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Original Article

Course of Disease in Patients with Microscopic Colitis: A European Prospective Incident Cohort Study

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Abstract

Background and Aims: The disease course of microscopic colitis [MC] is considered chronic but benign. However, this assumption is based on mainly retrospective studies, reporting on incomplete follow-up of selective cohorts. Systematic, prospective and unbiased data to inform patients and healthcare professionals on the expected course of the disease and real-life response to therapy are warranted.

Methods: A prospective, pan-European, multi-centre, web-based registry was established. Incident cases of MC were included. Data on patient characteristics, symptoms, treatment and quality of

life were systematically registered at baseline and during real-time follow-up. Four disease course phenotypes were discriminated and described.

Results: Among 381 cases with complete 1-year follow-up, 49% had a chronic active or relapsing disease course, 40% achieved sustained remission after treatment and 11% had a quiescent course. In general, symptoms and quality of life improved after 3 months of follow-up. A relapsing or chronic active disease course was associated with significantly more symptoms and impaired quality of life after 1 year.

Conclusions: A minority of MC patients follow a quiescent disease course with spontaneous clinical improvement, whereas the majority suffer a chronic active or relapsing disease course during the first year after diagnosis, with persisting symptoms accompanied by a significantly impaired quality of life.

Key Words: Microscopic colitis, disease course, prospective cohort study, disease activity, prognosis, treatment

1. Introduction

Microscopic colitis [MC] is a frequent cause of chronic or recurrent watery diarrhoea. It comprises collagenous colitis [CC], lymphocytic colitis [LC] and incomplete forms of CC and LC.[1,2] MC predominantly affects females and the elderly.[3,4] Until recently, the reported incidence rate of MC in the western world has increased steadily. This is at least partly due to an increased awareness of the disease and more frequent colonoscopy with biopsies in patients with chronic diarrhoea. Nevertheless, incidence rates vary considerably from less than four per 100 000 person years in the Netherlands to approximately 25 per 100 000 in Denmark and the USA.[5–8]

The disease course of MC is considered chronic but benign. Although two recently published large epidemiological studies showed an increased mortality in MC patients, this appeared to be related to comorbidity and smoking. Furthermore, there is a reduced risk of colorectal malignancy.[9,10] However, the actual course of the disease remains an assumption based on mainly retrospective studies, reporting on incomplete follow-up of selective cohorts[11–29] [Table 1]. In these studies, disease activity was almost uniformly based on patients' subjective response rather than systematic stool diaries. In the larger cohort studies with a long follow-up, over 25% relapsed after a median time of 4 years and about 75% of patients experienced prolonged disease remission after 8 years of follow-up.[11,30] Overall, the weighted proportion of persistent or recurrent disease, during a mean of 2.4 years of follow-up of 1707 patients was 32% [Table 1]. By contrast, follow-up of 123 patients treated in four randomized controlled clinical trials with budesonide demonstrated a relapse rate of 61% within 6 months after treatment cessation.[31]

The lack of systematic prospective and unbiased data currently hinders adequate information to patients and healthcare professionals on the expected course of disease and real-life response to therapy. This information is imperative, because disease activity is associated with a significantly impaired quality of life.[32] In addition, such data could provide the basis for a future rational follow-up and treatment strategy. Therefore, the European PRO-MC Collaboration established a registry to prospectively identify and follow-up incident MC cases. This paper presents the 1-year follow-up data.

2. Materials and Methods

2.1. PRO-MC Collaboration registry

The PRO-MC Collaboration was initiated by the European Microscopic Colitis Group [EMCG] in 2014. Sixteen centres in nine countries included patients in the registry. The first patient was included in June, 2016. Participating centres were provided with a digital histology slide kit on the internationally accepted diagnostic criteria for MC [http://www.emcg-ibd.eu/european-registry-promc.html] in order to train and inform local clinicians and pathologists on the diagnostic criteria for MC upfront.

The PRO-MC Collaboration is a web-based registry. Data from patients with newly diagnosed MC were prospectively collected at baseline, defined as the date of inclusion, and after 3, 6 and 12 months. Hereafter, an annual follow-up applies. At each visit, patient characteristics, disease activity, treatment, medication use, comorbidities, performed colonoscopies, hospitalizations and health-related quality of life were documented. Data were obtained via direct patient contact. After the baseline visit, follow-up by telephone consultation was allowed. Additional patient contacts were registered.

Health-related quality of life was assessed by the Short Health Scale [SHS] questionnaire. Assessment of disease activity, according to the Hjortswang criteria,[33] was based on a 1-week prospective defecation diary with Bristol stool scale prior to each study visit.[34] If no diary was available, daily stool frequency and consistency were verbally reported by the patient. SHS-forms and defecation diaries were provided in the subject's native language.

Pathology data including biopsy location and the applied histochemical stains were registered. The validity of histological diagnoses across several centres participating in the registry was confirmed in an associated histopathological study.[35]

The study protocol did not specify a treatment algorithm. The choice of treatment was decided by the local investigators. Most of these are associated with the EMCG and are familiar with the treatment guideline.[3] Treatment data in this registry therefore reflect every day clinical practice.

