Journal of Inflammation Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

The Impact of Cytomegalovirus Infection on Ulcerative Colitis Relapse: A Multicenter Retrospective Cohort Study

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Purpose: Cytomegalovirus (CMV) infection exacerbates intestinal inflammation in ulcerative colitis (UC) patients, yet the effect of CMV infection on UC relapse has not been fully elucidated. This study aimed to investigate the impact of CMV infection on UC relapse and identify associated risk factors.

Patients and Methods: This multicenter retrospective cohort study included UC patients who visited research centers from January 2016 to December 2020. Univariate and multivariate Cox regression analyses were conducted to explore risk factors for UC relapse. Propensity score matching was used to balance the differences in the clinical characteristics between the groups.

Results: A total of 298 UC patients participated in this study, including 19 with CMV colitis, 37 with CMV viremia, and 242 CMV-negative patients. The 2-year cumulative recurrence rate was higher in patients with CMV colitis than that in CMV-negative patients (84.21% vs 51.65%, $p = 0.01$). Univariate and multivariate Cox regression analyses confirmed that fecal calprotectin ≥ 250 μg/g, Montreal classification E3, CMV colitis, duration > 48 months, and serum albumin < 30 g/L were independent risk factors for UC relapse at 2 years, whereas the use of biologics for induction of remission was identified as an independent protective factor.

Conclusion: Our study suggests that the risk of relapse increases among UC patients with CMV colitis over two years. Risk factors for UC relapse at 2 years include fecal calprotectin ≥ 250 μg/g, Montreal classification E3, CMV colitis, UC duration > 48 months, and albumin < 30 g/L, whereas the use of biologics during induction is a protective factor.

Plain Language Summary: Patients with ulcerative colitis and cytomegalovirus colitis are at a higher risk of relapse over a 2-year period than those who are CMV negative. Additionally, we identified several risk factors for UC relapse at 2 years, including fecal calprotectin ≥ 250 μg/g, Montreal classification E3, CMV colitis, duration of UC ≥ 48 months, and albumin < 30 g/L, whereas the administration of biologics during remission induction contributed to reducing UC relapse.

Keywords: Ulcerative colitis, cytomegalovirus colitis, relapse, risk factors

Introduction

Ulcerative colitis (UC) is a chronic, recurrent, and non-specific inflammatory bowel disease that often leads to adverse outcomes such as diminished intestinal function, reduced quality of life, and increased risk of colorectal cancer.[1,2] Several factors contribute to the risk of UC relapse, including young age at diagnosis, extraintestinal manifestations, and the use of glucocorticoids.[3–5] Cytomegalovirus (CMV), a member of the Herpesviridae family, is an opportunistic

Received: 23 May 2024
Accepted: 13 November 2024
Published: 19 November 2024

pathogenic virus.[6] In UC patients, CMV infection and exacerbation of intestinal inflammation are heightened owing to compromised intestinal immune barriers, glucocorticoid and immunosuppressive use, malnutrition, and extensive lesions.[7,8] Previous studies have reported CMV reactivation rates of 21–34% in acute severe UC and 32–36% in refractory UC.[9,10] Patients with UC who experience CMV infection are at an elevated risk of glucocorticoid resistance, colectomy, and mortality.[11–13] However, the relationship between CMV infection and UC relapse remains controversial topic in clinical management. Therefore, our study aimed to investigate the effect of CMV infection on UC relapse and explore the risk factors associated with UC relapse.

Materials and Methods

Patients

This multi-center retrospective cohort study screened UC patients who visited research centers between January 2016 and December 2020. The participating centers included the First Affiliated Hospital with Nanjing Medical University, Second Affiliated Hospital of Soochow University, and Northern Jiangsu People's Hospital. This study was approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (2022-SR-253. A1). All UC patients in our study underwent CMV-related examinations and were excluded if they had immunodeficiency, history of colectomy, or incomplete clinical data. Demographic, clinical, and medical examination data were collected from medical records, and prognostic information was gathered for at least 24 months post-enrollment.

Definition of CMV Infection and Patient Grouping

CMV viremia was defined as a peripheral blood CMV DNA level > 500 copies /ml.[14] CMV colitis was defined by characteristic endonuclear features via hematoxylin-eosin staining or intracellular inclusion bodies and/or CMV-specific antigens identified by immunohistochemistry, accompanied by clinical symptoms (Figure 1).[15] In our study, patients with CMV colitis and/or CMV viremia were included in CMV-positive group, and the CMV negative patients were included in the CMV-negative group. In addition, CMV-positive patients were divided into the CMV colitis group (patients with CMV colitis) and the CMV viremia group (patients with CMV viremia). Furthermore, UC patients with concurrent CMV colitis and CMV viremia were included in the CMV colitis group.

