: Data curation; Investigation.

Michael Au: Data curation; Investigation.

Shobini Sivagnanam: Methodology; Writing – review & editing.

Vu Kwan: Project administration; Supervision.

Claudia Rogge: Project administration; Supervision.

Nikola Mitrev: Data curation; Investigation; Methodology; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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