2.2. Published follow-up studies

Medline was searched for cohort studies reporting outcome of patients with MC, CC and/or LC written in English and reporting on at least 20 patients. MeSH terms used were ((((((microscopic colitis) OR (collagenous colitis)) OR (lymphocytic colitis)) AND (human)) AND (English)) NOT (review)). Titles and abstracts of the 1539 hits [June 13, 2020] were reviewed and 20 publications were included.

2.3. Study objectives

The primary objective of the PRO-MC Collaboration was to describe the characteristics and disease course of newly diagnosed MC

Table 1. Literature review of studies reporting persistent or recurrent diarrhoea in cohorts of patients with microscopic colitis[a]

Study	Year of diagnosis	*n* of *N*[b]	MC	CC	LC	Age [years]	Follow-up [years]	Persistence or recurrence of activity [%]	Weight
Loreau[29]	2005–2007	131	131	87	43	70	9.6	28	0.075
Mullhaupt[16]	1986–1995	27 of 35	27	–	27	60	3.3	7	0.016
Goff[17]	<1992	27 of 31	27	27	–	66	3.5	37	0.016
Nyhlin[27]	1980–2008	212 of 277	212	115	97	65	6	24	0.121
Calabrese[11]	2007	54	54	19	35	40	8.9	22	0.031
Fernández-Bañares[10]	1993–2010	187 of 261	187	93	94	60	7.8	25	0.108
Jobse[18]	1992–2006	83	83	83	–	60	NA	24	0.048
Gentile[19]	1985–2010	74 of 80	74	–	–	67	4	46	0.043
Sveinsson[12]	1995–2004	98 of 125	98	57	41	71	6.4	15	0.056
Fernández-Bañares[26]	1992–2001	81 of 89	81	37	44	62	3	27	0.047
Bonner[13]	1992–1995	22 of 38	22	22	–	72	2	59	0.013
Bonderup[25]	1979–1990	14 of 24	14	14	–	54	11	71	0.008
Madisch[20]	1989–1990	47/65	47	47	–	68	10	30	0.027
Thörn[28]	2005–2009	213 of 272	213	–	–	64	NA	14	0.122
Ung[24]	2000	25 of 27	25	25	–	60	8	84	0.014
Olesen[14]	NA	145 of 310	145	–	199	59	1	37	0.083
Fraser[22]	1993–1999	55 of 94	55	–	–	NA	1	39	0.032
Baert[23]	1994–1996	108 of 210	108	69	39	64	0.5	21	0.062
Bohr[15]	1989–1995	104 of 163	104	104	–	55	3	63	0.060
Total			**1707**			**60.7**	**2.4**	**32**	**1.000**

[a]All studies except Fernández-Bañares[27] and Calabrese[12] were retrospective.
[b]The number of patients followed up [*n*] vs number [*N*] in the original cohort.

patients. Secondary objectives were to report treatment and quality of life at inclusion and during follow-up and to compare the MC subgroups.

2.4. Study population

Patients 18 years or older and attending the gastroenterology outpatient clinic or endoscopy unit with newly diagnosed MC (CC, LC or incomplete MC [MCi]) were eligible for participation. The diagnosis was based on presence of chronic watery, non-bloody diarrhoea at time of referral to endoscopy, absence of macroscopic abnormalities on colonoscopy and a histological diagnosis of MC as defined in recent guidelines.[1,3] The Danish population-based incident cohort included all patients with a new diagnosis of MC during 2017 in the region of Zealand, a task made possible through a regional coordination, priority consultation and a close collaboration with the single pathology department examining all biopsy specimens from patients in this region.

2.5. Definition of disease course

According to the Hjortswang criteria, disease activity was defined as an average of three or more daily stools, or one or more watery stools per day [Bristol stool scale 7], based on a 7-day diary.[33] Disease remission during follow-up was defined as the absence of both disease activity and active treatment including oral budesonide, other corticosteroids, aminosalicylates, thiopurines, methotrexate, biologicals or continuous use of loperamide. Use of fibres, cholestyramine or intermittent use of loperamide was not considered active MC treatment.

Four disease course phenotypes were defined after discussion amongst clinicians participating in the EMCG collaboration:

1] *Quiescent disease*. No disease activity and no active treatment at baseline or any follow-up visit, and no patient-reported disease activity between visits.
2] *Sustained disease remission after treatment*. Persistent disease remission, without a patient-reported episode of disease activity between visits, achieved after a period of disease activity and/or active treatment.
3] *Relapsing disease*. No sustained disease remission at follow-up, nor fulfilment of the criteria for 'chronic active disease'.
4] *Chronic active disease*. Disease activity and/or active treatment at baseline visit and all subsequent follow-up visits.

2.6. Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki [latest version, Fortaleza, Brazil, 2013]. Written informed consent was obtained before inclusion. Ethical approval was obtained by the medical ethical committees of region Sjaelland, Denmark [SJ-514]; Linköping, Sweden [2015/309-31 and 2016/71-32]; San Donato Milano, Italy [184/2016]; University Hospital 'Tsaritsa Yoanna – ISUL', Sofia, Bulgaria [EK-13.02.2017/2017]; NHS Research Authority, UK [16\SS\023]; Aerea Vasta Emilia Nord, Modena, Italy [1150/2018/OSS/AOUMO]; Kaunas Bioethics Committee, Lithauania [BE-2–10]; Hospital Universitari Mútua Terrassa [12/15]; Hospital Universitari Vall D'Hebron (PR[AG]31/2017); and Maastricht University Medical Center [15-4-201].

