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ORIGINAL ARTICLE

Observational Study

Diagnostic delay in inflammatory bowel diseases in a German population

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Abstract

BACKGROUND

Early diagnosis is key to prevent bowel damage in inflammatory bowel disease (IBD). Risk factor analyses linked with delayed diagnosis in European IBD patients are scarce and no data in German IBD patients exists.

AIM

To identify risk factors leading to prolonged diagnostic time in a German IBD cohort.

METHODS

Between 2012 and 2022, 430 IBD patients from four Berlin hospitals were enrolled in a prospective study and asked to complete a 16-item questionnaire to determine features of the path leading to IBD diagnosis. Total diagnostic time was defined as the time from symptom onset to consulting a physician (patient waiting time) and from first consultation to IBD diagnosis (physician diagnostic time). Univariate and multivariate analyses were performed to identify risk factors for each time period.

RESULTS

The total diagnostic time was significantly longer in Crohn's disease (CD) compared to ulcerative colitis (UC) patients (12.0 *vs* 4.0 mo; $P < 0.001$), mainly due to increased physician diagnostic time (5.5 *vs* 1.0 mo; $P < 0.001$). In a multivariate analysis, the predominant symptoms diarrhea ($P = 0.012$) and skin lesions ($P = 0.028$) as well as performed gastroscopy ($P = 0.042$) were associated with longer physician diagnostic time in CD patients. In UC, fever was correlated ($P = 0.020$) with shorter physician diagnostic time, while fatigue ($P = 0.011$) and positive family history ($P = 0.046$) were correlated with longer physician diagnostic time.

CONCLUSION

We demonstrated that CD patients compared to UC are at risk of long diagnostic delay. Future efforts should focus on shortening the diagnostic delay for a better outcome in these patients.

Key Words: Diagnostic time; Diagnostic delay; Crohn's disease; Ulcerative colitis; Germany

Core tip: Early diagnosis is key to reducing complications and improving response to medical therapy. This prospective questionnaire-based study aimed to identify risk factors impairing diagnostic time. We demonstrated that diagnostic delay was significantly longer in Crohn's disease than in ulcerative colitis and was mainly physician dependent. The multivariate analysis showed that disease-specific symptoms and rapidly available diagnostic tools resulted in reduction of physician diagnostic time.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the most common forms of inflammatory bowel disease (IBD). IBD is defined as destructive inflammatory disorder of the gastrointestinal tract resulting in chronic relapsing–remitting disease courses. IBD manifests primarily in the intestine but may also have extraintestinal manifestation (EIM). IBD has been shown to be associated with various autoimmune diseases that impact other organs or systems[1,2]. Due to its heterogeneous, nonspecific clinical presentation, and poor diagnostic precision of existing biomarker tests, diagnosis of IBD can be challenging and often results in a prolonged time from symptom onset to an established and correct diagnosis[3,4]. The median delay in diagnosis ranges from 5.0 to 9.5 months for CD and 3.1 to 4.0 months for UC, likely due to different medical standards and regional differences in disease behavior[4-7].

However, prompt diagnosis and treatment of these patients is critical. Recently published studies showed that early therapeutic intervention reduced the need for surgery, as well as severe disease progression with complications[5,8]. Early intensive treatment has been associated with improved responses to immunomodulators or targeted biologic

therapy[9]. Diagnostic delay affects patients' quality of life and the burden on the healthcare system[10]. Therefore, awareness of risk factors for delayed diagnosis in IBD patients is imperative.

It is noteworthy that most of the studies have evaluated the total diagnostic delay, whereas studies that systematically evaluate the time patients spend before consulting a physician as well as the time the physician takes to establish an IBD diagnosis separately are scarce[4,11]. Most of the studies were performed in countries with different medical provider systems and hence lack generalizability. Results from Central Europe are lacking [4,6,8,11,12]. Considering the east–west gradient in the incidence of IBD, more research is required on this clinical problem[13]. Therefore, we aimed to comprehensively assess risk factors for delayed diagnosis in a German IBD cohort to enhance our management of IBD patients.

MATERIALS AND METHODS

Study design

From May 2012 to May 2022, 513 patients with IBD were enrolled in this descriptive cross-sectional, questionnaire-based evaluation study at the IBD outpatient clinic.

The patients were recruited at the three hospital sites at the Charité-Universitätsmedizin Berlin (42.3% at Charité-Campus Mitte, 28.4% at Charité-Virchow Klinikum, 26.0% at Charité-Benjamin Franklin) and at Krankenhaus Waldfriede Berlin-Zehlendorf (18%). We included adult patients (no upper age limit) with confirmed CD or UC diagnosis for at least 6 months with completed questionaries and excluded patients who were unable to consent due to mental incapacity or language barriers as well as the diagnosis of indeterminate colitis. Study participants were interviewed once after written informed consent was obtained. A total of 430 patients were enrolled in the study. Fifty-four patients did not complete the questionnaire, 15 were excluded because of a diagnosis of indeterminate colitis, three were excluded because of a diagnosis of irritable bowel syndrome (IBS), four did not sign the informed consent form correctly, and sevens were excluded because of duplicate entries. A total of 430 (83.3%) adult patients were analyzed for this study.

The study was approved by the local ethics committee (EA2/170/11) and was conducted in accordance with the ethical standards of the Declaration of Helsinki of 1964 and its latest revision of 2013. The study protocol is also compliant with the STROBE criteria[14].

