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Latent cytomegalovirus infection does not influence long-term disease outcomes in inflammatory bowel disease, but is associated with later onset of disease

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ABSTRACT

Objectives: Cytomegalovirus (CMV) infection is common in the general population. CMV infection negatively affects disease course in transplant recipients and HIV patients. Whereas primary CMV infections may occur sporadically in seronegative patients, all seropositive patients with inflammatory bowel syndrome (IBD) are at risk for CMV reactivation due to the inflammatory mucosal and use of immunosuppressive medication. It is unclear whether latent CMV infection, and risk of reactivations, influences long-term disease outcomes. In this study, we aim to explore whether CMV infection affects disease outcomes in IBD patients.

Methods: We performed a cross-sectional cohort study with 1404 patients with IBD from a single center. Clinical characteristics and disease outcomes were prospectively collected. We scrutinized CMV serology test results and performed additional CMV serology testing if serum was available.

Results: Out of 699 IBD patients with CMV serology, 303 (43.3%) were seropositive, comparable to the general Dutch population. CMV seropositivity was associated with older age, longer IBD disease duration, non-Western origin, birth outside the Netherlands and a lower educational level (p -values $\leq .004$). CMV seropositivity was not associated with more complicated long-term disease outcomes of IBD (p -values $> .05$). Seropositive patients presented with symptoms and were diagnosed at an older age compared to seronegative patients (p -values $< .01$).

Conclusions: CMV seropositivity does not influence disease outcomes of IBD patients and seems to be associated with a delay in IBD onset. Guidelines regarding CMV screening in patients with IBD are currently based on a low level of evidence. These data support the recommendation that routine CMV serology measurement is not necessary in the clinical care of IBD.

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Introduction


Inflammatory Bowel Disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), is a chronic relapsing immune-mediated disease characterized by inflammation and ulceration of the gut mucosa [1]. In UC, inflammation is generally limited to the mucosal layer of the colon, whereas in CD, inflammation may involve all layers of the gut and may occur throughout the entire gastrointestinal tract [1]. The exact pathogenesis of IBD is complex, but it is likely that a combination of genetic susceptibility and environmental exposure leads to an exaggerated immune response to the luminal microbial load of the gut [2–4].

Cytomegalovirus (CMV), a member of the herpes virus family, is a virus that remains latently present in various tissues and cell types following primary infections. Although primary infections are usually asymptomatic or mild in immunocompetent individuals, immune-deficient individuals, including patients who are being treated with immunomodulating (IM) drugs are prone to developing severe illness, which may include CMV colitis, pneumonitis and even hemophagocytic syndrome [5–7]. Moreover, patients who are not completely immunocompetent remain at risk for developing CMV reactivations, which may cause end-organ disease such as colitis and pneumonitis [8]. Because CMV colitis clinically resembles IBD relapse, the presence of this virus has recently

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been studied in biopsies taken from patients with symptoms that could be caused by either disease [9]. So far research has been inconclusive as to the significance of CMV in biopsies [10]. As CMV may be latently present in mucosal tissues in all seropositive individuals, the simple finding of CMV DNA does not prove causality [11]. Nonetheless, CMV reactivations are likely in IBD patients who are being treated with IM drugs, and cases of treatment-resistant IBD have been reported showing viral replication in biopsies [12–14].

Seroprevalence of CMV varies between 40% and 100% of adults depending on the population studied. A cross-sectional seroprevalence study in the Netherlands showed that small children have the highest chance of acquiring the infection, with 22% of children already being seropositive at the age of 9 and nearly 30% seropositivity at the age of 19. Seroprevalence increases gradually to 45% between 40 and 49 years of age. Compared to many other regions of the world, these percentages are relatively low [10,15,16].

Because all CMV seropositive patients with IBD IM treatment are at risk of reactivation, we investigated if CMV seroprevalence is associated with less favorable outcome of IBD. To answer this question, we determined the serostatus of all patients in a well-characterized, large cohort of IBD patients to evaluate the clinical significance of CMV infection in IBD patients.