2.7. Statistics

Normally distributed, continuous variables are presented as mean ± standard error of the mean. Dichotomous variables are reported as percentages with 95% confidence intervals (CI). The Chi-square test was applied to analyse dichotomous variables, and the [paired] Student's *t*-test for continuous variables. Uni- and multivariate logistic regression was performed to assess predictive factors for a chronic disease course in the first year after inclusion. Variables with a p-value > 0.300 in the univariate analysis were selected for the multivariate model. The multivariate model was established

via a backward selection procedure of the selected variables. All calculations were performed by using SPSS [IBM SPSS Statistics, version 24].

3. Results

3.1. Study population

By December 2019, 16 centres from nine countries had registered 485 MC patients [Supplementary Table 1]. Within this cohort, a population-based regional incident cohort of 251 cases was included, derived from four centres in the Danish region of Zealand. In total, 91 of 485 cases were excluded based on [i] the absence of informed consent [*n* = 54], [ii] not being an incident case [*n* = 14], [iii] absence of a recorded baseline visit [*n* = 6] or [iv] absence of diarrhoea at the time of diagnostic endoscopy [*n* = 17]. Of the remaining 394 cases, 36 were lost to follow-up and 40 had not passed the 12-month visit by December 2019, leaving 318 valid incident cases with complete 12 months of follow-up. This final cohort consisted of 46% CC, 40% LC and 14% MCi cases. Most patients were female [72%] and the average age at baseline was 64 years [Table 2]. The median time between index endoscopy and baseline visit was 42 [28–64] days.

3.1.1. Symptoms, bowel movements and functional impairment

Baseline characteristics are provided in Table 2. The majority of patients reported a sudden onset of diarrhoea, present up to 6 months before inclusion [51%]. Urgency [82%] and nightly defecation [45%] were the most frequently reported other complaints and a considerable proportion of patients [48%] reported moderate abdominal pain, with a mean score of 5.4 ± 2.2 on a 0–10 numeric rating scale [Table 3]. The proportion of patients reporting symptoms declined significantly from 3 months after inclusion. No differences were observed in symptom prevalence at baseline between CC, LC and MCi [Supplementary Table 2].

As shown in Table 3, disease activity was present in 68% of all patients at baseline. Although the number of daily stools and daily watery stools declined after baseline, disease activity remained present in approximately one-quarter of the cohort throughout follow-up. Patient-reported functional impairment improved after 3 months of follow-up, with over 80% of patients reporting no or only mild impairment [Table 3]. This was reflected by a significantly improved SHS score in all domains compared to baseline [Figure 1; Supplementary Table 3].

3.1.2. Treatment

The treatment strategies decided at each visit are listed in Table 4. During follow-up, the proportion of patients receiving therapy to induce clinical remission decreased significantly from 56% [95% CI 51–62%] at baseline to 7% [95% CI 4–10%] at 12-month follow-up. The proportion of patients not requiring treatment increased significantly from 22% [95% CI 17–27%] to 44% [95% CI 39–50%], respectively. At 12-month follow-up, 26% [95% CI 22–31%] of patients received oral budesonide, compared to 54%

Table 2. Baseline characteristics of patients with completed 12-month follow-up

	Total cohort	Danish sub-cohort	Other centres
Total number	318	171	147
Female gender	72% [67–77%]	68% [61–75%]	76% [68–82%]
Age in years [mean ± SD]	64 ± 14	64 ± 14	61 ± 16
Age in years for males [mean ± SD]	66 ± 13	67 ± 12	64 ± 15
Age in years for females [mean ± SD]	63 ± 14	66 ± 13	60 ± 16
Body mass index [kg/m^2, mean ± SD]	25 ± 5	26 ± 5	25 ± 4
Coeliac disease, proportion with positive test[a]	2% [1–4%]	1% [0–2%]	3% [1–7%]
Bile acid diarrhoea, proportion with a positive test[b]	4% [2–6%]	4% [2–7%]	3% [1–6%]
History of cholecystectomy	11% [8–15%]	5% [2–9%]	18% [12–24%]
Histological diagnosis			
Collagenous colitis	46% [40–51%]	44% [37–52%]	48% [39–56%]
Lymphocytic colitis	40% [35–46%]	42% [35–50%]	38% [30–46%]
Incomplete microscopic colitis	14% [9–19%]	14% [9–19%]	14% [9–20%]
Current smoker	27% [22–32%]	32% [24–39%]	22% [15–29%]
Former smoker	28% [23–33%]	35% [27–42%]	21% [14–27%]
Never smoked	45% [39–50%]	33% [27–41%]	58% [49–65%]
Use of at least one drug	77% [73–82%]	89% [84–94%]	63% [56–71%]
Use of a proton pump inhibitor	22% [18–27%]	25% [19–31%]	19% [13–26%]
Use of a non-steroidal anti-inflammatory drug	7% [3–8%]	10% [6–15%]	1% [0–2%]
Use of a statin	23% [18–28%]	25% [18–32%]	22% [16–29%]
Use of a selective serotonin reuptake inhibitor	13% [10–17%]	16% [10–22%]	10% [5–15%]
Diagnosis made by [ileo]colonoscopy	97% [94–100%]	94% [90–100%]	99% [95–100%]
Time in days from index endoscopy to baseline [median and 95% CI]	42 [38–45]	38 [35–42]	48 [40–51]
Duration of symptoms before diagnosis			
<3 months	21% [16–26%]	32% [25–39%]	8% [3–12%]
3–6 months	30% [25–35%]	38% [31–46%]	19% [13–26%]
6–12 months	21% [17–25%]	15% [10–21%]	29% [22–36%]
>12 months	28% [19–36%]	15% [7–23%]	45% [33–58%]

Proportions are reported as percentage with 95% confidence intervals [95% CI].