Definition of UC Remission and Relapse

UC clinical remission was defined as the modified Mayo score ≤ 2 with no single subscore > 1.[16] UC relapse was defined as the modified Mayo score ≥ 3 and/or the need for additional drug-induced remission and/or hospitalization for UC.[17] Early recurrence was defined as recurrence within 3 months after remission of UC.[18] Incidental recurrence was defined as only 1 recurrence within 1 year after remission of UC.[18] Frequent recurrence was defined as ≥ 2 times/year after remission of UC.[18] Persistent non-remission was defined as UC symptoms that continued to be active and could not be relieved.[18] The date of onset of symptoms of UC activity was considered the date of recurrence, while recurrence time was defined as the time between the date of the first clinical remission and that of the first clinical recurrence after enrollment.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation or median and interquartile range, analyzed using t-tests or Mann–Whitney *U* tests. Categorical variables were presented as numbers and compared using Chi-square or Fisher's exact tests. Univariate and multivariate Cox regression analyses were used to identify the risk factors for UC relapse. Propensity score matching (PSM) using the R package "Matchit" was employed for balancing differences in clinical characteristics between the groups. Kaplan-Meier analysis and log-rank tests were used to assess cumulative recurrence rates. Statistical significance was set at bilateral $p < 0.05$, and SPSS 26.0 (IBM, New York, USA) and R 4.2.2 (Posit Software, Boston, USA) were used for analysis.

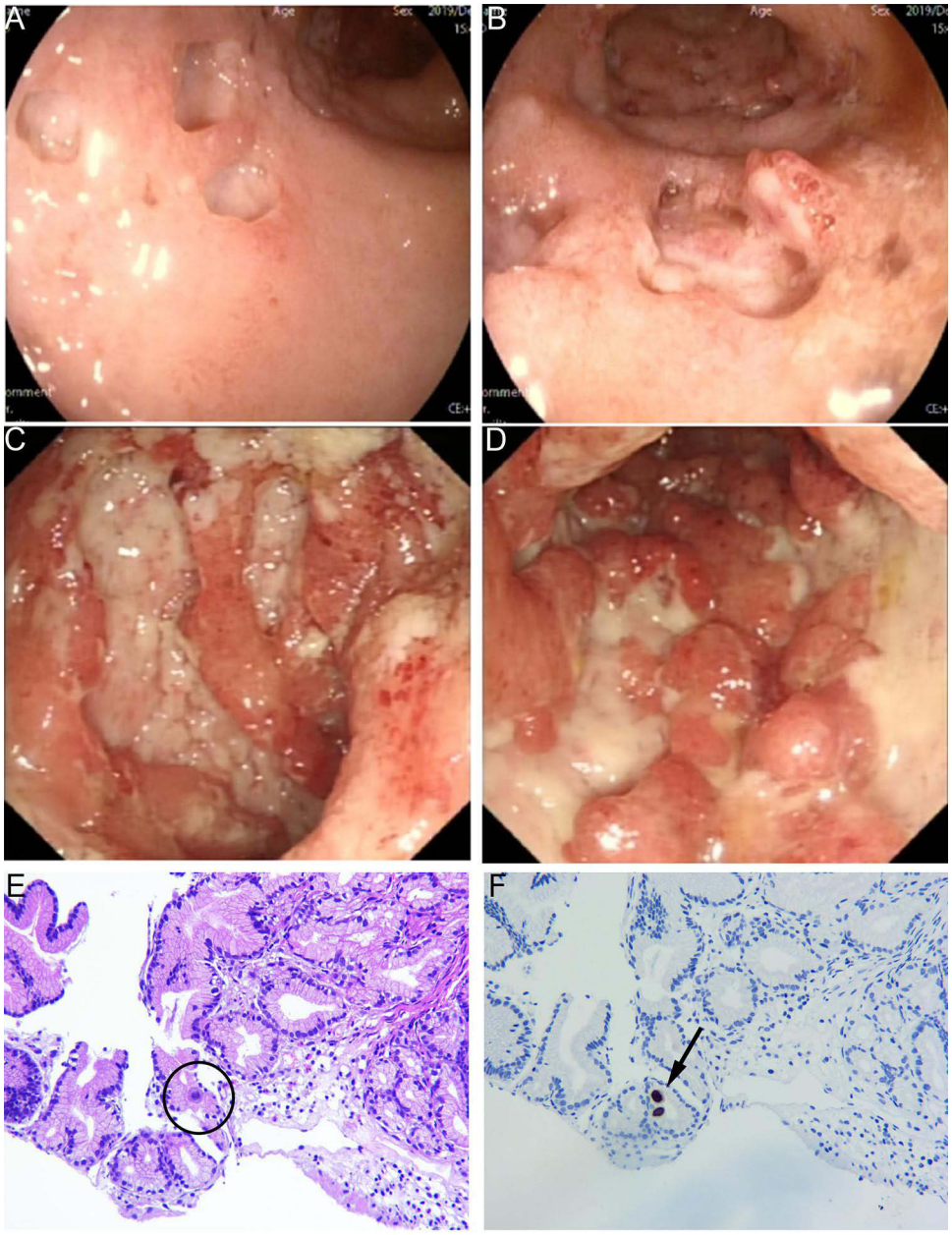

Figure 1 Endoscopic and pathological findings of UC patients with CMV colitis.
Notes: (**A**) Punchedout ulceration. (**B**) Punchedouted ulceration. (**C**) Longitudinal ulceration. (**D**) Cobblestone-like appearance. (**E**) Histological hematoxylin and eosin staining of CMV inclusion bodies (owl's eye) (black circles). (**F**) Immunohistochemical staining for cytomegalovirus (black arrow).

