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Gender Biases and Diagnostic Delay in Inflammatory Bowel Disease: Multicenter Observational Study

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Background: Female gender could be a cause of diagnostic delay in inflammatory bowel disease (IBD). The aim of this study was to investigate the diagnostic delay in women vs men and potential causes.

Methods: This multicenter cohort study included 190 patients with recent diagnosis of IBD (disease duration <7 months). Reconstruction of the clinical presentation and diagnostic process was carried out in conjunction with the semistructured patient interview, review, and electronic medical records.

Results: The median time from symptom onset to IBD diagnosis was longer in women than in men: 12.6 (interquartile range, 3.7-31) vs 4.5 (2.2-9.8) months for Crohn's disease (CD; $P = .008$) and 6.1 (3-11.2) vs 2.7 (1.5-5.6) months for ulcerative colitis (UC; $P = .008$). Sex was an independent variable related to the time to IBD diagnosis in Cox regression analysis. The clinical presentation of IBD was similar in both sexes. Women had a higher percentage of misdiagnosis than men (CD, odds ratio [OR], 3.9; 95% confidence [CI], 1.5-9.9; UC, OR 3.0; 95% CI, 1.2-7.4). Gender inequities in misdiagnosis were found at all levels of the health system (emergency department, OR 2.4; 95% CI, 1.1-5.1; primary care, OR 2.5; 95% CI, 1.3-4.7; gastroenterology secondary care, OR 3.2; 95% CI, 1.2-8.4; and hospital admission, OR 4.3; 95% CI, 1.1-16.9).

Conclusions: There is a longer diagnostic delay in women than in men for both CD and UC due to a drawn-out evaluation of women, with a higher number of misdiagnoses at all levels of the health care system.

Lay Summary

This paper shows a longer delay in the diagnosis of inflammatory bowel disease in women compared with men for both Crohn's disease and ulcerative colitis. These differences are present at all levels of the health care system, and misdiagnosis is also more common in women.

Key Words: diagnostic delay, inflammatory bowel disease, gender biases, misdiagnosis

Introduction

Early diagnosis of inflammatory bowel disease (IBD) is essential, as delayed diagnosis is associated with increased disease complications and early surgery.[1–3] In addition, early diagnosis of IBD could help optimize treatment.[4] This delay has not improved in recent years despite technological advances in medical care and improved diagnostic tests.[5,6] Many factors have been implicated in the delayed diagnosis of IBD, but the majority of studies have been retrospective, with the subsequent potential bias that makes it difficult to draw adequate conclusions.[3,5,7–11] In general, Crohn's disease (CD) is associated with a longer delay in diagnosis than ulcerative colitis (UC), but there are other factors, such as age and socioeconomic factors, that have shown mixed results across studies. The influence of gender in this diagnostic delay has not been thoroughly investigated, with the few available studies reporting contradictory results. Only some studies have shown a longer diagnostic delay in women[1,7] and differences in secondary care, but not in primary care.[10]

Our primary aim in the present study was to investigate whether a gender bias exists in the diagnosis of IBD, with a longer diagnostic delay in women. Our secondary aims were to characterize the clinical presentation of IBD in women and

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Key Messages

What is already known?

The diagnostic delay of inflammatory bowel disease has not improved in recent decades.

What is new here?

There is a longer diagnostic delay of inflammatory bowel disease in women than in men due to a drawn-out evaluation of female, with a higher number of misdiagnoses at all levels of the health care system.

How can this study help patient care?

Our results could help clinicians, health care workers and policy-makers to address gender inequalities in the diagnosis of inflammatory bowel disease, thereby reducing the delay in diagnosis of the disease.

men and systematically evaluate the diagnostic process at all levels of health care.

Materials and Methods

Patients

We carried out a multicenter study in a cohort of patients with IBD diagnosed from January 2018 to March 2020 in 4 hospitals in the Valencian Community of Spain. Consecutive patients diagnosed with IBD in the last 6 months who were older than 17 years of age and had clinical symptoms at onset were included. The inclusion criterion was a diagnosis of symptomatic CD or UC according to European Crohn's and Colitis Organization (ECCO) criteria.[12,13] The exclusion criteria were intellectual disability, dementia, major psychiatric disorders, and the presence of a language barrier.