SD: standard deviation of the mean.

[a]In total, 76% of the total cohort was tested for coeliac disease. In the Danish sub-cohort 76% was tested, while in the other centres this was 77%.

[b]In total, 8% of the total cohort was tested for bile acid malabsorption. In the Danish sub-cohort 10% was tested, while in the other centres this was 5%.

Table 3. Symptoms, stool frequency and disease activity at baseline and follow-up visits

	Baseline	3 months follow-up	6 months follow-up	12 months follow-up
Symptoms				
Nightly defecation	45% [40–51%]	7% [4–10%]	4% [2–6%]	6% [4–10%]
Urgency	82% [78–86%]	26% [21–31%]	27% [22–33%]	22% [18–27%]
Faecal incontinence	39% [33–44%]	6% [3–8%]	5% [3–8%]	5% [3–8%]
Abdominal pain	48% [44–54%]	22% [17–26%]	17% [13–22%]	11% [7–15%]
Severity of abdominal pain[a]	5.4 ± 2.2	4.4 ± 2.0	4.9 ± 2.0	4.5 ± 1.4
Patient-reported functional impairment				
Severe	18% [15–23%]	5% [2–7%]	2% [1–4%]	3% [1–5%]
Moderate	30% [25–35%]	13% [8–15%]	14% 10–18%]	12% [8–15%]
Mild	31% [26–36%]	26% [23–33%]	23% [17–27%]	19% [15–23%]
None	18% [15–23%]	56% [50–61%]	61% [56–67%]	67% [61–72%]
Stool frequency and disease activity				
One-week defecation diary and self-reported combined	*100%*	*94%*	*95%*	*99%*
Number of daily stools	3.7 ± 2.7	2.2 ± 1.5	2.1 ± 1.4	2.1 ± 1.6
Number of daily watery stools	2.1 ± 2.8	0.6 ± 1.3	0.5 ± 1.2	0.5 ± 1.2
Cases with active disease[b]	68% [62–73%]	26% [21–32%]	26% [21–31%]	28% [23–34%]
Only 1-week defecation diary available	*52%*	*80%*	*80%*	*83%*
Number of daily stools	3.0 ± 2.1	2.0 ± 1.2	1.9 ± 1.2	1.9 ± 1.2
Number of daily watery stools	1.6 ± 2.1	0.4 ± 0.9	0.5 ± 1.1	0.5 ± 1.1
Cases with active disease[b]	61% [53–68%]	23% [17–28%]	23% [17–28%]	24% [19–29%]
Self-reported, no diary available	*48%*	*14%*	*15%*	*16%*
Number of daily stools	4.4 ± 3.0	3.1 ± 2.4	2.8 ± 2.2	3.2 ± 2.6
Number of daily watery stools	2.6 ± 3.4	1.3 ± 2.4	0.9 ± 1.8	0.9 ± 1.6
Cases with active disease[b]	75% [67–81%]	48% [33–63%]	44% [31–58%]	53% [39–67%]

Proportions are reported as percentage with 95% confidence interval.

[a]The severity of abdominal pain is reported as mean ± SD, based on a 0–10 numeric rating scale and was only reported in those who reported any abdominal pain.

[b]Active disease was defined according to the Hjortswang criteria: ≥3 daily stools or ≥ 1 watery stool per day.