Results

Clinical Characteristics

A total of 351 UC patients who visited research centers and underwent CMV-related examinations from January 2016 to December 2020 were screened, of which 53 UC patients (6 UC patients had a history of colectomy before enrollment, and 47 UC patients had incomplete clinical data) were excluded. Finally, our study included 298 UC patients, consisting of 19 with CMV colitis, 37 with CMV viremia, and 242 CMV-negative patients (Figure 2).

In our study, the mean ages of the CMV-positive and CMV-negative patients were 48.71 ± 16.97 and 44.73 ± 16.76 years old, respectively, with 53.57% and 49.59% of the patients in each group being female. Moreover, significant differences between the two groups were observed in the duration of disease (1–6 months: 42.86% vs 23.14%; 7–12

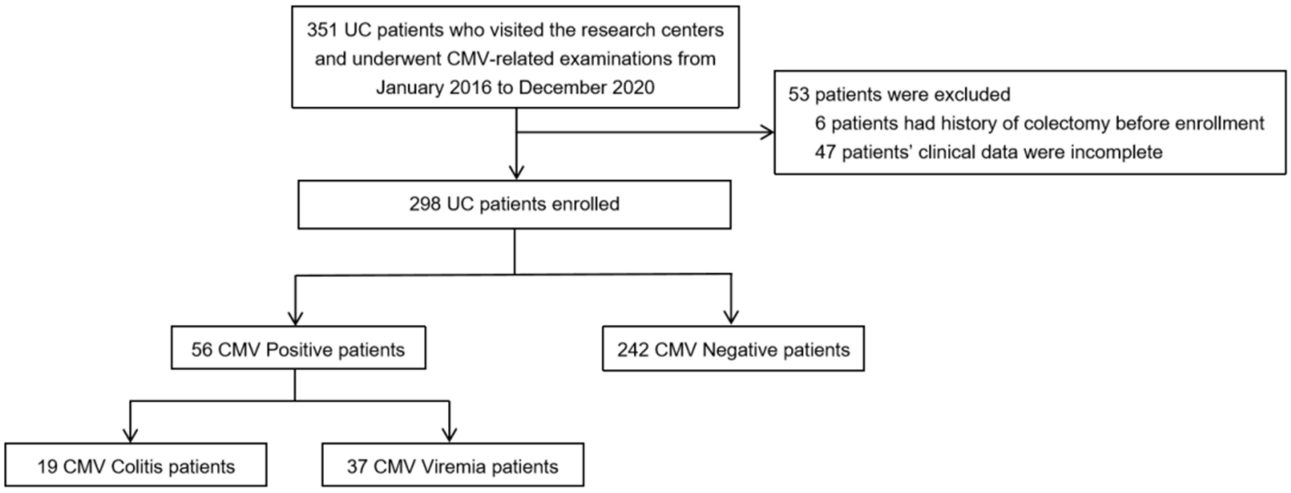

Figure 2 Flowchart of this study.

months: 26.79% vs 29.75%; 13–48 months: 14.29% vs 26.03%; > 48 months: 16.07% vs 21.07%, $p = 0.02$), the Montreal classification (E1: 1.79% vs 11.57%; E2: 14.29% vs 25.62%; E3: 83.93% vs 62.81%, $p = 0.01$), smoking history (21.43% vs 11.16%, $p = 0.04$), the modified Mayo score (0–2: 0.00% vs 4.96%; 3–5: 0.00% vs 14.88%; 6–10: 42.86% vs 52.48%; 11–12: 57.14% vs 27.69%, $p < 0.01$), albumin (ALB) (< 30 g/L: 32.14% vs 16.53%; ≥ 30 g/L: 67.86% vs 83.47%, $p = 0.01$), C-reactive protein (CRP) (< 10 g/L: 32.14% vs 54.13%; ≥ 10 g/L: 67.86% vs 45.87%, $p < 0.01$), and fecal calprotectin (FC) (< 250 ug/g: 67.86% vs 45.87%; ≥ 250 ug/g: 3.57% vs 25.62%, $p < 0.01$) (Table 1).

Table 1 Demographics, and Clinical Characteristics of the CMV Positive and CMV Negative Patients

		CMV Positive (n = 56)	CMV Negative (n = 242)	Statistics	*p* value
Age, years, mean ± SD		48.71 ± 16.97	44.73 ± 16.76	1.60	0.13
Sex, n (%)	Male	26 (46.43)	122 (50.41)	0.29	0.59
	Female	30 (53.57)	120 (49.59)		
Duration of disease, months, n (%)	1–6	24 (42.86)	56 (23.14)	9.68	0.02
	7–12	15 (26.79)	72 (29.75)		
	13–48	8 (14.29)	63 (26.03)		
	>48	9 (16.07)	51 (21.07)		
Smoking, n (%)		12 (21.43)	27 (11.16)	4.22	0.04
Montreal, n (%)	E1	1 (1.79)	28 (11.57)	10.00	0.01
	E2	8 (14.29)	62 (25.62)		
	E3	47 (83.93)	152 (62.81)		
Extraintestinal, n (%)		6 (10.71)	38 (15.70)	0.90	0.34
Modified Mayo, n (%)	0–2	0 (0.00)	12 (4.96)		<0.01
	3–5	0 (0.00)	36 (14.88)		
	6–10	24 (42.86)	127 (52.48)		
	11–12	32 (57.14)	67 (27.69)		
Laboratory parameters					
ALB, g/L, n (%)	<30	18 (32.14)	40 (16.53)	7.07	0.01
	≥30	38 (67.86)	202 (83.47)		
CRP, mg/L, n (%)	<10	18 (32.14)	131 (54.13)	8.80	<0.01
	≥10	38 (67.86)	111 (45.87)		
FC, ug/g, n (%)	<250	2 (3.57)	62 (25.62)	11.83	<0.01
	≥250	54 (96.43)	180 (74.38)		