Materials and methods

Patient cohort

For this cross-sectional cohort study, we included IBD patients enrolled in the 1000IBD cohort at the University Medical Center Groningen (UMCG), a tertiary referral center in the Netherlands [17]. Detailed demographics and disease characteristics are prospectively collected by treating IBD specialists during the course of ongoing patient care.

Long-term disease outcomes were defined as progression to biological therapy or surgery. We used the Montreal classification to define disease characteristics and complications such as fibrostenotic, penetrating or perianal disease in CD, and the extent and severity of colitis in UC [18].

Next, we identified patients for whom a CMV serology test was performed as part of clinical care (group A). When multiple CMV serology test results were available, the most recent results were used for this study. Subsequently, patients for whom no clinical CMV serology was available, were screened for the availability of previously collected serum samples, stored in our biobank by -80°C (PSI-UMCG [IRB no 08/279]). If available, additional CMV serology tests were performed to minimize potential selection bias (group B).

CMV measurements

All CMV serology tests were performed at the Department of Medical Microbiology, UMCG. Immunoglobulin G antibodies against CMV (anti-CMV IgG) were measured in plasma using the Abbott ARCHITECT CMV IgG test [19]. Anti-CMV IgG $\geq 5\text{U}/\text{mL}$ was used as the cut-off value for CMV seropositivity.

As primary infection in adults is uncommon, the possible effect of CMV results from reactivation of the latent virus [20]. Since only patients with a latent infection are at risk for reactivation, CMV seropositivity can be used as a proxy for evaluation of the role of CMV in the disease course of patients with IBD.

Statistical analysis

We first compared patient characteristics between patients with a clinical CMV serology test (group A) and the remaining cohort (Supplementary Table 1), and between all patients with CMV serology tests (clinical and additional tests; groups A and B) and the remaining cohort (Supplementary Table 2). Next, patient characteristics were compared between seropositive and seronegative patients (Table 1). For categorical variables, Chi-square tests were used and for continuous variables, depending on variable distribution, either one-way ANOVA or Kruskal–Wallis H tests were used. We used multiple logistic regression modeling to estimate the effect (odds ratio (OR) with 95% confidence interval (CI)) of CMV infection on long-term disease outcomes and disease characteristics as described by the Montreal classification. We adjusted for potential confounders including age, sex, ethnicity, country of birth, educational level, history of smoking, disease duration and CMV test groups (A or B) to minimize the possible influence of selection bias. Cases with missing data on the mentioned potential confounders were excluded from the analyses. Linear regression modeling was used to estimate the effect of CMV infection on the age at disease presentation. Linear regression models were adjusted for the potential confounders including sex, ethnicity, country of birth, educational level, history of smoking and CMV test groups (A or B). Model assumptions were met. All P -values were two-sided and p -values $< .05$ were considered significant. SPSS Statistics version 23 (IBM Corp., Armonk, NY) was used to perform statistical analyses.

Table 1. Comparison of baseline characteristics based on CMV status.

		CMV seropositive N: 303 (43.3%)	CMV seronegative N: 396 (56.7%)
Age ^b	Mean (SD)	49.3 (15.7)	41.4 (14.6)
Disease duration ^b	Median (IQR)	14 (9–22)	12 (7–18)
Sex			
Female	<i>n</i> (%)	177 (58.4)	230 (58.1)
Type of IBD			
Crohn's disease	<i>n</i> (%)	169 (55.8)	237 (59.8)
Ulcerative colitis	<i>n</i> (%)	120 (39.6)	140 (35.4)
IBD unidentified	<i>n</i> (%)	14 (4.6)	19 (4.8)
Origin ^b			
Western	<i>n</i> (%)	256 (91.1)	363 (98.4)
Country of birth ^b			
Netherlands	<i>n</i> (%)	250 (86.8)	362 (97.1)
Smoking status ^a			
Ever	<i>n</i> (%)	188 (62.3)	215 (54.4)
Educational level ^b			
Low	<i>n</i> (%)	169 (62.6)	178 (51.1)
High	<i>n</i> (%)	101 (37.4)	170 (48.9)
Age at symptom onset ^b	Median (IQR)	24 (17–40)	21 (15–29)
Age at diagnosis (exact) ^b	Median (IQR)	25 (17–41)	24 (18–33)

CMV: cytomegalovirus; *n*: number; SD: standard deviation; IQR: interquartile range.