Questionnaire

The administered questionnaire contained 16 questions that investigated demographic and disease-specific factors, which may directly or indirectly play a role for the delay of diagnosis. In addition to patient age and gender, urban or rural residence, medical history (predominant symptoms and general symptoms at diagnosis), severity of symptoms, location of disease, method of IBD diagnosis, and whether the patient had affected family members or had ever heard of IBD, were recorded. EIMs were defined as the presence of ankylosing spondylitis, aphthous stomatitis, erythema nodosum, peripheral arthritis, primary sclerosing cholangitis, psoriasis, pyoderma gangrenosum, or uveitis. Medication was categorized as basic (rectal treatment, mesalazine, budesonide) or advanced (cortisone, azathioprine, methotrexate, infliximab, adalimumab).

Three different time intervals were assessed in patient questionnaires (Figure 1). Patient waiting time was defined as time from onset of symptoms to first physician contact. Physician time to diagnosis was defined as time from first physician contact to the diagnosis of IBD. Total diagnostic time was the sum of both time periods and was defined as the time from IBD symptom onset to diagnosis.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). Figures were created using Prism 6 software (GraphPad Software, La Jolla, CA, USA). We used the Kolmogorov–Smirnoff test to determine the distribution of our data. Continuous variables were presented as median and interquartile range (IQR), differences were compared by the Kruskal–Wallis test or Mann–Whitney *U* test. Categorical data were expressed in the form of numbers and percentages and were compared by the χ^2 test. Univariate analysis of the different clinically relevant factors associated with diagnostic time was performed using the Kaplan–Meier survival method and the differences were compared using the log-rank test. We also presented hazard ratios (HR) for the univariate analysis. HRs exceeding unity (HR > 1) represented a better chance for early diagnosis. All variables with a $P < 0.1$ in univariate analysis were further used for multivariate analyses using Cox's proportional hazard model in a backward stepwise manner. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Patient characteristics for IBD are summarized in Table 1. We analyzed 223 patients with CD and 207 with UC. Patients were mainly female (54.4%) with a median age at diagnosis of 26 (20–25) years for CD and 28 (21–39) years for UC. The most common reported symptoms were diarrhea in CD (43.5%) and UC (48.8%), followed by abdominal pain in CD (33.2%) and blood in the stool in UC (33.8%). The predominant site of disease at the time of diagnosis was the terminal ileum in CD (68.6%) and the colon in UC (74.4%). Most UC and CD patients were diagnosed based on colonoscopy (78.5 *vs* 96.1%; $P < 0.001$) compared with computed tomography (3.1 *vs* 0.5%; $P = 0.037$) or magnetic resonance imaging (2.2 *vs*

Table 1 Patient characteristics, *n* (%)

Parameter	CD (*n* = 223)	UC (*n* = 207)	*P* value
Sex, M/F	95/128	101/106	0.198
Age at enrolment (yr)	40 (30-50)	41 (32-52)	0.509
Age at diagnosis (yr)	26 (20-35)	28 (21-39)	0.565
Residence at diagnosis			0.554
Village	12 (5.4)	14 (6.8)	0.537
Small-town	18 (8.1)	18 (8.7)	0.801
Medium-sized town	24 (10.8)	14 (6.8)	0.149
Large city	165 (74.0)	152 (73.9)	0.977
Abroad	1 (0.4)	5 (2.4)	0.081
Patient waiting time (mo)	2.0 (0.5-6.0)	1.0 (0.5-4.0)	0.051
Physician time to diagnosis (mo)	5.5 (0.75-23.5)	1.0 (0-5.0)	< 0.001
Total diagnostic time (mo)	12.0 (6.0-24.0)	4.0 (1.5-12.0)	< 0.001
Predominant symptom			
Diarrhea	97 (43.5)	101 (48.8)	0.239
Constipation	1 (0.4)	1 (0.5)	0.954
Abdominal pain	74 (33.2)	16 (7.7)	< 0.001
Heartburn	1 (0.4)	0 (0)	0.336
Bloating	0 (0)	3 (1.4)	0.070
Blood in stool	11 (4.9)	70 (33.8)	< 0.001
Nausea/vomiting	9 (4.0)	0 (0)	0.004
Skin	1 (0.4)	1 (0.5)	0.954
Joint pain	4 (1.8)	0 (0)	0.054
Fistula	5 (2.2)	0 (0)	0.031
Weight loss	1 (0.4)	0 (0)	0.336
Fever	1 (0.4)	1 (0.5)	0.954
Fatigue	5 (2.2)	5 (2.4)	0.897
Other symptoms	8 (3.6)	3 (1.4)	0.164
Location			
Upper GI	19 (8.5)	2 (1.0)	< 0.001
Small bowel	73 (32.7)	16 (7.7)	< 0.001
Terminal ileum	153 (68.6)	21 (10.1)	< 0.001
Colon	101 (45.3)	154 (74.4)	< 0.001
Rectum	49 (22.0)	111 (53.6)	< 0.001
Severity			
Very mild	7 (3.1)	9 (4.3)	0.519
Mild	11 (4.9)	23 (11.1)	0.019
Moderate	38 (17.0)	55 (26.6)	0.018
Strong	88 (39.5)	69 (33.3)	0.187
Very strong	75 (33.6)	49 (23.7)	0.023
Physician			
Gastroenterologist	85 (38.1)	97 (46.9)	0.066