Notes: Data are expressed as the mean ± standard deviation (SD) or number (%).
Abbreviations: ALB, Albumin; CRP, C-reactive protein; FC, Fecal calprotectin; 5-ASA, 5-Amino salicylic acid.

During the induced remission, the utilization rate of 5-Aminosalicylic acid (5-ASA) did not differ significantly between the CMV-positive and CMV-negative groups (96.43% vs 99.59%, $p = 0.09$). However, the utilization rates of glucocorticoids (62.50% vs 28.51%, $p < 0.01$) and biologics (23.21% vs 5.79%, $p < 0.01$) were significantly higher in the CMV-positive group than in the CMV-negative group. No significant differences were observed between the proportions of patients in the CMV-positive and CMV-negative groups who used 5-ASA (87.50% vs 95.04%, $p = 0.06$), biologics (23.21% vs 23.14%, $p = 1.00$), or azathioprine (5.36% vs 2.07%, $p = 0.17$) during maintained remission (Table 2).

Comparison of Recurrence in CMV Colitis Group and CMV Negative Group

The number of patients in the CMV-negative group was significantly higher than that in the cytomegalovirus colitis group (Table S1). To delve deeper into the impact of CMV colitis on UC relapse, we employed the 1:4 PSM method to mitigate the differences in patient numbers and clinical characteristics between the two groups and diminish the influence of variables and confounding factors unrelated to CMV colitis on UC relapse. Balanced variables included age, sex, disease duration, smoking, Montreal classification, extraintestinal manifestations, modified Mayo score, ALB, CRP level, and FC. After 1:4 PSM, the CMV colitis group consisted of 19 patients, whereas the CMV-negative group included 76 patients; no significant differences were observed between the two groups (Table S1).

Before PSM, during the 1-year follow-up, 12 of the 19 UC patients in the CMV colitis group relapsed, resulting in a 1-year cumulative recurrence rate of 63.16%. In comparison, 100 of 242 UC patients in the CMV-negative group relapsed (41.32%) during the same period. Extending the observation period to two years, 16 of 19 patients with CMV colitis relapsed (84.21%), whereas 125 of 242 CMV-negative patients relapsed (51.65%). The 2-year cumulative recurrence rate was significantly higher in the CMV colitis group than in the CMV-negative group (84.21% vs 51.65%, Log-rank, $p = 0.01$). Additionally, there were no significant differences in recurrence rates between the two groups for various recurrence types, including early recurrence (36.84% vs 20.25%, $p = 0.14$), incidental recurrence (47.37% vs 32.23%, $p = 0.27$), frequent recurrence (15.79% vs 9.09%, $p = 0.41$), and persistent non-remission (21.05% vs 10.33%, $p = 0.24$) (Table 3).

After PSM, the 2-year cumulative recurrence rate of CMV colitis group was significantly higher than that of CMV-negative group (84.21% vs 53.95%, Log-rank, $p = 0.04$), but there was no significant difference in 1-year cumulative recurrence rate between CMV colitis group and CMV-negative group (63.16% vs 48.68%, Log-rank, $p = 0.27$). In addition, there were no significant differences in the recurrence rates of different relapse types between the two groups. Including early recurrence (36.84% vs 26.32%, $p = 0.53$), incidental recurrence (47.37% vs 48.68%, $p = 1.00$), frequent recurrence (15.79% vs 6.58%, $p = 0.20$) and persistent non-remission (21.05% vs 11.84%, $p = 0.29$) (Table 3).

Comparison of Recurrence in CMV Viremia Group and CMV Negative Group

Differences in clinical characteristics were observed between the CMV viremia and CMV negative groups (Table S2). To delve deeper into the impact of CMV viremia on UC relapse, we employed the 1:1 PSM method to mitigate variations in clinical characteristics between the two groups and diminish the influence of variables and confounding factors unrelated

Table 2 Treatment Details of the CMV Positive and CMV Negative Patients

	CMV Positive (n = 56)	CMV Negative (n = 242)	Statistics	*p* value
Induction of remission				
5-ASA, n (%)	54 (96.43)	241 (99.59)		0.09
Glucocorticoid, n (%)	35 (62.50)	69 (28.51)	23.12	<0.01
Biologics, n (%)	13 (23.21)	14 (5.79)	16.77	<0.01
Maintenance of remission				
5-ASA, n (%)	49 (87.50)	230 (95.04)		0.06
Biologics, n (%)	13 (23.21)	56 (23.14)	0.00	1.00
Azathioprine, n (%)	3 (5.36)	5 (2.07)		0.17

Notes: Infliximab, adalimumab, and vedolizumab are included in the biologics.