^aIndicates significant difference between groups, p -value $< .05$.

^bIndicates significant difference between groups, p -value $< .01$.

Ethical approval and consent to participate

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee. Ethical approval for this study was granted in 2017 (no. 2017/407) as well as for the PSI UMCG biobank in 2008 (no. 2008/279) by the University Medical Center Groningen Ethics Committee. Written informed consent was obtained for all participants of the Biobank.

Results

In total, we obtained CMV serology test results for 699 (49.8%) patients, of which 413 tests (59.1%) were performed as part of clinical care (group A) and an additional 286 tests (40.9%) were performed specifically for this study (group B). Patients for whom CMV serology was measured as part of clinical care (group A) as well as the total group of tested patients (groups A and B) were younger at the time of diagnosis (Montreal A) than patients without CMV test results. Patients with UC for whom CMV serology was measured as part of clinical care had more proximal disease extension and more severe disease (Montreal E and S). The total group (groups A + B) of patients with UC and CD with available CMV serology more frequently progressed to the need for biological therapy, while only group A had a higher surgery rate compared to the remaining patients in our cohort (all *p*-values < .05). There were no differences in surgery rate nor Montreal classification between groups A and B (Supplementary Tables 1 and 2).

CMV seroprevalence and development of IBD

Overall, the CMV seroprevalence in our cohort was 43.3% and comparable between men and women. Seropositive

patients were more likely to be of non-Western origin, born outside the Netherlands, to have a history of smoking and a lower educational level compared to seronegative patients (all *p*-values < .05). Seropositive patients were significantly older (49.3 vs. 41.4 years), and had a longer disease duration (14.0 vs. 12.0 years). There were no associations between CMV infection and subtypes of IBD nor sex.

Remarkably, seropositive patients were 3 years older at onset of symptoms (24.0 vs. 21.0 years), as well as 3 years older at the time of IBD diagnosis (25.0 vs. 24.0 years; both *p*-values < .001, Table 2). The differences remained significant after correcting for confounding factors (age at onset of symptoms [3.62 years, 95% CI 1.86 – 6.28, *p*-value < .001]; age at diagnosis [3.33 years, 95% CI 1.45 – 5.61, *p*-value < .001]). When UC and CD are analyzed separately, this association remains significant only in UC age at onset of symptoms [2.49 years, 95% CI 1.01 – 8.68, *p*-value = .014] and age at diagnosis [2.95 years, 1.74 – 8.77, *p*-value = 0.004], while a trend is visible for CD. The time between onset of symptoms and IBD diagnosis was not associated to CMV seropositivity (*p*-value = .84).

CMV Seropositivity and IBD disease course

CMV seropositivity was not a risk factor for long-term disease outcomes including the need for biological therapy or surgery, nor for a more complicated disease course including fibrostenotic, penetrating or perianal disease in patients with CD, or more proximal disease and severity of colitis in patients with UC (all *p*-values > .10, Table 3).

Discussion

We report a CMV seroprevalence rate of 45% in patients with IBD, which is comparable to the general Dutch population [20]. We replicate known risk factors for CMV

Table 2. Univariate comparison of Montreal classification and disease outcomes based on CMV status.