Hospital	104 (46.6)	73 (35.3)	0.017
General practitioner	18 (8.1)	19 (9.2)	0.682
Expert in IBD	9 (4.0)	9 (4.3)	0.871
Another consultant	4 (1.8)	8 (3.9)	0.187
Others	2 (0.9)	2 (0.9)	0.172
Diagnostic tests			
Colonoscopy	175 (78.5)	199 (96.1)	< 0.001
Gastroscopy	5 (2.2)	1 (0.5)	0.111
Sonography	4 (1.8)	1 (0.5)	0.193
Computed tomography	7 (3.1)	1 (0.5)	0.037
Magnetic resonance imaging	5 (2.2)	1 (0.5)	0.028
Diagnosis change	23 (10.3)	35 (16.9)	0.070
Positive family history	35 (15.7)	35 (16.9)	0.808
Parents	13 (37.1)	10 (28.6)	0.445
Siblings	12 (5.4)	8 (22.9)	0.290
Aunt/uncle	2 (0.9)	8 (22.9)	0.040
Grandparents	4 (1.8)	9 (25.7)	0.124
Knowledge of IBD	49 (22.0)	39 (18.8)	0.437
Affected person	27 (55.1)	20 (51.3)	0.721
Media	10 (20.4)	7 (17.9)	0.772
Internet	8 (16.3)	6 (15.4)	0.904
Profession	6 (12.2)	9 (23.1)	0.179
Medication			
Mesalazine	149 (66.8)	180 (87.0)	< 0.001
Budesonide	68 (30.5)	24 (11.6)	< 0.001
Cortisone	54 (24.2)	115 (55.6)	< 0.001
Azathioprine	2 (0.9)	29 (14.0)	0.007
Methotrexate	7 (3.1)	1 (0.5)	0.607
Infliximab	7 (3.1)	5 (2.4)	0.649
Adalimumab	17 (7.6)	1 (0.5)	0.042
Local treatment	13 (5.8)	64 (30.9)	< 0.001

CD: Crohn's disease; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; GI: Gastrointestinal tract.

0.5 %; $P = 0.028$). The CD diagnosis was mainly made in hospital (46.6% CD *vs* 35.5% UC). UC diagnosis was predominantly made by private practice gastroenterologists (38.1% CD *vs* 46.9% UC). The CD patients reported more severe symptoms compared with UC patients (33.6% CD *vs* 23.7% UC; $P = 0.023$) and had more EIMs (26.0% CD *vs* 12.1% UC; $P < 0.001$).

Diagnostic time

Total diagnostic time was longer for CD (12.0 months; IQR 6.0–24.0) than UC (4.0 months; IQR 1.5–12.0; $P < 0.001$). While the patient waiting time was comparable between CD and UC (2.0 months; IQR 0.5–6.0) *vs* 1.0 month; IQR 0.5–4.0; $P = 0.051$), the physician diagnostic time was longer in CD patients (5.5 months; IQR 0.75–23.5) than UC patients (1.0 month; IQR 0–5.0; $P < 0.001$). Time to event analysis for all three intervals for CD and UC, separately, are depicted as Kaplan–Meier curves (Figure 2).

CD

Patient waiting time: In the univariate analysis, patient waiting time was shorter with female sex ($P = 0.089$), living abroad ($P = 0.020$), the predominant symptoms of abdominal pain ($P = 0.038$), fistula ($P = 0.032$), nausea/vomiting ($P =$

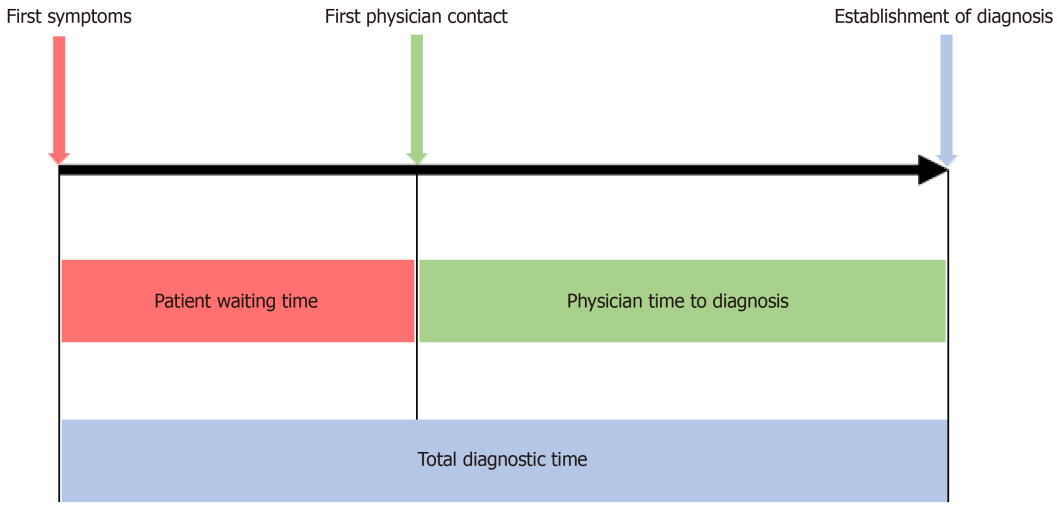

Figure 1 Diagnostic time intervals. Based on the patients' questionnaires, three relevant time intervals were calculated: (1) patient waiting time [interval from the first inflammatory bowel disease (IBD) symptoms till consulting a physician]; (2) physician diagnostic time (interval from first physician contact to IBD diagnosis); and (3) total diagnostic time (interval from the first IBD symptoms till establishment of IBD diagnosis).