Health System Characteristics

The health system of the Valencian Community has an important network of health resources that cover universal access to health care in accordance with the regulations of the Spanish government. The health system of the Valencian Community has a common electronic health history with an integrated connection between hospitals and primary and secondary care centers.

Sample Size Calculation

The sample size was calculated by a pilot study with the first 50 IBD subjects enrolled in the study. The pilot study found a mean diagnostic delay of 33.4 ± 12.5 weeks in men and 40.6 ± 16.5 weeks in women. Based on these results, the required sample size was estimated to be 170 patients (85 males and 85 females) to reject the null hypothesis of no gender inequity in diagnostic delay by applying the Student *t* test with a significance level of 0.05 and a power of 0.8.

Data Collection

Data collection was performed within 6 months of IBD diagnosis and included 2 phases: the diagnostic phase and the prediagnostic phase.

Diagnostic phase

Clinical and demographic characteristics, hemoglobin levels, and disease activity were assessed at the time of IBD diagnosis. The Harvey-Bradshaw index[14] was used to assess CD and the Mayo score to assess UC patients.[15] Fecal calprotectin and C-reactive protein were used as biomarkers.

Prediagnostic phase

The clinical history and diagnostic process were reconstructed in conjunction with a semistructured patient interview and review of the electronic medical records. Analytical measures (hemoglobin, fecal markers) and health resource consumption at each level of the health system were assessed. Patients completed a questionnaire about the symptoms that were present before diagnosis (Supplementary Table 1).

Definitions

Clinical variables

Disease phenotype was classified according to the Montreal classification.[16] The cutoff value differentiating mild from moderate-severe IBD was set to 8 for Harvey-Bradshaw (<8 indicates mild) and 6 for Mayo Score (<6 indicates mild).[14,15] Extraintestinal manifestations of IBD were extracted from the confirmed diagnosis in medical records according to European Evidence-based Consensus on Extraintestinal Manifestations in IBD.[17] According to ECCO guidelines and the World Health Organization (WHO), anemia is defined as hemoglobin <12.0 g/dL in female and <13.0 g/dL in male.[18]

Demographic variables

Education was split into low level (secondary school or lower) and high level (college or higher). The definition of active employment included being an employee or self-employed and excluded temporary employment or cessation of being self-employed. Comorbidity was characterized as coexisting diseases or conditions that affect an individual's physiological reserve condition or requiring chronic treatment. Identification between biological sex and gender identity was explicitly asked in the structured interview. In all the participants, the biological sex coincided with the gender identity.

IBD diagnosis

The moment of IBD diagnosis was established as the time when, after receiving all complementary tests, a diagnosis of IBD was established in the electronic medical record by a physician. The physician responsible for the diagnosis of IBD was defined as the physician who establishes the diagnosis of IBD by orienting the case and ordering the diagnostic tests.

Time to IBD diagnosis and diagnostic delay

Time to IBD diagnosis was defined as the time from onset of symptoms to diagnosis of IBD. Within this time frame, 2 intervals were established to assess diagnostic delay: patient delay, which was the time from symptom onset to consultation with the first physician, and system delay from the first medical consultation to the diagnosis of IBD.[7]

Clinical presentation before IBD diagnosis

Clinical presentation was characterized by the results of the prediagnosis IBD symptom questionnaire and presence of anemia according to ECCO guidelines and the WHO.[18]

Misdiagnoses

Misdiagnosis was defined as a diagnostic evaluation with a conclusion other than IBD established in the clinical report after the onset of symptoms. Functional gastrointestinal disorder was defined as any disorder defined in the ROME IV criteria.[19]

Levels of care

The levels of care were stratified into emergency care, primary care, secondary care (specialist outpatient clinics), and hospital admission.

Outcomes

The primary aim of the study was to investigate whether gender differences exist in the diagnostic delay of IBD. Secondary aims were to characterize the clinical presentation of IBD in women and men and to assess the diagnostic process and misdiagnoses at different levels of health care.