	Crohn's disease (N: 406)			Ulcerative colitis (N: 260)		
	CMV–	CMV+	<i>p</i> value	CMV–	CMV+	<i>p</i> value
Age at diagnosis			.13			<.01
< 17 yrs	48 (20.3)	24 (14.2)		23 (16.4)	15 (12.5)	
17–40 yrs	153 (64.6)	108 (63.9)		97 (69.3)	62 (51.7)	
> 40 yrs	35 (14.8)	37 (21.9)		20 (14.3)	43 (35.8)	
Disease location			.36			.91
Ileal (L1)	81 (34.2)	59 (34.9)		8 (5.7)	6 (5.0)	
Colonic (L2)	46 (19.4)	33 (19.5)		40 (28.6)	32 (26.7)	
Ileocolonic (L3)	100 (42.2)	75 (44.4)		87 (62.1)	77 (64.2)	
Upper-GI disease (L4)	24 (10.3)	25 (14.8)	.18			
Disease behavior			.27			.88
Inflammation only (B1)	118 (49.8)	82 (48.5)		6 (4.3)	4 (3.3)	
Stricturing (B2)	81 (34.2)	60 (35.5)		29 (20.7)	26 (21.7)	
Penetrating (B3)	33 (13.9)	27 (16.0)		56 (40.0)	40 (33.3)	
Perianal (Bp)	76 (32.6)	55 (32.5)	.99	43 (30.7)	35 (29.2)	
Need for surgery	107 (45.1)	85 (50.3)	.31	34 (24.3)	27 (22.5)	.74
Medication use ^a			.07			.56
Steroids only	18 (7.7)	21 (12.9)		33 (25.2)	28 (24.3)	
Immunosuppressive drugs	55 (23.6)	47 (28.8)		59 (45.0)	59 (51.3)	
Biologicals	160 (68.7)	95 (58.3)		39 (29.8)	28 (24.3)	

MV-OR: multivariate-adjusted odds ratio; 95%CI: 95% confidence interval.

^aAll medication types are analyzed as ever or never used in patients ongoing disease course. Biologicals include infliximab, adalimumab, golimumab and certolizumab.

Table 3. Cytomegalovirus and disease outcomes using multivariate adjusted logistic regression models.

	Crohn's disease (N: 406)				Ulcerative colitis (N:260)		
	MV-OR (95%CI) ^a	Cases	p-value		MV-OR (95% CI) ^a	Cases	p-value
Disease location			.27	Disease extent			.19
Ileal (L1)	1.0 Ref,	113		Proctitis (E1)	1.0 Ref,	13	
Colonic (L2)	1.09 (0.56–2.10)	67		Distal (E2)	0.99 (0.26–3.79)	62	
Ileocolonic (L3)	1.35 (0.78–2.32)	152		Pancolitis (E3)	1.58 (0.44–5.71)	145	
Upper-GI disease (L4)	1.50 (0.76–2.99)	45	.24				
Disease behavior			.88	Disease severity			.47
Inflammatory only (B1)	1.0 Ref,	170		Mild (S1)	1.0 Ref,	48	
Strictureing (B2)	0.89 (0.53–1.52)	117		Moderate (S2)	1.05 (0.48–2.28)	84	
Penetrating (B3)	0.99 (0.50–1.96)	51		Severe (S3)	1.33 (0.59–3.01)	73	
Perianal (Bp)	1.07 (0.66–1.75)	111	.78				
Need for surgery	0.78 (0.47–1.29)	167	.33	Need for colectomy	0.95 (0.47–1.93)	48	.88
Need for biologicals ^b	0.68 (0.42–1.10)	218	.12	Need for biologicals ^b	1.07 (0.53–2.16)	51	.89

MV-OR: multivariate-adjusted odds ratio; 95%CI: 95% confidence interval; anti-TNF α : anti-tumor necrosis factor alpha.

^aAll MV-adjusted ORs were corrected for sex, age (in years), ethnicity (Caucasian/non-Caucasian), disease duration (in years), cigarette smoking (ever/never), educational level (low/high), country of birth (the Netherlands/other country), type of CMV test (as part of clinical care/additionally performed for this study).

^bBiologicals include: infliximab, adalimumab, golimumab and certolizumab (ever/never).

seropositivity, including birth outside the Netherlands, non-Western origin, and lower educational level [15,20,21]. A similar study to this present study performed in China reported a CMV seroprevalence rate of 78% in patients with IBD, which may partially be explained by these risk factors [22]. In addition, our results suggest that CMV seropositivity is associated with a later onset of IBD, a three-year delay in effect. To our knowledge, this effect has not previously been described.