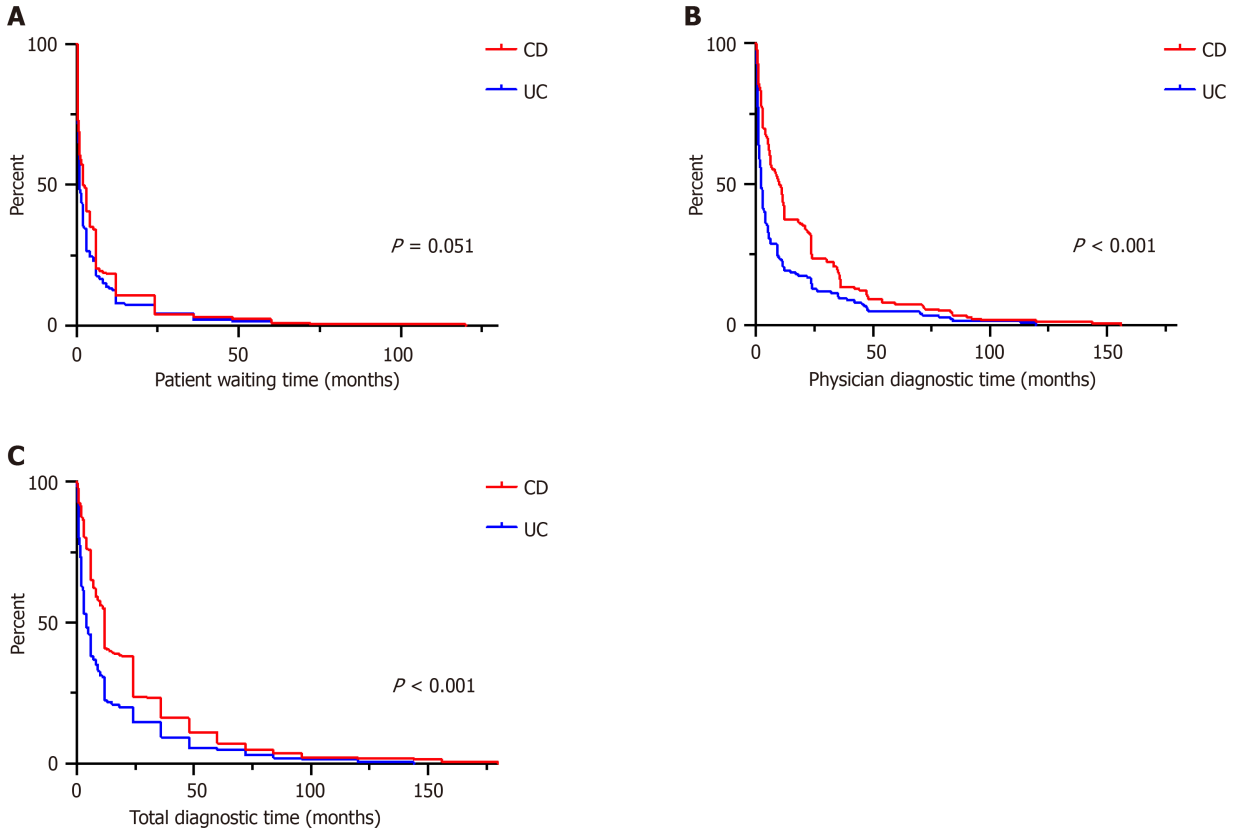

Figure 2 Diagnostic time in Crohn's disease *versus* ulcerative colitis patients. A: Patient waiting time almost equals in Crohn's disease (CD) and ulcerative colitis patients; B: Significantly prolonged physician diagnostic time in CD patients; C: Significantly prolonged total diagnostic time in these patients. CD: Crohn's disease; UC: Ulcerative colitis.

0.075), strong disease severity (P = 0.023), and positive family history of IBD (P = 0.005). Longer patient waiting time was associated with blood in stool (P = 0.069) and diarrhea (P < 0.001). The clinical factors influencing patient waiting time in CD are summarized in Table 2.

Multivariate analysis determined the predominant symptoms of abdominal pain (HR 1.428; P = 0.018), fistula (HR = 2.841; P = 0.027) and positive family history (HR = 1.734; P = 0.004) were associated with shorter patient waiting time (Table 3).

Physician diagnostic time: Univariate analysis of physician diagnostic time revealed that the predominant symptoms of diarrhea (P = 0.003), skin lesions (P = 0.044), joint pain (P = 0.066), and weight loss (P = 0.044), as well as the common