Statistical Analysis

Descriptive statistics and an inferential study were used to examine differences between baseline characteristics in male and female. The mean standard deviation was used for quantitative variables with a parametric distribution, and the median and interquartile range (IQR) for those with a nonparametric distribution. To investigate differences in time to IBD diagnosis by gender, we used survival curves. Univariate survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. To control for the sex variable in relation to the time of IBD diagnosis, Cox regression was performed on clinical and demographic variables that were significantly different between men and women. An inferential study was conducted to study differences in clinical presentation, delay in diagnosis, and misdiagnosis between men and women. Given the knowledge from previous studies of the different diagnostic times in CD and UC, all statistical studies were stratified by sex and type of IBD.[3,5,7,9] Qualitative variables were correlated using the χ^2 test. The quantitative variables were studied in accordance with the Student *t* test if they had a parametric distribution and with the Mann-Whitney *U* test if they had a nonparametric distribution. For all analyses, $P < .05$ was considered significant. We used SPSS statistical package for Windows, version 25.0.

Ethical Considerations

The Ethics Committee of HGUA-ISABIAL approved the study (PI 2018/047). All patients signed informed consent.

Results

A total of 218 consecutive IBD subjects were eligible for the study; 20 declined to participate in the study, 5 had a language barrier, 2 had major psychiatric disorders, and 1 had dementia. Of the 190 remaining subjects, 100 (52.6%) had CD and 90 (47.4%) had UC. The total cohort comprised 102 (53.2%) men and 88 (46.3%) women. The median age at IBD diagnosis was 43 years (29-55.5). The clinical and demographic characteristics at diagnosis and the differences between men and women are shown in Table 1. Women more frequently showed history of mood and/or anxiety disorder (18.2% vs 2.0%) and had less frequent active employment (43.2% vs 59.8%). The diagnosis of IBD was made in primary care in 12 (6.3%) patients, in secondary care in 104 (54.7%) patients, and on admission to the hospital in 74 (38.9%) patients, with no gender inequities in the setting where the diagnosis was made.

Time to Diagnosis of IBD

From the onset of symptoms, diagnosis of IBD was established significantly later in women than in men (Figure 1A). The median (IQR) time to diagnosis of IBD was 4.5 months (2.1-12.9) and was significantly longer in women than in men (7.8 months [3.3-18.9] vs 3.8 months [1.7-7.8]; $P < .001$). Cox regression analysis of sex and variables with different distributions between men and women showed a shorter time to IBD diagnosis in men and in subjects with anemia (Table 2).

The median time from symptom onset to IBD diagnosis was 6.3 months (2.5-19.4) in CD and 3.5 months (1.8-8.3) in UC ($P = .003$). In both types of IBD, the median time to diagnosis for women was twice that of men (Table 3). Survival analysis of both diseases showed a longer diagnostic delay in women than in men, but in UC, this gender gap only existed in the first year of symptom onset, and it was extended beyond the first year in CD (Figures 1B and 1C).

Diagnostic Delay Intervals

Patient delay

The median time from symptom onset to first medical consultation for all subjects included in the study was 0.7 months (0.26-2), and there was no difference between women and men (0.7 months [0.23-4.3] vs 0.8 [0.29-1.7]; $P = .428$). This lack of gender inequity was also observed when CD and UC were analyzed separately (Table 3).

System delay

After the first medical examination, the median time to IBD diagnosis was 3.4 months (1.1-7.4) in the total cohort, 4.2 months (1.95-11.1) in women, and 2.2 (0.82-5.1) in men ($P < .001$). In both CD and UC, a longer time to diagnosis was observed in women than in men (Table 3).

The first level of care consulted was the emergency department in 38 (20%) patients, primary care in 139 (73.2%) patients, and secondary care in 13 (6.8%) patients; no sex differences were observed in this distribution. At the end of the diagnostic process, 120 (63.1%) patients were evaluated in the emergency department, 166 (87.3%) patients in primary care, 130 (68.4%) patients in secondary care, and 84 (44.2%) patients required hospital admission. A higher proportion of women were evaluated in primary care compared with men, but there were no differences at the other levels of the health system, except more women with CD were evaluated in secondary care (Supplementary Table 2).

