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Observational Study

Diagnostic delay in inflammatory bowel diseases in a German population

Diagnostic delay in German IBD patients

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Abstract

BACKGROUND

AIM

Therefore, the aim of this study is to identify risk factors impairing diagnostic time.

METHODS

Between 2012 and 2022, a total of 430 IBD patients from four Berlin hospitals were enrolled in a prospective study and asked to complete a 16-item questionnaire to determine their diagnostic IBD course. Total diagnostic time was defined as the time from first symptoms 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 CD patients compared to UC patients (12.0 vs. 4.0 months; p<0.001), mainly due to increased physician diagnostic time (5.5 vs. 1.0 months; p<0.001). Multivariate analysis identified the predominant symptoms diarrhea (*P* = 0.012) and skin lesions (*P* = 0.028) as well as gastroscopy (*P* = 0.042) were associated with longer physician diagnostic time in CD patients. In UC, multivariate analysis showed that 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 in a German IBD cohort that CD patients in comparison to UC patients are at risk for long diagnostic delay that is less patient- and more physician-dependent. Disease-specific symptoms and rapidly available diagnostic tools resulted in reduced physician diagnostic time. Efforts should be undertaken to shorten the diagnostic delay for a better outcome in these patients.

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

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Core Tip: Early diagnosis is key to reduce complications and improve response to medical therapy. This prospective questionnaire-based study aimed to identify risk factors impairing diagnostic time. In this study we demonstrated that diagnostic delay was significantly longer in CD compared to UC patients and was mainly physician-

depended. The multivariate analysis showed that disease-specific symptoms and rapidly available diagnostic tools resulted in reduction of physician diagnostic time.

INTRODUCTION

Crohn`s disease (CD) and ulcerative colitis (UC) are the most common forms of inflammatory bowel disease (IBD) defined as chronic relapsing and destructive inflammatory disorders of the gastrointestinal tract caused by multifactorial origin. Discussed are polygenic, environmental microbial and immunological causes, that can lead to a pathological immune reaction of the intestine. This process could facilitate for bacterial or viral agents to activate the mucosal immune system leading to intestinal and systemic inflammation [1]. IBD manifests primarily in the intestine but may also be unique in the context of extraintestinal manifestations or any other associated autoimmune disease of any other organs or organ systems [1,2]. Due to this heterogeneous and non-specific clinical presentation, as well as the low accuracies of biomarker tests, diagnosis of IBD can be challenging and often results in a prolonged time from the first symptoms to an established final 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 months likely due to different medical standards and regional differences in disease behaviour [4–7].

However, prompt diagnosis and treatment of these patients is of critical. Recently published studies have shown that early therapeutic intervention reduces the need for surgery as well as severe disease progression with complications [5,8]. Furthermore, early intensive treatment has been associated with improved responses to immunomodulators or targeted biologic therapy [9]. There is also strong evidence that diagnostic delay affects patients' quality of life and places a burden on the health care 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]. Furthermore, as most of the studies were performed in countries with different medical provider systems, further results from Central Europe patients are lacking [4,6,8,11,12]. Considering the east-west gradient in the incidence of IBD more research should be done on these patients [13]. Therefore, we aim to comprehensively assess risk factors for delayed diagnosis in a German IBD cohort to contribute to a better understanding and management of IBD patients.

MATERIALS AND METHODS

Study design

From May 2012 to May 2022, a total of 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 three hospital sites at the Charité – Universitätsmedizin Berlin and one other public hospital: 42.3 % at Charité – Campus Mitte, 28.4% at Charité – Virchow Klinikum, 26.0% at Charité – Benjamin Franklin and 18% at Krankenhaus Waldfriede Berlin-Zehlendorf.

We included adult patients with confirmed CD/UC diagnosis with duly complete questionaries and excluded patients who were unable to consent due to mental incapacity or language barriers. Study participants were interviewed once after written informed consent was obtained. 430 (83.3%) questionnaires could be included in the study after reviewing the inclusion and exclusion criteria. 54 patients did not complete the questionnaire, 15 questionnaires were excluded because of a diagnosis of indeterminate colitis, 3 were excluded because of a diagnosis of irritable bowel syndrome (IBS), 4 patients did not sign the informed consent form correctly and 7 patients were excluded because of duplicate entries. A total of 430 adult patients who had been diagnosed with either CD or UC at least six months prior to the survey were enrolled in 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

We used a questionnaire completed by IBD patients themselves comprising 16 questions to investigate demographic and disease-specific factors that may directly or indirectly play a role for the delay of diagnosis. In addition to patient age and sex of the patients, urban or rural residence, medical facts such as predominant symptoms and general symptoms at diagnosis, severity of symptoms, site of disease, who and how IBD was diagnosed, and whether the patient had affected family members or had ever heard of IBD as well as initial medical treatment, were recorded. Extraintestinal manifestations (EIM) were defined as the presence of ankylosing spondylitis, aphthous stomatitis, erythema nodosum, peripheral arthritis, primary sclerosing cholangitis, psoriasis, pyoderma gangrenosum, or uveitis. Initial medication was categorized as mild (rectal treatment, mesalazine, budesonide) and strong (cortisone, azathioprine, methotrexate, infliximab, adalimumab).