Table 2 Univariate analysis

Parameter		Patient waiting time		Physician diagnostic time	
		HR	*P* value	HR	*P* value
Sex, female *vs* male	CD	1.235	0.089	0.852	0.222
	UC	0.954	0.714	0.897	0.407
Age, ≤ 40 *vs* > 40 yr	CD	1.071	0.654	1.176	0.329
	UC	1.407	0.031	1.109	0.508
Year of diagnosis, ≤ 2000 *vs* > 2000	CD	1.081	0.520	0.975	0.846
	UC	0.947	0.666	0.976	0.856
Predominant symptom					
Diarrhea, yes *vs* no	CD	0.826	0.116	1.484	0.003
	UC	1.141	0.305	1.065	0.640
Constipation, yes *vs* no	CD	2.045	0.440	1.835	0.517
	UC	1.011	0.991	0.882	0.893
Abdominal pain, yes *vs* no	CD	1.307	0.038	0.834	0.191
	UC	1.096	0.701	0.708	0.167
Heartburn, yes *vs* no	CD	0.975	0.979	0.826	0.844
Bloating, yes *vs* no	UC	0.218	0.010	0.789	0.664
Blood in stool, yes *vs* no	CD	0.609	0.069	1.272	0.419
	UC	1.014	0.916	0.999	0.993
Nausea/vomiting, yes *vs* no	CD	1.216	0.520	0.675	0.233
Skin, yes *vs* no	CD	1.164	0.872	5.178	0.044
	UC	0.295	0.138	3.637	0.108
Joint pain, yes *vs* no	CD	0.844	0.703	0.323	0.039
Fistula, yes *vs* no	CD	2.450	0.032	0.656	0.334
Weight loss, yes *vs* no	CD	0.387	0.236	5.178	0.044
Fever, yes *vs* no	CD	0.387	0.236	0.620	0.619
	UC	6.191	0.026	1.207	0.838
Fatigue, yes *vs* no	CD	1.482	0.335	1.452	0.390
	UC	1.652	0.225	1.937	0.101
Symptoms					
Diarrhea, yes *vs* no	CD	0.590	< 0.001	0.947	0.732
	UC	1.331	0.068	1.028	0.867
Constipation, yes *vs* no	CD	1.103	0.644	0.747	0.209
	UC	1.031	0.921	0.808	0.513
Abdominal pain, yes *vs* no	CD	0.988	0.934	0.963	0.812
	UC	1.018	0.889	0.952	0.708
Heartburn, yes *vs* no	CD	0.988	0.947	0.735	0.110
	UC	0.697	0.140	1.014	0.955
Bloating, yes *vs* no	CD	0.827	0.150	0.842	0.235
	UC	0.814	0.132	0.960	0.770
Blood in stool, yes *vs* no	CD	0.932	0.572	0.889	0.393
	UC	0.970	0.856	0.913	0.586

Nausea/vomiting, yes *vs* no	CD	1.264	0.075	1.082	0.574
	UC	1.210	0.334	0.966	0.864
Skin, yes *vs* no	CD	0.801	0.261	0.628	0.036
	UC	0.663	0.157	0.947	0.859
Joint pain, yes *vs* no	CD	0.882	0.403	0.733	0.066
	UC	0.780	0.309	0.836	0.478
Fistula, yes *vs* no	CD	1.280	0.231	0.937	0.770
	UC	0.694	0.421	0.766	0.574
Weight loss, yes *vs* no	CD	1.019	0.875	0.900	0.416
	UC	1.400	0.016	0.893	0.429
Fever, yes *vs* no	CD	1.196	0.239	1.142	0.420
	UC	1.381	0.150	1.654	0.026
Fatigue, yes *vs* no	CD	1.094	0.457	0.959	0.746
	UC	0.961	0.757	0.767	0.045
EIM, yes *vs* no	CD	0.902	0.450	0.784	0.104
	UC	0.745	0.129	0.913	0.651
Location					
Upper GI, yes *vs* no	CD	1.198	0.400	1.256	0.323
	UC	0.813	0.748	0.668	0.545
Small bowel, yes *vs* no	CD	0.910	0.461	0.929	0.594
	UC	1.007	0.976	0.818	0.411
Terminal ileum, yes *vs* no	CD	0.964	0.778	1.183	0.237
	UC	0.849	0.432	1.087	0.700
Colon, yes *vs* no	CD	1.135	0.292	0.927	0.565
	UC	1.014	0.924	1.012	0.934
Rectum, yes *vs* no	CD	1.075	0.616	1.043	0.791
	UC	0.864	0.251	0.907	0.457
Disease severity, strong vs mild	CD	1.359	0.023	1.240	0.154
	UC	1.098	0.469	1.247	0.096
Diagnosis made in hospital, yes vs no	CD	0.915	0.464	0.992	0.952
	UC	1.314	0.039	1.013	0.923
Diagnosis made by gastroscopy, yes vs no	CD	1.059	0.891	2.857	0.011
	UC	1.520	0.644	0.804	0.815
Family history, positive vs negative	CD	1.587	0.005	1.073	0.697
	UC	0.767	0.120	0.708	0.053
Medication, strong vs mild	CD	1.067	0.647	0.965	0.816
	UC	0.967	0.794	0.991	0.944

The bold binary parameter denotes to what the hazard ratio is referring to. Items with *P*-value < 0.1 in univariate analysis were entered into the multivariate model. CD: Crohn's disease; EIM: Extraintestinal manifestation; GI: Gastrointestinal tract; UC: Ulcerative colitis.

symptoms of skin lesions (P = 0.036), joint pain (P = 0.066), and performance of diagnostic gastroscopy (P = 0.011) were linked with shorter physician diagnostic time. The univariate analysis of risk factors for physician diagnostic time are presented in Table 2.

Table 3 Multivariate analysis for Crohn's disease

Parameter	Patient waiting time		
	HR	95%CI	*P* value
Abdominal pain[1]	1.428	1.062-1.919	0.018
Fistula[1]	2.841	1.125-7.175	0.027
Positive family history	1.734	1.196-2.514	0.004

[1]Predominant symptom.
CI: Confidence interval; HR: Hazard ratio.