Table 3 Recurrence of the CMV Colitis and the CMV Negative Patients Before and After PSM

	Before PSM			After PSM		
	CMV Colitis (n = 19)	**CMV Negative (n = 242)**	***p* value**	**CMV Colitis (n = 19)**	**CMV Negative (n = 76)**	***p* value**
Type of recurrence, n (%)						
Early recurrence	7(36.84)	49(20.25)	0.14	7(36.84)	20(26.32)	0.53
Incidental recurrence	9(47.37)	78(32.23)	0.27	9(47.37)	37(48.68)	1.00
Frequent recurrence	3(15.79)	22(9.09)	0.41	3(15.79)	5(6.58)	0.20
Persistent no-remission	4(21.05)	25(10.33)	0.24	4(21.05)	9(11.84)	0.29
Cumulative recurrence, n (%)						
1-year cumulative recurrence	12(63.16)	100(41.32)	0.05	12(63.16)	37(48.68)	0.27
2-year cumulative recurrence	16(84.21)	125(51.65)	0.01	16(84.21)	41(53.95)	0.04

to CMV viremia on UC relapse. Balanced variables included age, sex, disease duration, Montreal classification, modified Mayo score, CRP level, and FC. After 1:1 PSM, the CMV viremia group consisted of 37 patients, whereas the CMV-negative group included 37 patients; no significant differences were observed between the two groups (Table S2).

After PSM, during the 1-year follow-up, 17 of 37 patients in the CMV viremia group experienced relapse (45.95%), whereas 15 of 37 CMV-negative patients relapsed (40.54%). Throughout the 2-year follow-up period, 21 of 37 CMV viremia patients experienced relapse (56.76%) compared to 22 of 37 CMV-negative patients (59.46%). There were no significant differences in the 1-year and 2-year cumulative recurrence rates between the CMV viremia and CMV negative groups. Additionally, there were no significant differences in recurrence rates between the two groups for various recurrence types, including early recurrence (24.32% vs 18.91%, $p = 0.78$), incidental recurrence (35.14% vs 35.14%, $p = 1.00$), frequent recurrence (5.41% vs 13.51%, $p = 0.43$), and persistent non-remission (16.22% vs 10.81%, $p = 0.73$) (Table S3).

Comparison of Recurrence in CMV Positive Group and CMV Negative Group

There were discernible disparities in clinical characteristics between the CMV-positive and CMV-negative groups (Table S4). To mitigate these discrepancies, we employed 1:2 PSM. Balanced variables included age, sex, disease duration, smoking history, Montreal classification, modified Mayo score, ALB, CRP, and FC. After 1:2 PSM, the CMV-positive group comprised 56 patients, whereas the CMV-negative group included 112 patients; no statistically significant disparity was observed between the two groups (Table S4).

After PSM, at the 1-year follow-up, 29 of the 56 patients in the CMV-positive group experienced relapse (51.79%), whereas 54 of the 112 CMV-negative patients relapsed (48.21%). Over the 2-year follow-up period, 37 of 56 CMV-positive patients experienced relapse (66.07%) compared to 67 of 112 CMV-negative patients (59.82%). No statistically significant difference was observed in the cumulative recurrence rates at both the 1-year and 2-year marks between the CMV-positive and CMV negative groups. Moreover, there were no notable differences in the recurrence rates between the two groups for various recurrence types, including early recurrence (28.57% vs 25.89%, $p = 0.85$), incidental recurrence (39.29% vs 38.39%, $p = 1.00$), frequent recurrence (8.93% vs 8.93%, $p = 1.00$), and persistent non-remission (17.86% vs 12.50%, $p = 0.48$) (Table S5).

Risk Factors for UC Relapse

Univariate and multivariate Cox regression analyses were conducted to analyze risk factors for relapse in UC patients, both univariate and multivariate Cox regression analyses were conducted. The univariate Cox regression analysis revealed that FC $\geq$ 250 ug/g (hazard ratio [HR] 4.07, 95% confidence interval [CI] 2.35–7.04, $p < 0.01$), E3 (HR 2.97, 95% CI 1.40–6.32, $p = 0.01$), E2 Montreal Classification (HR 2.43, 95% CI 1.18–4.97, $p = 0.02$), CMV colitis (HR 2.07, 95% CI 1.23–3.45, $p = 0.01$), the duration of disease > 48 months (HR 1.62, 95% CI 1.03–2.54, $p = 0.04$), glucocorticoid (HR 1.54, 95% CI 1.13–2.11, $p = 0.01$), and serum ALB < 30 g/L (HR 1.86, 95% CI 1.31–2.65, $p < 0.01$)

were identified as risk factors for 2-year relapse in UC patients. Additionally, the use of biologics during inducing remission (HR 0.49, 95% CI 0.25–0.96, $p = 0.04$) was recognized as a protective factor for 2-year relapse in UC patients.