Regarding the use of fecal parameters during the diagnostic process, fecal calprotectin was performed in 85 (44.7%) patients and fecal occult blood tests in 56 (29.5%) patients, with no sex differences (Fecal calprotectin, female 43 [48.9%] vs male 42 [41.2%]; $P = .288$; fecal occult blood test, female 21 [23.9%] vs male 35 [34.3%]; $P = .115$).

Table 1. Clinical and demographic characteristics of the study population (n = 190).

	Women (n = 88)	Men (n = 102)	P
Median age, years (IQR)	41.5 (27.2-52.7)	45 (30.7-58.2)	0.232
Disease type			
CD	53 (60.2)	47 (46.1)	
UC	35 (39.8)	55 (53.9)	0.051
Disease duration, months (IQR)	4.4 (3.1-5.9)	4.5 (3.2-5.9)	0.757
Median BMI, kg/m^2 (IQR)	22.7 (20.1-26.1)	25.1 (22.4-28.2)	0.001*
Tobacco use			
Smoker	20 (22.7)	18 (17.6)	0.031*
Former smoker	25 (28.4)	48 (47.1)	
Non-smoker	43 (48.9)	36 (35.3)	
Marital status			
Married/partner	51 (58)	60 (58.8)	0.904
Single/divorced/widowed	37 (42)	42 (41.2)	
Education			
Low level	62 (70.5)	71 (69.6)	0.899
High level	26 (29.5)	31 (30.4)	
Active employment	38 (43.2)	61 (59.8)	0.022*
Comorbidity	43 (48.9)	41 (40.2)	0.230
Previous history of MAD	16 (18.2)	2 (2)	< 0.001*
CD Montreal classification			
Age group			
A2: 17–40 years	24 (45.3)	24 (51.1)	0.564
A3: ≥40 years	29 (54.7)	23 (48.9)	
Location of Crohn's (>1 location possible)			
L1: Ileal	26 (49.1)	29 (61.7)	0.205
L2: Colonic	10 (18.9)	5 (10.6)	0.250
L3: Ileocolonic	17 (32.1)	12 (25.5)	0.472
L4: Upper GI	3 (5.7)	3 (6.4)	1
Crohn's behavior			
B1: Inflammatory	40 (75.5)	35 (74.5)	0.959
B2: Stricturing	8 (15.1)	8 (17)	
B3: Penetrating	5 (9.4)	4 (8.5)	
Perianal involvement	5 (9.4)	2 (4.3)	0.311
UC Montreal classification			
E1: Proctitis	13 (37.1)	11 (20)	0.198
E2: Left-sided colitis	13 (37.1)	25 (45.5)	
E3: Extensive colitis	9 (25.7)	19 (34.5)	
IBD activity			
Mild	40 (45.5)	44 (43.1)	0.748
Moderate/severe	48 (54.5)	58 (56.9)	
Median CRP, mg/L (IQR)	11 (2.4-58.8)	6.6 (1.9-34.5)	0.149
Median fecal calprotectin, µg/g (IQR)	602 (122-1994)	532 (94.2-1320)	0.422
Anemia	34 (38.6)	25 (24.5)	0.036*
EIM	14 (15.9)	7 (6.9)	0.047*
Family history of IBD	26 (29.5)	16 (15.7)	0.022*

Values are n (%) unless otherwise noted. Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; BMI, body mass index; MAD, mood and/or anxiety disorders; CRP, C-reactive protein; EIM, extra-intestinal manifestations; IQR, interquartile range.
*statistically significant at $P < .05$.