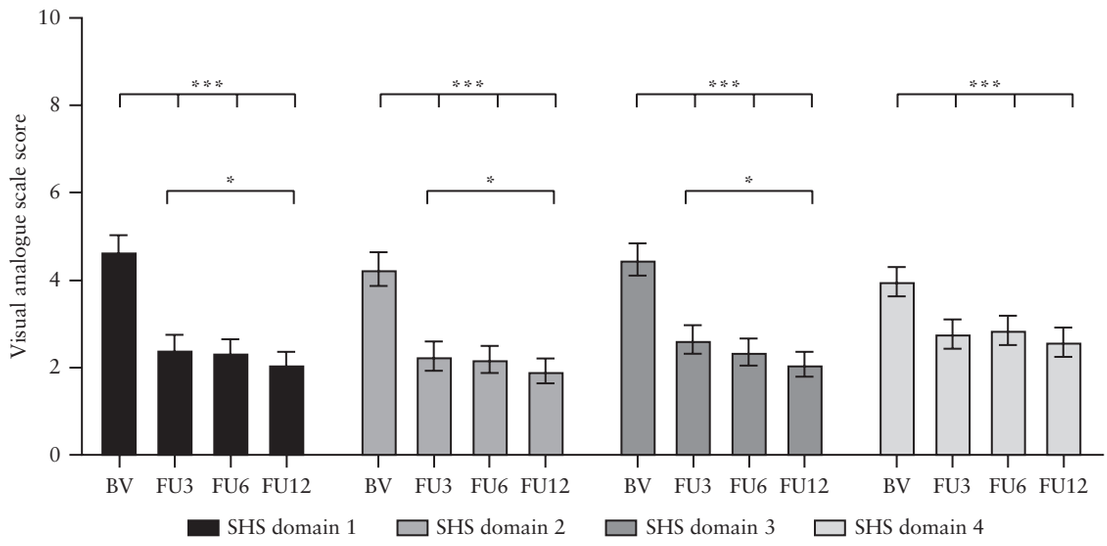

Figure 1. Mean Short Health Scale [SHS] scores with 95% confidence interval [scores 0–10 on a visual analogue scale] for the total study population [$n = 318$] per SHS domain at baseline visit and follow-up visits. Domain 1: severity of bowel symptoms; domain 2: interference of bowel problems with daily life; domain 3: worries about the bowel disease; domain 4: general well-being. BV: baseline visit; FU3: follow-up at 3 months; FU6: follow-up at 6 months; FU12: follow-up at 12 months. *$p < 0.05$, for FU3 compared to FU12; ***$p < 0.001$, for BV compared to all three follow-up visits.

[95% CI 49–60%] at baseline. The number of patients treated with loperamide or fibres increased, but was not statistically different. Treatment with immunomodulators, biologicals or mesalazine was exceptionally rare. No patients had surgery performed for MC and only two cases [1%] had a MC-related hospitalization.

3.1.3. Disease course and risk factors

About half of all patients [49%] exhibited a relapsing or chronic active disease course in the first 12 months after diagnosis [Table 5]. Ten per cent were in remission at baseline and did not encounter a relapse during the first year of follow-up, implying a quiescent

Table 4. Treatment strategy and modalities at baseline and follow-up visits

	Baseline	3 months follow-up	6 months follow-up	12 months follow-up
Treatment strategy [regardless of drug]				
Expectative	22% [17–27%]	40% [36–48%]	41% [36–47%]	44% [39–50%]
Induction therapy	56% [51–62%]	13% [10–18%]	11% [8–15%]	7% [4–10%]
Maintenance therapy	6% [4–9%]	18% [15–24%]	23% [18–28%]	25% [21–31%]
Tapering of dosage	4% [2–6%]	11% [8–16%]	7% [4–9%]	4% [2–6%]
On demand[a]	11% [8–15%]	12% [9–17%]	17% [13–22%]	19% [15–23%]
Treatment modality				
No drugs	22% [17–27%]	40% [36–48%]	41% [36–47%]	44% [39–50%]
Budesonide	54% [49–60%]	26% [22–33%]	27% [22–33%]	26% [22–31%]
Mesalazine	1% [0–2%]	0%	0%	0%
Immunomodulators[b]	0%	0%	2% [0–3%]	2% [0–3%]
Biologicals	0%	0%	0%	0%
Bile acid binder	3% [1–4%]	5% [3–7%]	3% [1–5%]	3% [1–5%]
Loperamide	15% [11–20%]	15% [11–20%]	18% [14–22%]	21% [17–26%]
Fibres	13% [9–16%]	15% [12–20%]	17% [13–22%]	17% [13–21%]
Other drugs	6% [3–9%]	5% [2–7%]	8% [5–11%]	6% [4–9%]

Proportions are reported as percentage with 95% confidence interval.

[a]This implies that patients are carefully instructed by their clinician to take drugs when clinical symptoms worsen.

[b]Immunomodulators include thiopurines and methotrexate.

Table 5. Disease course during the first year after diagnosis

	All subtypes	CC	LC	MCi
	n = 318	*n* = 146	*n* = 128	*n* = 44
Quiescent [%]	11% [7–14%]	8% [4–13%]	12% [6–17%]	14% [4–25%]
Sustained remission after treatment [%]	40% [35–46%]	39% [32–47%]	39% [31–47%]	48% [34–64%]
At 3 months after inclusion and thereafter [%]	21% [17–25%]	25% [18–31%]	15% [9–21%]	25% [14–39%]
At 6 months after inclusion and thereafter [%]	6% [4–9%]	5% [1–8%]	10% [6–16%]	2% [0–7%]
At 12 months after inclusion [%]	13% [9–17%]	9% [5–14%]	14% [9–21%]	21% [9–34%]
Relapsing [%]	34% [29–40%]	38% [30–45%]	33% [26–42%]	25% [14–39%]
Chronic active [%]	15% [11–19%]	15% [10–21%]	16% [10–22%]	13% [4–25%]

Proportions are reported as percentage with 95% confidence interval.

CC: collagenous colitis; LC: lymphocytic colitis; MCi: incomplete microscopic colitis.

disease course. In addition, a substantial proportion of patients achieved sustained disease remission after treatment, increasing from 21% 3 months after baseline to 40% 12 months after baseline.

The course of disease was not statistically significantly different in [i] patients aged < 60 years, 60–70 years or > 70 years at diagnosis, [ii] females compared to males, [iii] current compared to non-current smokers at baseline, and [iv] CC, LC or MCi [Supplementary Tables 4 and 5]. Moreover, the time between index endoscopy and baseline visit was not significantly different in cases with a quiescent, relapsing or chronic active disease course. Compared to patients with chronic active disease, those with quiescent disease less frequently had symptoms for more than 12 months before baseline [40%; 95% CI 25–54% vs 9%; 95% CI 0–21%, respectively].