The predominant symptoms of diarrhea (HR = 1.438, $P = 0.012$), skin lesions (HR = 9.746, $P = 0.028$), and performance of diagnostic gastroscopy (HR = 2.570, $P = 0.042$) were associated with shorter physician diagnostic time in the multivariate analysis (Table 4).

Total diagnostic time: In patients with CD, total diagnostic time was longer with the symptom of joint pain (HR = 0.696, $P = 0.048$) and shorter with performance of diagnostic gastroscopy (HR = 3.019, $P = 0.018$; data not shown). Location of disease, place of residence at time of diagnosis or year of diagnosis (≤ 2000 *vs* > 2000) had no effect on the three relevant time intervals shown in Table 2 and were therefore not included in the multivariate model.

UC

Patient waiting time: Univariate analysis of UC patients showed that age ≤ 40 years ($P = 0.031$), predominant symptoms of fever ($P = 0.026$), diarrhea ($P = 0.068$) and weight loss ($P = 0.016$), and diagnosis made in a hospital setting ($P = 0.039$) were associated with shorter patient waiting time. The predominant symptom of bloating ($P = 0.010$) was associated with longer patient waiting time.

In the multivariate analysis, the predominant symptom of bloating was associated with longer patient waiting time (HR = 0.207; $P = 0.029$), whereas diarrhea was associated with shorter patient waiting time (HR = 1.463, $P = 0.034$) (Table 5).

Physician diagnostic time: In UC, fever ($P = 0.026$), fatigue ($P = 0.045$), strong disease severity ($P = 0.096$) and negative family history of IBD ($P = 0.053$) were associated with shorter physician diagnostic time (Table 2). In the multivariate analysis, fever was associated with shorter physician diagnostic time (HR = 1.813; $P = 0.020$) and fatigue (HR = 0.685; $P = 0.011$) was associated with longer physician diagnostic time. Surprisingly, a positive family history for IBD (HR = 0.681; $P = 0.046$) was also associated with longer physician diagnostic time (Table 6).

Total diagnostic time: On multivariate analysis, fever was associated with shorter total diagnostic time (HR = 0.743, $P = 0.032$) and the predominant symptom of fatigue with longer total diagnostic time (HR = 0.285, $P = 0.007$; data not shown). Location of disease, place of residence at diagnosis, or year of diagnosis were not linked with any of the three diagnostic intervals.

DISCUSSION

This is the first study in an adult German IBD population to evaluate diagnostic delay, which in addition provides further focus on patient-related and physician-related risk factors. We confirmed the previous observations of markedly longer total diagnostic time in CD patients, which in our study was shown to be mainly physician related[4,5,8]. Disease-specific symptoms and easily available diagnostics led to a reduction in physician diagnostic time. A positive family history decreased patient waiting time, whereas it had no effect on the physician diagnostic time in CD patients. Positive family history increased physician diagnostic time in UC patients. Inexplicably, no significant improvement in diagnostic time has been observed over the last 50 years, as demonstrated by comparing diagnostic time from before and after the turn of the millennium.

The IBD incidence has markedly increased worldwide over the last several decades[15,16]. However, regional differences in care patterns are well described and make cross-comparisons difficult due to differences in access and utilization of healthcare services, socioeconomic status, environmental factors, and varying degrees of implementation of clinical guidelines[8,13]. Previously there were no data on diagnostic delay from a German national cohort. However, knowledge of risk factors for diagnostic delay is crucial to reduce time to diagnosis and improve patient outcomes. Previous studies have extensively demonstrated that diagnostic delay is associated with an increased risk of IBD-related complications and need for colorectal surgery, as well as significantly reduced quality of life and lack of response to medical therapy[7,8,12,17]. However, identified risk factors may not be applicable in patients of different background and in different healthcare systems and evaluation in a German cohort hence is critical.

In our German CD patients, the total diagnostic time was on average 12 months, which was longer in UC with only 4 months (Figure 2C). This finding is consistent with previously published data regarding diagnostic time in CD *versus* UC

Table 4 Multivariate analysis of physician diagnostic time in Crohn´s disease

Parameter	Physician diagnostic time		
	HR	95%CI	*P* value
Diarrhea[1]	1.438	1.085-1.906	0.012
Skin lesions[1]	9.746	1.273-74.609	0.028
Gastroscopy	2.570	1.037-6.371	0.042

[1]Predominant symptom.
CI: Confidence interval; HR: Hazard ratio.

Table 5 Multivariate analysis for ulcerative colitis

Parameter	Patient waiting time		
	HR	95%CI	*P* value
Bloating[1]	0.207	0.050-0.848	0.029
Diarrhea	1.463	1.030-2.079	0.034

[1]Predominant symptom.
CI: Confidence interval; HR: Hazard ratio.

Table 6 Multivariate analysis of physician diagnostic time in ulcerative colitis

Parameter	Physician diagnostic time		
	HR	95%CI	*P* value
Fatigue	0.685	0.512-0.917	0.011
Fever	1.813	1.096-2.999	0.020
Positive family history	0.681	0.466-0.994	0.046

CI: Confidence interval; HR: Hazard ratio.

patients. Cantoro *et al*[18] reported a median diagnostic time of 7.1 *vs* 2.0 months in Italian patients, Vavricka *et al*[6] reported 9 *versus* 4 months in Swiss patients, and Nguyen *et al*[5] described 9.5 *versus* 3.1 months in American patients. This marked difference between CD and UC could be attributed to a higher frequency of nonspecific symptoms, such as abdominal pain, in CD compared with UC.