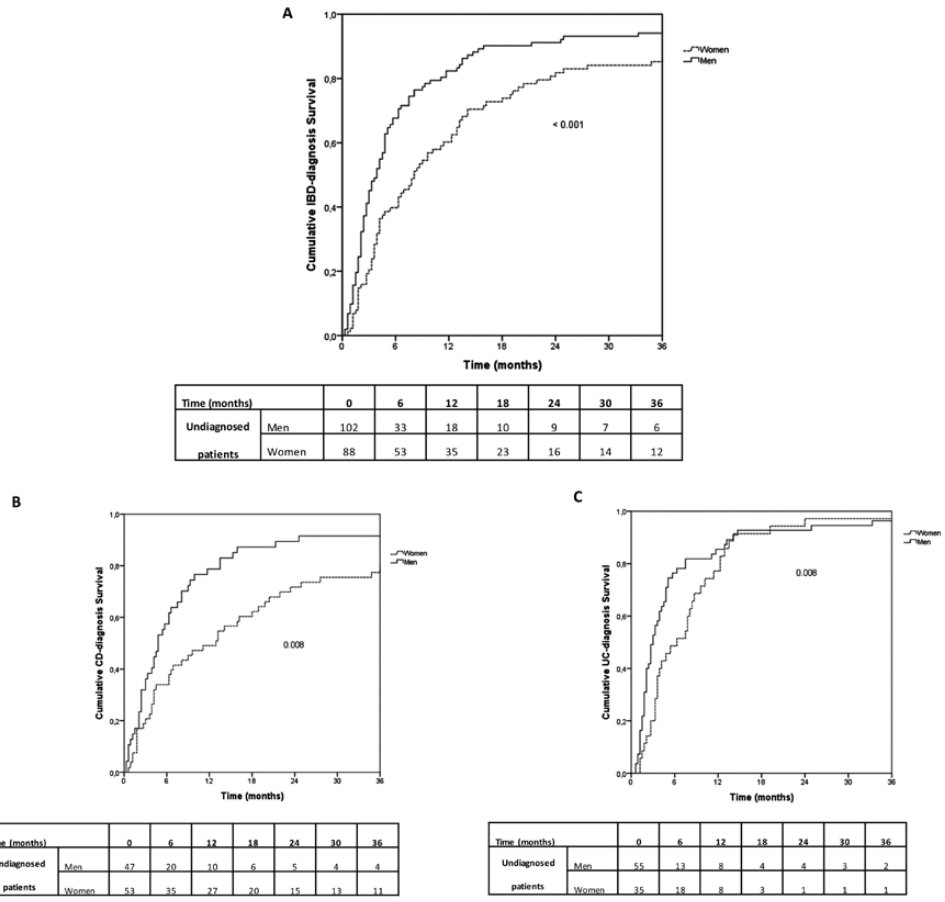

Figure 1. Cumulative probability of diagnosis according to sex. A, Inflammatory bowel disease curves (n = 190). B, Crohn's disease curves (n = 100). C, Ulcerative colitis curves (n = 90).

Table 2. Cox regression of time to IBD diagnosis.

Risk Factor	Parameter Estimate (B)	*P*	Hazard Ratio	95% CI
Sex, male	0.426	0.012*	1.5	1.1-2.1
BMI < 25 kg/m^2	–0.182	0.243	0.83	0.61-1.1
Current smoker	0.153	0.408	1.1	0.81-1.6
No active employment	0.265	0.089	1.3	0.96-1.7
Previous history of MAD	0.06	0.826	1.06	0.62-1.8
Anemia	0.352	0.037*	1.4	1.02-1.9
EIM	–0.51	0.83	0.95	0.59-1.5
Family history of IBD	–0.282	0.123	0.75	0.52-1.07

Abbreviations: BMI, body mass index; MAD, mood and/or anxiety disorders; EIM, extra-intestinal manifestations; IBD, inflammatory bowel disease; CI, confidence interval.
*statistically significant at $P < .05$.

Clinical Presentation Before IBD Diagnosis

The previous history of symptoms and presence of anemia prior to diagnosis were different in CD and UC (Supplementary Table 3). Patients with CD more frequently presented with abdominal pain, vomiting, anal symptoms, weight loss, fever, asthenia, arthralgias, and anemia than patients with UC. Patients with UC more frequently had rectal bleeding than patients with CD.

Symptoms and signs at onset of IBD by sex are provided in Table 4. In general, the clinical presentation was similar in women and men. For CD, bowel incontinence was more frequent in women (47.2% vs 19.1%), as well as asthenia (86.8% vs 70.2%) and arthralgias (64.2 vs 42.6). In contrast to UC, no sex differences were found in the symptoms prior to IBD diagnosis.