Regarding the impact of CMV seropositivity on IBD disease outcomes, contradictory findings have been reported [9,23–26]. In our large, well-characterized IBD cohort, we did not find any association between CMV seropositivity and unfavorable IBD disease outcomes such as steroid-refractory colitis, as expressed by the need for biological therapy or subsequent colectomy. Our data do show, however, that IBD gastroenterologists often still test for CMV antibodies in patients with IBD, in particular in patients with a more severe disease course and younger age, albeit against ECCO guidelines [27].

Since primary CMV infection in adults is uncommon and unlikely to be asymptomatic in immune-deficient hosts, the clinical impact of CMV most likely results from reactivation of the latent virus [6]. If this reactivation were of significant clinical impact, however, one would expect to find higher rates of unfavorable outcome, such as treatment-refractory colitis and subsequent surgery or use of biologicals in patients with latent CMV infection, which was not the case in our study. This suggests that CMV reactivations either have a self-limiting inflammatory effect or that CMV is indeed an innocent bystander in relapsing disease in most patients, that does not affect long-term disease outcomes in the general IBD population. Our findings support recommendations in the ECCO guidelines and smaller cohort studies, that CMV serology testing is not recommended either in routine care or prior to the start of immunosuppressive medication [13,27]. CMV colitis should still be considered in the diagnostic workup prior to IBD diagnosis or in patients presenting with deterioration of previously stable IBD unresponsive to intensified therapy [27].

Unexpectedly, patients with a latent CMV infection had an average of three-year delay in the onset of IBD compared to IBD patients without a latent CMV infection. We are well aware that this finding is merely an association and we do not imply causation. A protective effect of CMV infections against the development of IBD, however, seems unlikely given the comparable CMV seroprevalence rates between patients with IBD and the general population [20].

The strength of our study is our large prospective, well-characterized cohort. This resulted in the replication of known risk factors for CMV infection and allowed us to reliably investigate the role of CMV on IBD disease outcomes. Our study is limited by several factors. Since we use CMV seropositivity as a proxy for reactivation, we cannot report whether CMV infection caused colitis, let alone at which time point. As a consequence, the possible temporary effects of CMV reactivation, such as hospitalization and necessary antiviral therapies, remain unknown.

Prospective follow-up studies of seronegative and positive patients might provide this insight. The presence of CMV DNA in colonic biopsies is unknown for this cohort. However, determining the exact time of CMV reactivation remains very difficult, as anti-CMV IgM does not always develop, and the presence of CMV DNA present in colonic biopsies may only reflect latency without clinical significance [10]. Hence, data on CMV DNA in biopsies would not have changed the overall conclusion of this specific study.

In conclusion, we have shown that CMV seropositivity does not influence disease outcomes of patients with IBD. The onset of IBD is delayed in CMV seropositive patients. These data support the recommendation given in the ECCO guideline and confirm that routine measurement of CMV serology is not necessary in IBD.

Ethical approval

Ethical approval was obtained for the Biobank used in this study (University Medical Center Groningen, Medical Ethics Committee, registration no. 2017/407 and no. 08/279,

respectively). Written informed consent is obtained from all participants of the Biobank.

Author contributions

KWJS: study design, data collection, data analysis, writing the first draft of the manuscript

MDV: study design, data collection, data analysis, writing the first draft of the manuscript

MCV: patient recruitment, data collection, critical revision of the manuscript

EAMF: patient recruitment, data collection, critical revision of the manuscript

HMvD: patient recruitment, data collection, critical revision of the manuscript

RKW: patient recruitment, data collection, critical revision of the manuscript

BZA: study design, critical revision of the manuscript

CLB: study design, patient recruitment, data collection, critical revision of the manuscript

GD: study design, patient recruitment, data collection, critical revision of the manuscript

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No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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