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

Statistical analysis

Statistical analysis was performed using SPSS Statistics 22 software (SPSS Inc., Chicago, IL, USA). Figures were created using Prism 6 software (GraphPad Software, Inc., La Jolla, USA). We used the Kolmogorov-Smirnoff test to determine the distribution of our data. Continuous variables are presented as median and interquartile range (IQR), differences were compared by the Kruskal-Wallis test or Mann-Whitney U test.

Categorical data are expressed in the form of number and percentages and were compared by the chi-squared test.

Univariate analysis of the different clinically relevant factors associated with diagnostic time was performed using Kaplan–Meier survival method and the differences were compared by log-rank test. We also present hazard ratios (HR) for the univariate analysis. Hazard ratios exceeding unity (HR > 1) represent a better chance for early diagnosis. All variables with a p-value < 0.1 in univariate analysis were further used for multivariate analyses using Cox's proportional hazard model in a backward stepwise manner. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Patient characteristics for IBD patients are summarized in Table 1. A total of 223 patients with Crohn´s disease and 207 patients with ulcerative colitis were enrolled into the study. Patients were predominantly female (54.4%) with a median age of 26 (20 – 25) years in CD and 28 (21 – 39) years in UC at diagnosis, respectively. The most common reported symptoms were diarrhea in CD 43.5 % vs. 48.8 % in UC followed by abdominal pain in CD (33.2 %) and blood in stool in UC (33.8 %). The predominant site of disease at the time of diagnosis were the terminal ileum in CD (68.6 %) and the colon in UC (74.4 %), respectively. Therefore, significantly more patients were diagnosed with UC based on colonoscopy (78.5 vs. 96.1%; p < 0.001) *vs* CT (3.1 vs. 0.5 %; *P* = 0.037) and MRI (2.2 vs. 0.5 %; *P* = 0.028) in CD. Diagnosis was predominantly made in hospitals for CD (46.6 vs. 35.5 %) and by a gastroenterologist in UC (38.1 vs. 46.9 %). The CD patients reported more severe symptoms (33.6 % vs. 23.7 %; *P* = 0.023) compared to UC patients with significantly more EIM (26.0 % vs. 12.1 %; p< 0.001).

Total diagnostic time in CD was significantly longer in CD compared to UC (12.0 months [IQR 6.0 – 24.0] vs. 4.0 months [IQR 1.5 – 12.0]; p< 0.001). While the patient waiting time was similar in CD and UC (2.0 months [IQR 0.5 – 6.0] vs. 1.0 months [IQR 0.5 – 4.0]; *P* = 0.051), the physician diagnostic time was significantly longer in CD

patients (5.5 months [IQR 0.75 – 23.5] vs. 1.0 month [IQR 0 – 5.0]; p< 0.001). All three diagnostic time intervals for CD and UC are depicted as a Kaplan-Meier curves in Figure 2.

Crohn's disease

Patient waiting time

In the univariate analysis of CD, patient waiting time was negatively associated with female sex (P = 0.089), living abroad (P = 0.020) predominant symptoms of abdominal pain (P = 0.038), fistula (P = 0.032), nausea/vomiting (P = 0.075), strong disease severity (P = 0.023), positive family history of IBD (P = 0.005) and positively correlated 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 identified the predominant symptoms abdominal pain (HR 1.428; P = 0.018) and fistula (HR=2.841; P = 0.027) and positive family history (HR=1.734; P = 0.004) are negatively correlated with 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 symptoms of skin lesions (P = 0.036) and joint pain (P = 0.066), and diagnostic gastroscopy (P = 0.011) were negatively associated with physician diagnostic time. The univariate analysis of risk factors for physician diagnostic span are presented in Table 2.

The predominant symptoms diarrhea (HR=1.438, P = 0.012) and skin lesions (HR 9.746, P = 0.028) as well as diagnostic gastroscopy (HR 2.570, P = 0.042) were negatively associated with physician diagnostic time in the multivariate analysis (Table 3).