In the final multivariate analysis, the total number of daily stools at baseline was predictive for a chronic disease course. With every additional stool the odds ratio for a chronic disease course increased by 1.14 [95% CI 1.03–1.27]. Nightly defecation at baseline was also a predictor for a chronic disease course during the first year (odds ratio 2.64 [95% CI 1.31–5.32]) [Supplementary Table 9].

3.1.4. Symptoms and quality of life in relation to disease course

At baseline, there was a clear trend towards more symptoms, higher pain scores and more functional impairment in cases that would follow a chronic active or relapsing disease course. In particular, the proportion of cases reporting nightly defecation seemed discriminatory for a chronic active course [Figure 2; Supplementary Table 6]. After 1 year of follow-up, symptoms improved significantly [Figure 2]. However, all symptoms, and especially urgency, persisted significantly more frequently in cases with a chronic active or relapsing phenotype [Figure 2]. This was reflected by persistence of a moderate to severe functional impairment in 25–30% of these cases. The SHS sum score [i.e. sum of scores of the four SHS domains at a specific time point] remained persistently high, despite a modest, albeit significant improvement in SHS at the 12-month follow-up [Figure 3]. In contrast, those with quiescent disease reported a significantly better mean SHS sum score at baseline and after 1 year. Those with sustained remission after treatment reported an SHS sum score comperable to those with quiescent disease, at the 12-month follow-up.

3.1.5 . Data consistency

Overall, the results of the Danish sub-cohort were identical to those of the other centres [Table 2; Supplementary Tables 5, 7 and 8]. An exception was fewer cases reporting abdominal pain at baseline in the Danish sub-cohort [39%; 95% CI 32–47% vs 59%; 95% CI 51–66%, respectively]. Furthermore, use of at least one drug at inclusion was more frequently reported in Danish

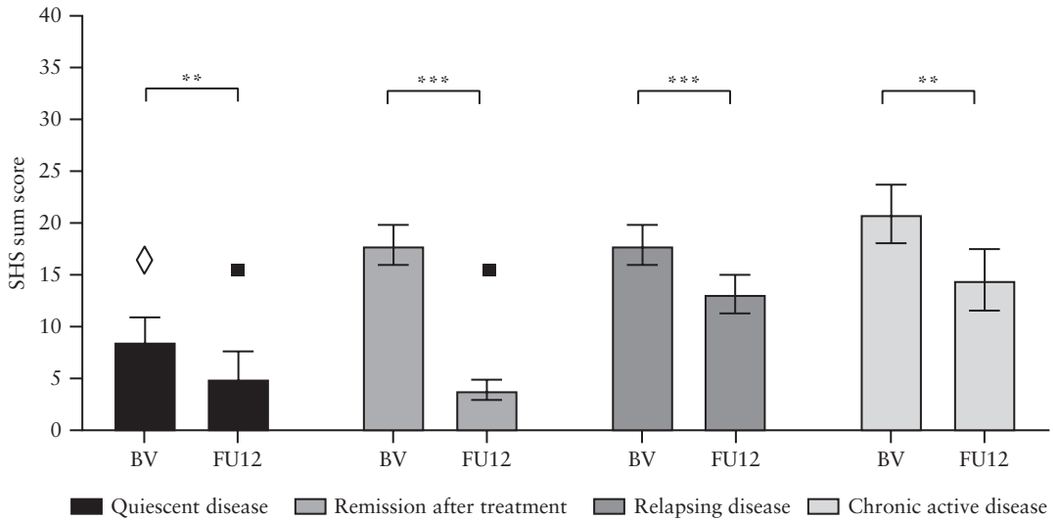

Figure 2. The proportion of patients who reported symptoms at baseline visit [BV] and at the 12-month follow-up [FU12] visit, presented per disease course phenotype. *$p < 0.05$; *** $p < 0.001$. ◊ Statistically significant difference [$p < 0.05$] compared to quiescent disease, sustained remission after treatment and relapsing disease at baseline visit. ▪ Statistically significant difference [$p < 0.05$] compared to both relapsing disease and chronic active disease at the 12-month follow-up visit. ●Statistically significant difference [$p < 0.05$] compared to quiescent disease at baseline visit.