Misdiagnoses

Misdiagnoses were frequently issued in our cohort of patients, as they were reported in 117 (61.6%) of the 190 patients before the correct diagnosis of IBD. These misdiagnoses were more frequent in CD (n = 70, 70%) than in UC (n = 47, 52.2%; P = .012; OR, 1.5; 95% CI, 1.1-2.3). Women had a

Table 3. Time to diagnosis of IBD by sex.[a]

Crohn's disease (n = 100)	Women (n = 53)	Men (n = 47)	P
Time from symptom onset to IBD diagnosis	12.6 (3.7-31)	4.5 (2.2-9.8)	0.008*
Time from symptom onset to initial physician visit	0.6 (0.15-8)	0.9 (0.16-1.6)	0.663
Time from initial physician visit to IBD diagnosis	5.9 (2.3-15.6)	3.3 (0.88-8.7)	0.018*
Ulcerative colitis (n = 90)	**Women (n = 35)**	**Men (n = 55)**	**P**
Time from symptom onset to IBD diagnosis	6.1 (3-11.2)	2.7 (1.5-5.6)	0.008*
Time from symptom onset to initial physician visit	0.96 (0.43-3)	0.56 (0.3-2.1)	0.371
Time from initial physician visit to IBD diagnosis	3.4 (1.2-6.9)	1.9 (0.8-4.1)	0.036*

[a]Values are median (interquartile range) in months.
*statistically significant at $P < .05$.

Table 4. Clinical symptoms and signs prior to IBD diagnosis by sex.

	Crohn's disease (n = 100)			Ulcerative colitis (n = 90)		
	Women (n = 53)	Men (n = 47)	P	Women (n = 35)	Men (n = 55)	P
Diarrhea	47 (88.7)	36 (76.6)	0.108	25 (71.4)	43 (78.3)	0.467
Rectal bleeding	14 (26.4)	17 (36.2)	0.291	34 (97.1)	53 (96.4)	0.841
Abdominal pain	43 (81.1)	35 (74.5)	0.422	22 (62.9)	25 (45.5)	0.107
Vomiting	19 (35.8)	10 (21.3)	0.109	6 (17.1)	3 (5.5)	0.072
Anal symptoms	9 (17)	7 (14.9)	0.776	2 (5.7)	2 (3.6)	0.641
Urge to defecate	34 (64.2)	26 (55.3)	0.368	25 (71.4)	35 (63.6)	0.445
Bowel incontinence	25 (47.2)	9 (19.1)	0.003*	12 (34.3)	20 (36.4)	0.841
Weight loss	32 (60.4)	33 (70.2)	0.303	17 (48.6)	28 (50.9)	0.829
Fever	13 (24.5)	13 (27.7)	0.722	5 (14.3)	5 (9.1)	0.445
Asthenia	46 (86.8)	33 (70.2)	0.042*	27 (77.1)	32 (58.2)	0.065
Arthralgias	34 (64.2)	20 (42.6)	0.031*	16 (45.7)	17 (30.9)	0.155
Other symptoms[a]	17 (32.1)	6 (12.8)	0.022*	7 (20)	5 (9.1)	0.138
Anemia	17 (32.1)	11 (23.4)	0.335	6 (17.1)	8 (14.5)	0.740

Values are n (%).
[a]Other symptoms include mouth lesions, nausea, skin lesions, headache, dysphagia, myalgia, dizziness, constipation, dyspnea, bloating, anorexia, fecal mucus, paresthesia, and red eye.
*statistically significant at $P < .05$.

higher frequency of misdiagnoses than men (n = 68, [77.3%] vs n = 49, [48%]; $P < .001$; OR, 3.6; 95% CI, 1.9-6.9). These differences between women and men were maintained in CD (n = 44, [83%] vs n = 26, [55.3%]; $P = .003$; OR, 3.9; 95% CI, 1.5-9.9), as well as UC (n = 24, [68.6%] vs n = 23, [41.8%]; $P = .013$; OR, 3; 95% CI, 1.2-7.4).