Furthermore, multivariate Cox regression analysis confirmed that FC ≥ 250 μg/g (HR 4.37, 95% CI 2.30–8.31, $p < 0.01$), Montreal classification E3 (HR 2.75, 95% CI 1.25–6.03, $p = 0.01$), CMV colitis (HR 2.03, 95% CI 1.16–3.55, $p = 0.01$), disease duration > 48 months (HR 1.74, 95% CI 1.06–2.85, $p = 0.03$), and serum ALB < 30 g/L (HR 1.61, 95% CI 1.05–2.54, $p = 0.03$) were risk factors for 2-year relapse in UC patients. Furthermore, the use of biologics during remission induction (HR 0.21, 95% CI 0.09–0.46, $p < 0.01$) and the use of azathioprine during remission maintenance (HR 0.21, 95% CI 0.06–0.70, $p = 0.01$) were recognized as protective factors for 2-year relapse in UC patients. In summary, the independent risk factors for UC relapse at 2 years included FC ≥ 250μg/g, Montreal classification E3, CMV colitis, duration of disease > 48 months, and serum ALB < 30 g/L, while the independent protective factor was the use of biologics during induction of remission (Table 4) (Figure 3).

Table 4 Univariable and Multivariable Cox Regression Analysis of the Risk of Relapse of the UC Patients

Variable	Univariable	*p* value	Multivariable	*p* value
	HR (95% CI)		HR (95% CI)	
Age	1.00(0.99~1.01)	0.59	1.00(0.99~1.01)	0.72
Sex, Female	0.81(0.60~1.11)	0.19	0.75(0.53~1.06)	0.10
Duration of disease, months				
1–6	1.00		1.00	
7–12	1.04(0.68~1.61)	0.85	0.93(0.58~1.50)	0.78
13–48	1.34(0.87~2.09)	0.19	1.4(0.887~2.22)	0.15
>48	1.62(1.03~2.54)	0.04	1.74(1.06~2.85)	0.03
Smoking	1.12(0.73~1.73)	0.60	0.70(0.43~1.15)	0.16
Extraintestinal	1.21(0.81~1.82)	0.35	1.52(0.99~2.35)	0.06
Montreal				
E1	1.00		1.00	
E2	2.43(1.18~4.97)	0.02	1.63(0.76~3.46)	0.21
E3	2.97(1.40~6.32)	0.01	2.75(1.25~6.03)	0.01
Modified Mayo				
0–2	1.00		1.00	
3–5	1.87(0.54~6.41)	0.32	0.89(0.23~3.48)	0.86
6–10	2.64(0.83~8.35)	0.10	0.78(0.21~3.00)	0.72
11–12	3.14(0.99~10.01)	0.05	0.91(0.22~3.65)	0.89
Laboratory parameters				
ALB<30g/L	1.86(1.31~2.65)	<0.01	1.61(1.05~2.45)	0.03
CRP≥10mg/L	1.06(0.78~1.44)	0.73	0.81(0.57~1.15)	0.23
FC≥250ug/g	4.07(2.35~7.04)	<0.01	4.37(2.30~8.31)	<0.01
CMV status				
CMV negative	1.00		1.00	
CMV viremia	1.16(0.74~1.86)	0.68	1.33(0.78~2.25)	0.30
CMV Colitis	2.07(1.23~3.45)	0.01	2.03(1.16~3.55)	0.01
Induction of remission				
5-ASA	2.28(0.32~16.30)	0.41	0.79(0.09~6.73)	0.83
Glucocorticoid	1.54(1.13~2.11)	0.01	1.28(0.87~1.88)	0.21
Biologics	0.49(0.25~0.96)	0.04	0.21(0.09~0.46)	<0.01
Maintenance of remission				
5-ASA	1.16(0.59~2.28)	0.66	1.76(0.83~3.73)	0.14
Biologics	1.09(0.76~1.56)	0.64	1.47(0.95~2.29)	0.09
Azathioprine	0.60(0.19~1.87)	0.38	0.21(0.06~0.70)	0.01