Studies that systematically evaluate the reasons for diagnostic delay are scarce. In this study we also differentiated between patient-related and physician-related causes for the delay. Of note, the diagnostic delay in CD patients was mainly attributed to increased physician diagnostic delay (5.5 months in CD *vs* 1.0 month in UC). In UC patients, the patient-related time interval was almost equal to the physician-related time interval (2.0 months *vs* 1.0 month). This finding compares favorably with the previously reported data[5]. One explanation is the marked symptom variance of patients with CD compared to patients with UC, with a large symptom overlap between IBD and functional disease complaints. In our study, nonspecific symptoms such as abdominal pain or nausea/vomiting were increased in CD (Table 1). CD patients were 2.2 times more likely than UC patients to have an EIM of IBD at the time of disease onset. The effect of atypical *versus* typical IBD symptoms on time to diagnosis is again demonstrated by the time interval to physician diagnosis. In our study, the presence of prolonged diarrhea and skin manifestations was independently associated with early physician diagnosis in CD patients (Table 3). High symptom severity was linked with faster diagnosis, likely due to triggering further investigation. In UC patients, fever shortened the physician's diagnostic time, whereas the nonspecific symptom, fatigue, prolonged the diagnostic interval. Surprisingly, rectal bleeding was more commonly reported in our UC patients but was not associated with faster diagnosis (Table 2). In our study a performance of gastroscopy was associated with decreased physician diagnostic time in CD patients, possibly being a surrogate marker indicating better access to diagnostic endoscopy (Table 3).

In the context of diagnostic delay in CD patients, the impact of a positive family history should also be noted. Surprisingly, a positive family history was independently associated with shorter patient waiting time in CD patients, but did not influence physician diagnostic time (Figure 3). Even when patients are aware of their genetic predisposition, the diagnosis is not easily made by the physician. This could be attributed to lack of knowledge, delayed referral or long

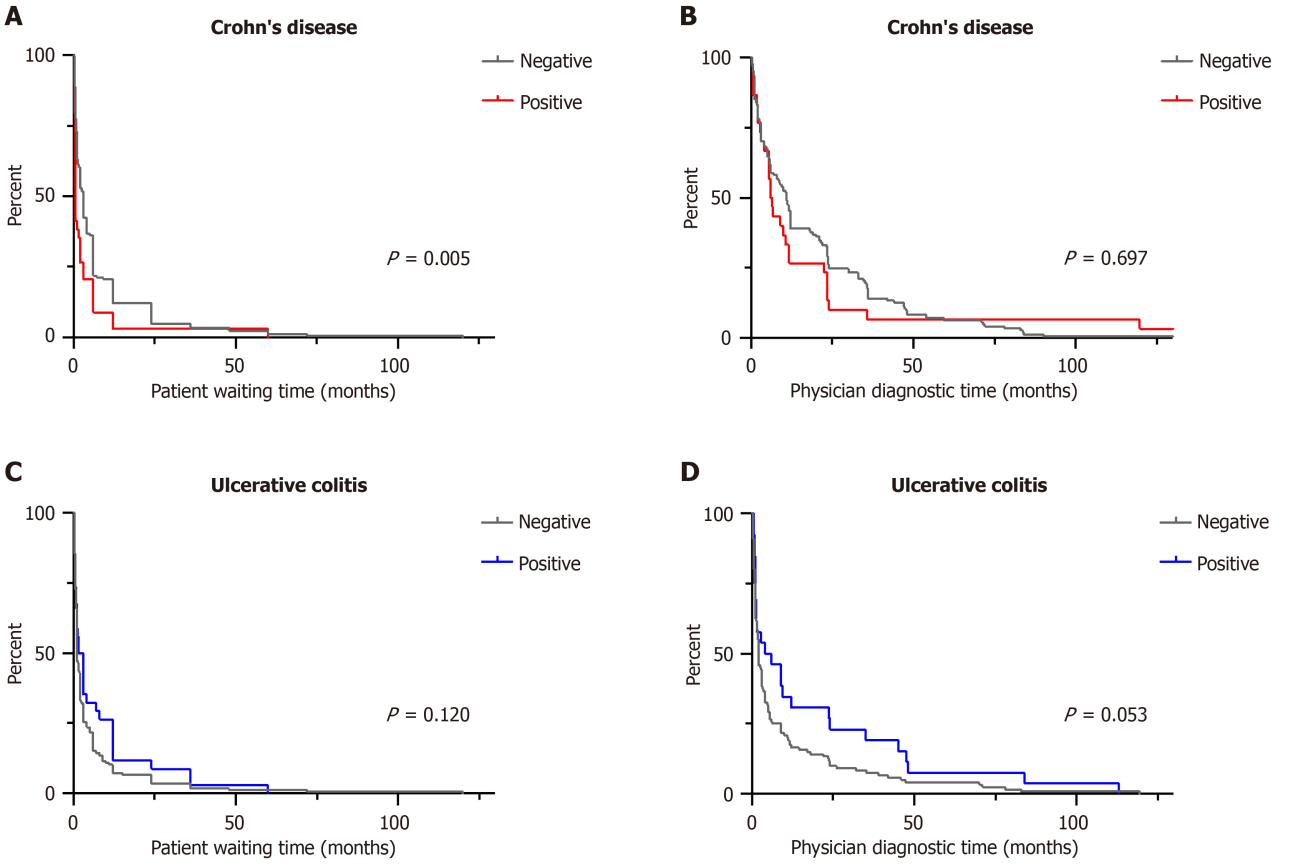

Figure 3 Diagnostic time depending on family history for inflammatory bowel disease. A: A positive family history of inflammatory bowel disease was associated with reduced patient waiting time in Crohn's disease (CD); B: But did not affect physician diagnostic time in CD patients; C: A positive family history did not affect patient waiting time in ulcerative colitis (UC) patients; D: But delayed physician diagnostic time in UC patients.