Total diagnostic time

In patients with CD, the total diagnostic time was positively associated with joint pain (HR 0.696, $P = 0.048$) and negatively associated with gastroscopy (HR 3.019, $P = 0.018$; data not shown).

Of note, site of disease, place of residence at diagnosis or year of diagnosis had no effect on the three relevant time intervals shown in Table 2 and were therefore not included in the multivariate model.

Ulcerative colitis

Patient waiting time

Univariate analysis of UC patients showed that age ≤ 40 years ($P = 0.031$), predominant symptom other than bloating ($P = 0.010$), predominant symptom fever ($P = 0.026$), diarrhea ($P = 0.068$), weight loss ($P = 0.016$), and hospital diagnosis ($P = 0.039$) were negatively associated with patient waiting time.

In the multivariate analysis, the predominant symptom bloating was positively associated with patient waiting time (HR 0.207; $P = 0.029$), whereas diarrhea was negatively associated with patient waiting time (HR 1.463, $P = 0.034$) as presented in Table 4.

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 negatively associated with physician diagnostic time (Table 2). In the multivariate analysis, fever was negatively associated with physician diagnostic time (HR 1.813; $P = 0.020$) and fatigue (HR 0.685; $P = 0.011$) was positively associated with physician diagnostic time. Surprisingly, a positive family history for IBD (HR 0.681; $P = 0.046$) was also positively associated with physician diagnostic time (Table 4).

Total diagnostic time

On multivariate analysis, fever was negatively associated with total diagnostic time (HR 0.743, $P = 0.032$) and positively correlated in patients with the predominant symptom of fatigue (HR 0.285, $P = 0.007$; data not shown).

Again, site of disease, place of residence at diagnosis, or year of diagnosis showed no effect on any of the three diagnostic intervals.

DISCUSSION

This is the first German study to evaluate diagnostic delay and further focus on patient-related and physician-related risk factors in a large adult IBD cohort. According to previous studies, we confirmed a significantly longer diagnostic time in CD patients, which in our study was mainly physician-related [4,5,8]. Disease-specific symptoms and readily available diagnostics led to a reduction in physician diagnostic time. Paradigmatically, a positive family history independently decreased patient waiting time, whereas it had no effect on the physician diagnostic time in CD patients and interestingly increased physician diagnostic time in UC patients. Inexplicably, no significant improvement in diagnostic time has been observed over the last 50 years, as evidenced by the same diagnostic time spans before and after the millennium (data not shown).

The IBD incidence has markedly increased worldwide over the last decades [15,16]. However, regional differences are well known and make cross-comparisons difficult due to differences in access and utilization of health care services, socioeconomic status, environmental factors, and implementation of guidelines [8,13]. To date, there are no data on diagnostic delay from a German national cohort exist. However, knowledge of risk factors for diagnostic delay is crucial to reduce the diagnostic delay and thus improve outcomes for these patients. Previous studies have extensively demonstrated that diagnostic delay is associated with an increased risk of IBD- related complications and colorectal surgery, as well as significantly reduced quality of life and response to

medical therapy [7,8,12,17]. However, it is not appropriate to extrapolate of these study results to a German study cohort.

In our German CD patients, the total diagnostic time was 12 months on average, which was significantly longer than in UC patients with 4 months (Figure 2C). This finding was consistent with previously published data regarding to diagnostic time in CD vs. UC patients. Cantoro *et al* reported a median diagnostic time of 7.1 vs. 2.0 months in Italian patients, Vavricka *et al* reported 9 vs. 4 months in Swiss patients, and Nguyen *et al* described 9.5 *vs* 3.1 months in U.S. patients [5,6,18]. This markedly difference might be due to often more unspecific symptoms in CD than in UC with more abdominal pain and discomfort.

Studies that systematically evaluate the reasons for diagnostic delay are scarce. In this study we also decided to differentiate between patient-related and physician-related delay. Of note, the diagnostic delay in CD patients was mainly attributed to increased physician diagnostic delay (5.5 in CD vs. 1.0 months in UC). In UC patients, the patient related time interval was almost equal to the physician related time interval (2.0 vs. 1.0 months). This finding compares favourably with the previously reported data [5]. One explanation is the marked symptom variance of patients with CD compared to patients with UC with an overlap of functional disease complaints. In our study, non-specific symptoms such as abdominal pain or nausea/vomiting were significantly increased in CD (Table 1). Furthermore, CD patients were 2.2 times more likely than UC patients to have an extraintestinal manifestation (EIM) of IBD at the disease onset than UC patients. The effect of atypical features *vs* typical IBD hallmarks is again demonstrated by the time to physician diagnosis. In our study, the presence of prolonged diarrhea and skin manifestations were independently associated with early physician diagnosis in CD patients (Table 3). Furthermore, high-intensity symptoms were considered more worthy of further investigation, leading to faster diagnosis. In UC patients, fever shortened the physician`s diagnostic time, whereas the non-specific symptom fatigue prolonged the diagnostic interval. Surprisingly, rectal bleeding was more commonly

reported in our UC patients but was not associated with faster diagnosis in the subgroup analysis (Table 2).