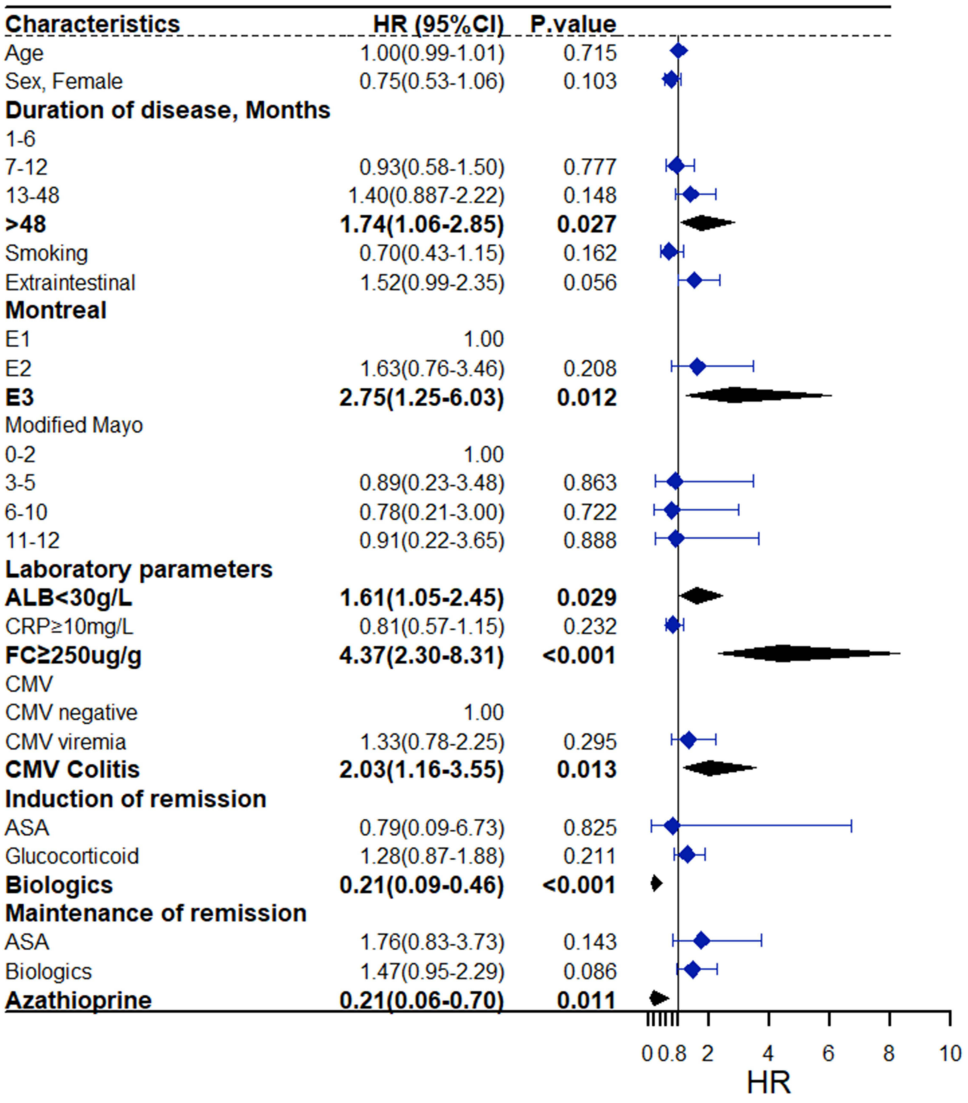

Figure 3 Forest plot of multivariate Cox analysis for 2-year recurrence risk factors in UC patients.

Discussion

The incidence of CMV infection is notably elevated in UC patients.[19] Previous studies have indicated that UC patients experiencing infection are more susceptible to glucocorticoid resistance and colectomy.[20,21] Recurrent relapses of UC and repeated episodes of intestinal inflammation can lead to increased formation of intestinal mucosal scars and affect intestinal function, posing challenges to treatment and impacting patients' quality of life. However, to date, the effect of infection on UC relapse has not been fully elucidated. In our study, with a median follow-up time of 40 months, the overall recurrence rate was 63.42%, and the 1-year and 2-year cumulative recurrence rates for UC patients were 43.29% and 54.36%, respectively, consistent with findings from previous studies.[22,23] The 2-year cumulative recurrence rate was higher in the CMV colitis group than in the CMV-negative group (84.21% vs 51.65%, $p = 0.01$). However, no significant difference was observed in the 1-year and 2-year cumulative recurrence rates between the CMV viremia and CMV negative groups. CMV viremia seemed to have no significant effect on UC relapse, which may be attributed to the limited sample size and follow-up duration. Therefore, close attention should be paid to reducing relapse in UC patients with CMV colitis. However, the effect of CMV viremia on UC relapse requires further prospective studies with larger sample sizes.

Univariate and multivariate Cox regression analyses revealed that CMV colitis was an independent risk factor for UC relapse within 2 years, whereas CMV viremia had no significant impact on UC relapse. Mucosal inflammation in UC patients and the use of immunomodulatory drugs to control disease activity may contribute to intestinal CMV infection, which in turn increases mucosal inflammation, diminishes the effects of glucocorticoids and immunosuppressants, and may increase the risk of UC relapse.[19,21]

Moreover, in our study, univariate and multivariate Cox regression analyses identified a duration of > 48 months, Montreal classification E3, FC ≥ 250 μg/g, and ALB < 30 g/L g/L as independent risk factors for UC relapse. Previous studies have also reported that patients with a longer disease course are more likely to experience relapse.[24,25] The Montreal classification, which is widely used in the clinical categorization of UC patients, is beneficial for prognosis assessment and treatment selection.[26] Emerging research suggests that more extensive lesions are generally associated with higher rates of hospitalization, colectomy, and colorectal cancer.[27,28] Our findings reveal that E3 type UC is a risk factor for UC recurrence, which is consistent with previous reports. FC, a protein released during the inflammatory response following neutrophil activation or necrosis, is widely used to monitor UC disease activity.[29] Compared to colonoscopy, FC is noninvasive and cost-effective. Numerous studies have demonstrated that elevated FC is linked to adverse UC outcomes including disease activity, clinical relapse, and colectomy.[29,30] Our findings suggest that FC ≥ 250 μg/g is associated with an increased risk of UC relapse, consistent with previous reports. ALB, which serves as a marker of UC disease activity, is susceptible to degradation in the presence of inflammatory responses; lower ALB levels typically indicate higher inflammatory factor levels and increased inflammatory activity.[31] A retrospective multi-center study led by Konstantinos Papamichael provided additional evidence that ALB levels below 40 g/L independently predict colectomy in UC patients.[32] Our study found that patients with ALB levels < 30 g/L were at risk of UC relapse. Therefore, it is important to closely monitor ALB levels in UC patients during treatment.