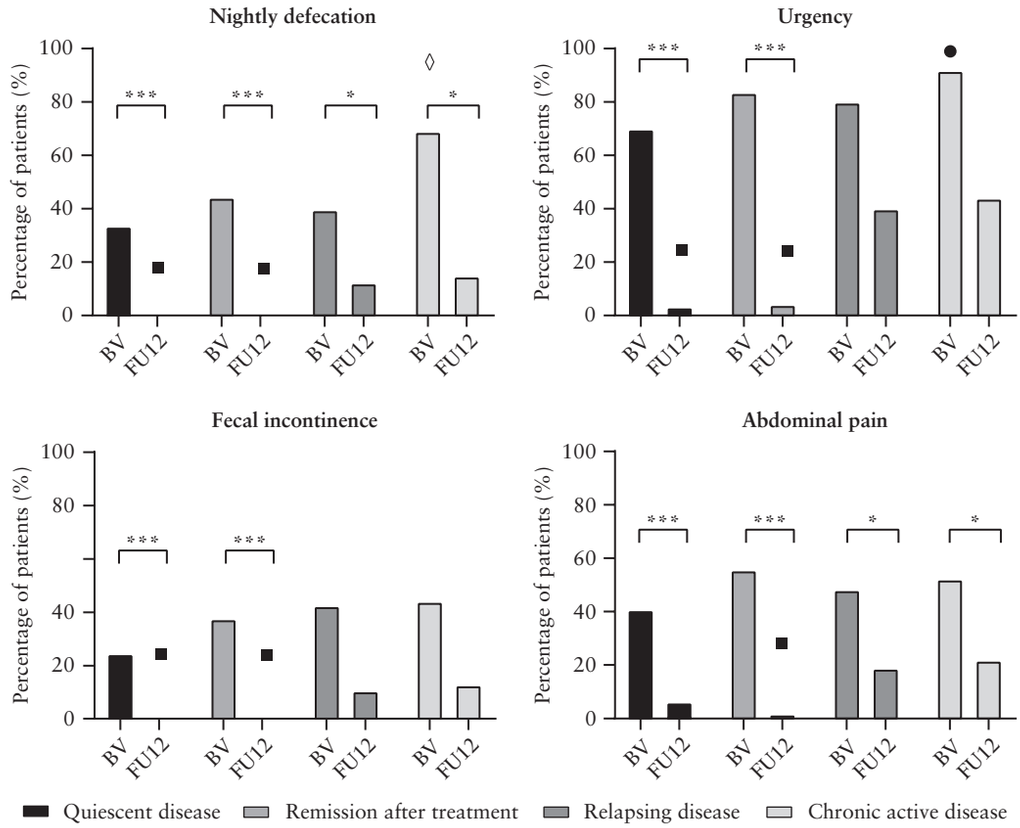

Figure 3. Short Health Scale [SHS] sum score [cumulative SHS score of all four SHS domains] at baseline visit [BV] and the 12-month follow-up visit [FU12], presented per disease course phenotype. **$p < 0.01$; *** $p < 0.001$. ◊ Statistically significant difference [$p < 0.001$] compared to sustained remission after treatment, relapsing disease and chronic active disease, at baseline visit. ▪ Statistically significant difference [$p < 0.001$], compared to both relapsing disease and chronic active disease, at the 12-month follow-up visit.

cases, as was the use of non-steroidal anti-inflammatory drugs at baseline. This was also true for the duration of symptoms before diagnosis, and the median time between endoscopy and inclusion was significantly shorter [Table 2]. Disease activity at baseline was more often determined by patient recall rather than stool diaries [Supplementary Table 7]. The difference in the use of fibres between the Danish sub-cohort and other centres was statically significant [Supplementary Table 8]. Eventually, the course of disease

in the Danish population-based cohort was equal to those of non-Danish centres [Supplementary Table 5].

4. Discussion

This paper presents the first systematic and prospective follow-up of patients with newly diagnosed MC. The disease course, symptoms and impact on quality of life in the first year after diagnosis are described, discriminating four distinct disease course phenotypes. All included patients had chronic watery diarrhoea at the time of referral for endoscopy and the histopathological diagnosis was validated by re-evaluation of the histopathological findings in six centres.[35]

Until now, knowledge on the course of MC disease has been based on retrospective and/or selective cohorts. As summarized in Table 1, there was a 32% risk of relapsing or chronic active disease after a mean follow-up of 2.4 years in 1707 cases, but with a large variation. As these studies had several methodological shortcomings, our results cannot be directly compared to these studies. The majority had incomplete follow-up and reported on patients diagnosed at a time at which the awareness of MC as a common cause of chronic watery diarrhoea was low. Therefore, the patients were probably not representative for the whole MC population. Whether they included patients with comparable disease severity remains unknown. All but two studies were retrospective. Most used chart review and many studies did not clearly define disease. Only Nyhlin et al.[28] used SHS and the Hjortswang criteria[33] while Loreau et al.,[30] Mullhaupt et al.[17] and Miehlke et al.[22] defined remission as fewer than three or four stools or loose stools. The study reported by Fernandez-Bañares[11] was prospective but included many patients with concomitant bile acid diarrhoea. Thörn et al. included patients both with and without diarrhoea and the follow-up was retrospective.[29] The median age of patients included in a small prospective study by Calabrese et al. was only 40 years and therefore not representative for the whole MC population.[12] Therefore, our systematic prospective data provide valuable information about disease behaviour.

In general, patient characteristics were similar in all participating centres [Table 2; Supplementary Tables 4–6] and MC subtypes [Supplementary Table 7]. Besides nightly defecation, clinical symptoms at baseline were not significantly different between the four phenotypes, suggesting that presence or absence of symptoms at diagnosis does not predict the course of disease. In contrast to previous reports,[31] stool frequency did not predict the course of disease. Although treatment did lead to a decrease in symptoms, urgency or some degree of functional impairment remained present in 30–40% of all patients at follow-up. Active disease was associated with urgency, nightly defecation and moderate abdominal pain. At baseline, these symptoms were more frequently documented than currently reported in the literature.[36] The co-occurrence of coeliac disease was low and only slightly higher than in the background population, which is in accordance with the finding that gluten intake is not a risk factor for MC.[37] Most patients used at least one drug at baseline visit. The proportion of cases using an MC-associated drug [proton pump inhibitor, non-steroid anti-inflammatory drugs, selective serotonin re-uptake inhibitors or statin] at baseline visit was comparable to 'current users' in two large retrospective studies.[38,39] Nevertheless, the reported proportions might be an underrepresentation as diarrhoea-causing drugs might have been stopped before inclusion. Because the data on drug use at baseline are purely descriptive, no conclusions can be drawn regarding causality. In addition, there is currently no evidence in the literature that continuation of MC-associated drugs might influence disease course.[36]

We confirmed that active disease is associated with a severely compromised quality of life,[32,33] as half of the patients reported moderate to severe functional impairment with correspondingly high SHS scores at baseline. Interestingly, the initial improvement in quality of life during the first 3 months of follow-up did not continue during the following months, reflecting a moderate, but continuous burden of disease, particularly in patients with a chronic active or relapsing disease course.