The diagnosis of CD is also complicated by frequent involvement of proximal small bowel accompanied by nonspecific symptoms and limited test accuracy of conventional examination. Whereas colon is easier accessible, upper endoscopy is easier available due to faster diagnostic procedure. Indeed, in our study a gastroscopy was associated with decreased physician diagnostic time in CD patients possibly due to the easier upper gastrointestinal examination (Table 3). Obviously, novel noninvasive instruments are warrant to shorten this diagnostic delay especially in CD patients. Interestingly, in the aforementioned Italian cohort the diagnostic delay was mainly attributed to the physician diagnostic time [18]. In Germany, a growing awareness of functional bowel disorders increases the challenge to distinguish between irritable bowel syndrome (IBS) and organic bowel disease.

In the context of diagnostic delay in CD patients, the effect of 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 even gain significance in the univariate analysis of physician diagnostic time (Figure 3). In brief, even when patients are aware of their genetic predisposition the diagnosis is not easily made by the physician. This could be explained by lack of knowledge, delayed referral or long waiting times for relevant diagnostic procedures. In Germany, the health insurance is universal and cover all relevant diagnostic procedures. Moreover, adults receive regular preventive medical care from a general practitioner. The time between the primary care visit and the specialist appointment may be crucial to intervene before disease complications occur. The prevalence of gastrointestinal complaints (5 – 11%) is higher compared to IBD (0.2%) in primary care [19,20]. Furthermore, functional bowel disorders like IBS often mimic early manifestations of CD, delaying referral to a gastroenterologist. Thus, 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.

Moon *et al* demonstrated comparable results regarding the negative impact of family history on establishment of diagnosis [11]. However, conflicting results have been reported in literature [12]. This inconsistency might be partly explained by variable definitions and epidemiological aspects.

As therapies continue to advance and the incidence of IBD has steadily increased in the recent years, IBD is receiving more and more attention [13]. Despite these advances, recent studies have shown no change in diagnostic duration over the past decades [18]. In line with these data, we found out that the diagnostic duration in CD and UC has not changed from 1964 to 2021. It is clear, that physician ignorance and access to specialists including dedicated diagnostics, presumably outweigh the advancement of diagnostic modalities. This lack of change has been a persistent problem for the last 57 years with a massive impact on the quality of life of patients and therefore warrants further action in this area. Moreover, knowing that early treatment improves disease outcome, it is of tremendous importance to focus our awareness on these patients.

First and foremost, we want to emphasize the importance of screening tools in primary care. Clinical routine is more and more determined by time constraints and rising knowledge about rare diseases. The "Red Flags Index for Suspected Crohn's Disease" by Danese *et al* has shown a good diagnostic accuracy to discriminate healthy controls from IBS and early Crohn's disease [21]. 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, chronical 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 non-invasive biomarker fecal calprotectin is a sensitive marker for gut inflammation and is now widely established to distinguish between IBS and

IBD [22]. But it must be noted that Calprotectin can also be elevated in other differential diagnosis 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 level of knowledge about disease complaints as well as the handling of medical resources are important factors in regard to disease identification. Thirdly, public awareness programs and patient educational training focussing on heredity, empower patients to become active participants in a patient-centered care which otherwise require good communication skills of the physician. Direct access to specialist appointments for patients may be also helpful to reduce the diagnostic delay. Using all these tools, the patient`s quality of life, disease outcome and diagnostic delay can be improved [23].

Our study has some limitations that need to be mentioned. First, this study focusses on the course of IBD diagnosis and therefore neglects possible contributing well known disease-modifying factors such as smoking habits or educational level. We did not ask about disease-related complications which would be of particular interest as these are outcome relevant. In our analysis we could not find a statistically significant correlation of the potency of the initial medication as a marker of disease severity and the diagnostic time periods. However, we do 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. Secondly, our study design is questionnaire-based self-administered, which may lead to a recall bias. Thirdly, our Berlin patients are only partially populations-based for Germany. Finally, our patient population is composed of patients from third referral centers which may introduce a relevant selection bias.

CONCLUSION

Despite these limitations, we have shown the first German adult IBD cohort that CD patients even more than UC patients are at risk a long diagnostic delay which is mainly

physician dependent. Disease-specific symptoms and readily available diagnostics resulted let to 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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