waiting times for relevant diagnostic procedures. In Germany, health insurance is universal and includes all relevant diagnostic procedures. Moreover, adults receive routine preventive medical care from a general practitioner. The time between the primary care visit and the specialist appointment may be a crucial period to intervene and prevent disease complications. The prevalence of general gastrointestinal complaints (5%–11%) is markedly higher compared to IBD (0.2%) in primary care[19,20]. Functional bowel disorders like IBS often mimic early manifestations of CD, which may delay referral to a gastroenterologist. Moon *et al*[11] demonstrated comparable results regarding the negative impact of family history on time to diagnosis. However, conflicting results have been reported in the literature[12]. This inconsistency might be partly explained by different patient populations in different regions. In summary, the significance of patients' symptoms and family history should not be underestimated. Our results emphasize the importance of the medical history especially when IBD is suspected.

As therapies continue to advance and the incidence of IBD has steadily increased in recent years, IBD continues to gain more attention[13]. Despite these advances, recent studies have shown no change in time to diagnosis over the past few decades[18]. In line with these data, we discovered that the total diagnostic time in CD and UC has not changed between 1964 to 2021. It is clear, that clinicians' lack of knowledge and patients'access to specialists including dedicated diagnostics, outweighs the advancement of diagnostic modalities. This lack of change has been a persistent problem for the last 57 years with a huge impact on the quality of life of patients, and as a result, warrants further action. Knowing that early treatment improves disease outcome, it is important to focus our awareness on this lack of rigor in the existing literature.

Firstly, we want to emphasize the importance of screening tools in primary care. Clinical routine is increasingly determined by time constraints and expanding knowledge about rare diseases. The "Red Flags Index for Suspected CD" by Danese *et al*[21] has established method of diagnostic accuracy to discriminate healthy controls from IBS and early CD. Easily accessible tools, such as the 8-item questionnaire (CalproQuest) can help to identify potential IBD patients[20]. Questions for perianal fistula, first-degree relatives, weight loss, chronic abdominal pain (not after meals), nocturnal diarrhea, mild fever and rectal urgency can help to screen patients for IBD, especially CD. Implementation of these screening tools in early clinical practice might be the first step to meet the requirements of a timely diagnosis in CD. In addition, the noninvasive biomarker, fecal calprotectin, is a sensitive marker for gut inflammation and is now widely established to distinguish between IBS and IBD[22]. However, it must be noted that calprotectin can also be elevated in other differential diagnoses such as gastritis, polyps, diverticulitis or during the use of proton pump inhibitors.

Secondly, educational programs for general practitioners should specifically target early symptoms, signs, and characteristics of IBD with difficult-to-predict courses, and diverse complications. The respective practitioner level of knowledge about disease symptoms as well as the diagnostic workup are important factors regarding disease identification.

Thirdly, public awareness programs and patient educational training focusing on disease heredity, empower patients to become active participants in a patient-centered care model. Additionally, direct access to specialist appointments for patients may also be helpful to reduce the diagnostic delay. Utilizing these tools can improve patients' quality of life, disease outcome and diagnostic delay[23].

Our study had several limitations. This study focused on the course of IBD diagnosis and did not include well-known disease-modifying factors such as smoking habits or educational level. We did not include disease-related complications, but recognize the influence and relevance they may have on disease outcome. In our analysis we could not find a significant correlation of the type of initial medication as a surrogate marker of disease severity and the diagnostic time periods. However, we did not consider this to be a weakness of our study because the primary focus was on the time to diagnosis. This study was not designed as a longitudinal study. Our study design was patient-reported questionnaire-based, which may have led to recall bias. Our Berlin patients do not represent a population-based cohort for Germany. Finally, our population was composed of patients from tertiary referral centers, which may have introduced relevant selection bias.

CONCLUSION

Despite these limitations, we present in the first German adult IBD cohort that CD patients, more than UC patients, are at risk of a long diagnostic delay, which is mainly physician dependent. Disease-specific symptoms and readily available diagnostics resulted in a reduction in physician diagnostic time. We conclude that good interdisciplinary collaboration, physicians' awareness, and screening tools are imperative to reduce diagnostic delay and therefore improve treatment starting position, course of disease and patient satisfaction.

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FOOTNOTES

Author contributions: Blüthner E analyzed and interpreted data, drafted and submitted the manuscript; Dehe A designed and performed research; Büning C performed research; Siegmund B interpreted the data; Prager M performed research; Maul J performed research; Krannich A analyzed data; Preiß J performed research; Wiedenmann B interpreted the data; Rieder F and Khedraki R reviewed and edited the manuscript, Tacke F interpreted the data; Sturm A performed research; Schirbel A designed and performed research as well as interpreted the data; all authors have revised and approved the final manuscript.

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