The most frequently prescribed treatment was oral budesonide delayed release capsules, the only treatment shown to be effective and safe in both CC and LC in randomized trials.[40–42] At every follow-up contact, approximately one-third of the patients received budesonide, either as induction therapy or as maintenance. Fibres, loperamide and an on-demand treatment strategy were applied increasingly during follow-up. The efficacy and safety of this approach has not been assessed in controlled clinical trials.[36] Initial disease severity was reflected by the fact that more than half started induction therapy with budesonide at baseline. Another 10% of the patients had started budesonide prior to the baseline visit at which the budesonide dose was tapered or maintained. Treatment strategies appeared similar across centres. Biologicals were not used, which is probably due to the limited follow-up of 1 year.

The main purpose of this study was to gain insight into the disease course of MC. In theory, a disease could follow a course with continuous activity or continuous remission with or without treatment; patients could achieve sustained clinical remission after treatment; or experience a relapse of symptoms after a succesful treatment course. This concept formed the basis for the proposed disease course phenotypes of MC. Because there are no validated tools to define the course of disease in MC, a combination of the Hjortswang criteria for disease activity[33] and treatment data was applied. Including treatment into the criteria next to stool frequency was essential, because a low stool frequency might not per definition imply absence of activity if it is due to treatment. The currently defined disease course phenotypes are applicable in daily practice and useful to inform clinicians and patients about the potential course of MC. Prolonged follow-up of this cohort for up to 5 years will generate more information and insight about relapse rates and persistency of remission. It should be noted that inclusion of treatment into the disease course definitions might have led to an overrepresentation of the actual number of cases with chronic active or relapsing disease course, due to possible local variations in tapering strategies or clinical indications to start or prolong treatment.

In the present study, use of fibres, cholestyramine or intermittent use of loperamide was not considered active MC treatment, because these have not been shown to have an effect in MC. Continuous use of loperamide was considered active treatment despite the lack of controlled data in MC.[3,15,16] Loperamide has proven efficacious and safe in several randomized, placebo-controlled trials in patients with chronic diarrhoea, in particular abolishing faecal incontinence.[43–45] Cholestyramine is only indicated in patients with concomitant bile acid diarrhoea, for which only a minority of the study population was formally tested. The use of on-demand treatment with budesonide reflected an increased demand for disease self-management. Further clinical trials should test this treatment strategy and the efficacy of shorter courses of budesonide. The efficacy of fibres and loperamide in patients with mild recurrent disease activity should also be examined.

Our systematic follow-up demonstrated that only 11% of patients followed a quiescent disease course with spontaneous

resolution of symptoms. In contrast, 15% had chronic active disease and an additional 34% had relapsing disease throughout the first year. Such high relapse and activity rates underscore the need for ad hoc follow-up by gastroenterologists to ensure timely response and to maintain patient confidence. Interestingly, the previously highlighted observation that active smoking is a risk factor for ongoing activity or relapse of symptoms[46] was not corroborated in this cohort.

Both the total number of stools per day and nightly defecation at baseline are strong predictors for a chronic active disease course in the first year after diagnosis. Future analyses of long-term data will lead to more insight in the predictive factors for the disease course in MC.

The strength of the current study is its prospective, pan-European cohort that reflects current everyday clinical practice, generating relevant information for both physicians and patients about the disease course of MC. The validity of the data is strengthened by the inclusion of a complete and validated population-based subcohort within the registry. Interestingly, these Danish patients did not differ notably from the rest of the study cohort at baseline and had a similar course of disease. The few differences identified were minor. Therefore, we consider our results to be robust and to reflect the course of disease in a non-selected population of patients with MC. We did not observe any differences between MC subtypes, with regard to clinical characteristics, treatment or course of disease. The distribution of centres and their number of inclusions did not allow a valid analysis of a north–south gradient.

In conclusion, our study demonstrates that a minority of MC patients follow a quiescent disease course with spontaneous clinical improvement. However, a significant proportion of MC patients suffer a chronic active or relapsing course of disease during the first year after diagnosis, with persisting symptoms accompanied by a significantly impaired quality of life. The course of disease is similar in all MC subtypes. Consequently, MC patients need lengthy follow-up with access to dedicated clinicians and we need to develop long-term treatment and follow-up strategies to allow timely response to active disease.

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Conflict of Interest

None to declare.

Author Contributions

Design of the study [B.V., A.M., H.H., S.M., L.M.]; patient recruitment and data collection [all authors]; data analysis [B.V., L.M.]; writing the manuscript [B.V., L.M.]; reviewing the final manuscript [all authors].

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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