In our study, the use of biologics during remission induction was an independent protective factor against UC relapse. With the advent of the biologics era, UC patients now have a broader array of treatment options. Beyond inducing and maintaining remission, biologics have proven effective in reducing relapse rates and the need for colectomy, thereby improving the prognosis of UC patients.[33] Numerous studies have shown an increased risk of UC relapse after discontinuation of biologics.[34,35] For patients with UC and CMV infection, a comprehensive approach involving supervised treatment and proactive use of biologics during remission induction may significantly reduce the risk of relapse.

In the univariate factor analysis, the effect of azathioprine maintenance remission on UC relapse was not significant, and further multivariate analysis showed that azathioprine maintenance remission was a protective factor for UC relapse. This may be due to the fact that the true effect of azathioprine maintenance remission was masked by other confounding factors in the univariate analysis and the protective factor of azathioprine maintenance remission of UC recurrence was found after eliminating the influence of other factors in the multivariate analysis. The European Organization for Crohn's Disease and Colitis recommends azathioprine to maintain a long-term glucocorticoid-free clinical remission.[36] Sustained azathioprine use in a palliative manner can contribute to reducing relapse rates and enhancing the prognosis of UC patients.

Different recurrence types, such as early recurrence, frequent recurrence, and persistent non-remission, have been shown in studies to be linked to the prognosis of UC patients, influencing outcomes such as colectomy and colorectal cancer.[37,38] Therefore, our study also explored the impact of CMV on various relapse types, including early relapse, incidental relapse, frequent relapse, and persistent non-remission, and revealed that infection had no significant impact on the different recurrence types observed in UC.

Our study marks the first exploration of the impact of infection on UC relapse and the varying prognoses across different infection states. Through the comparison of the UC relapse among groups, such as the CMV colitis group and CMV negative group, and the CMV viremia group and CMV negative group, we aimed to comprehensively assess the influence of infection on UC relapse. Simultaneously, we conducted a preliminary identification of the risk factors associated with UC relapse, establishing a basis for future research by analyzing their interconnections based on the existing literature.

However, it is crucial to acknowledge the limitations of the present study. Despite adopting a multicenter study model, the sample size was limited, and the participants were exclusively from East China. This may have contributed to the absence of significant differences in the results among the various relapse types. Expanding the sample size and diversifying the population distribution could enhance the reliability of our conclusions. Additionally, our study lacked further CMV-related histology in patients without significant CMV-related clinical and endoscopic findings. Thereafter, The gastrointestinal symptoms linked to CMV colitis may impact our evaluation of UC relapse. It is therefore possible that a relapse attributed solely to UC may not reach the level of inflammation necessary to be recognized as such without the influence of underlying CMV-related inflammation. As a result, what might otherwise be considered a mild increase in UC inflammation—one that would typically not qualify as a relapse—could surpass an established threshold of inflammation, thus becoming identifiable as a relapse. To explore this possibility, it would likely be necessary to analyze a significantly larger cohort of patients, taking into consideration the severity of the underlying CMV inflammation. As a result, individuals classified as "non-CMV colitis" may still have an underlying CMV-related colitis. Finally, the inherent limitations of retrospective studies call for validation of our findings through prospective studies.

In conclusion, our study found that UC patients with CMV colitis were more likely to relapse over a 2-year period, whereas CMV viremia did not exert a significant effect on UC relapse. Moreover, the risk factors associated with UC relapse within 2 years included fecal calprotectin ≥ 250 μg/g, Montreal classification E3, CMV colitis, UC duration > 48 months, and ALB < 30 g/L, whereas the administration of biologics during remission induction was identified as a protective factor.

Abbreviations

CMV, cytomegalovirus; UC, ulcerative colitis; HE, hematoxylin-eosin; IHC, immunohistochemistry; ALB, albumin; CRP, C-reactive protein; FC, faecal calprotectin; IQR, interquartile range; SD, standard deviation; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; 5-ASA, 5-aminosalicylic acid.

Ethical Approval

This study was reviewed and approved by independent ethics committees of each center, mainly the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2022-SR-253.A1). Written, informed consent was waived, since this study used retrospective data obtained only from hospital medical records. This study was completed in accordance with the Helsinki Declaration.

Acknowledgments

Special thanks to Professor Tang Shaowen from Nanjing Medical University, Professor Liu Jin from the First Affiliated Hospital of Nanjing Medical University, and Professor Liu Zhihao from Jiangsu Center for Disease Control and Prevention for their support with the statistical analysis of this study.

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; All authors took part in drafting, revising or critically reviewing the article; All authors gave final approval of the version to be published; All authors have agreed on the journal to which the article has been submitted; and all authors agree to be accountable for all aspects of the work.

Funding

Jiangsu Province Hospital (the First Affiliated Hospital of Nanjing Medical University) Clinical Capacity Enhancement Project, JSPH-MB-2022-2; National Natural Science Foundation General Project 82370535 and 82070568; Suzhou Science and Technology Plan (tackling problems in key technologies) SKY2021024; Key medical disciplines of Jiangsu Province (NO ZDXK202206).

Disclosure

The authors declare that they have no conflict of interest.

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