Regarding the level of health care where misdiagnoses occurred, 57 (48.7%) patients experienced a misdiagnosis at one level of care, 40 (34.2%) at 2 levels, 15 (12.8%) at 3 levels, and 5 (4.3%) at 4 levels. Misdiagnoses occurred in 55% of the patients evaluated in the emergency department, 53.6% of patients evaluated in primary care, 22.3% of patients evaluated in secondary care, and 16.7% of patients requiring hospital admission. Table 5 shows the distribution of misdiagnoses by level of care; women were more frequently misdiagnosed at all levels of health care. When we analyzed secondary care by the type of specialist who had assessed the patients, we observed more diagnostic errors in women (n = 18, 29.5%) than in men (n = 7, 11.5%; $P = .014$) among the 122 patients assessed by gastroenterologists (OR, 3.2; 95% CI, 1.2-8.4), but this was not the case among the 11 patients assessed by other specialists (n = 1, 20% vs n = 2, 50%; $P = .3$; OR, 0.25; 95% CI, 0.17-3.7).

The distribution of misdiagnoses according to health care sector is reported in Supplementary Table 4. Gastrointestinal infection was the most frequently misdiagnosed disease (29.5%), followed by functional gastrointestinal disorder (13.7%), which was more frequently made in women than in men (n = 20, 22.7% vs n = 6, 4.9%; $P = .001$; OR, 4.7; 95% CI, 1.7-12.3), mainly in those finally diagnosed as CD.

Discussion

In this study, which specifically focused on the role of gender in the diagnostic delay for IBD, we found clear differences in the time from the onset of symptoms to the final diagnosis between men and women, as women were diagnosed a median 4 months later than men. This diagnostic delay occurs in

Table 5. Distribution of misdiagnoses according to health care level by sex.

	Global	Women	Men	*P*	OR; 95% CI
Emergency department					
Misdiagnosis in global IBD	66/120 (55)	39/59 (66.1)	27/61 (44.3)	0.016*	2.4; 1.1-5.1
Misdiagnosis in CD	46/69 (66.7)	29/38 (76.3)	17/31 (54.8)	0.060	2.6; 0.94-7.4
Misdiagnosis in UC	20/51 (39.2)	10/21 (47.6)	10/30 (33.3)	0.304	1.8; 0.57-5.7
Primary care					
Misdiagnosis in global IBD	89/166 (53.6)	54/83 (65.1)	35/83 (42.2)	0.003*	2.5; 1.3-4.7
Misdiagnosis in CD	52/87 (59.8)	34/50 (68)	18/37 (48.6)	0.069	2.2; 0.9-5.3
Misdiagnosis in UC	37/79 (46.8)	20/33 (60.6)	17/46 (37)	0.038*	2.6; 1.04-6.5
Secondary care					
Misdiagnosis in global IBD	29/130 (22.3)	19/65 (29.2)	10/65 (15.4)	0.058	2.2; 0.96-5.3
Misdiagnosis in CD	19/72 (26.4)	13/43 (30.2)	6/29 (20.7)	0.368	1.6; 0.54-5
Misdiagnosis in UC	10/58 (17.2)	6/22 (27.3)	4/36 (11.1)	0.156	3; 0.74-12.1
Hospitalization					
Misdiagnosis in global IBD	14/84 (16.7)	11/43 (25.6)	3/41 (7.3)	0.025*	4.3; 1.1-16.9
Misdiagnosis in CD	12/52 (23.1)	9/31 (29)	3/21 (14.3)	0.216	2.4; 0.57-10.4
Misdiagnosis in UC	2/32 (6.3)	2/12 (16.7)	0/20 (0)	0.133	NA

Values are n/N (%). Abbreviations: OR, odds ratio; CI, confidence interval; IBD, irritable bowel disease; CD, Crohn's disease; UC, ulcerative colitis; NA, not calculable.
*statistically significant at $P < .05$.

both CD and UC, but it was more pronounced in CD cases. Thus, gender has emerged as an independent cause of diagnostic delay. Moreover, this diagnostic delay is only attributable to the health system, coming from the higher number of misdiagnoses and involving all levels of health care. We found no substantial differences in the clinical presentation of IBD between men and women. In addition, misdiagnosis with other clinical entities occurs more frequently in women, particularly with confusion between functional gastrointestinal disorders and IBD.

There are different potential causes of this diagnostic delay in females with IBD. As with other pathologies such as ischemic heart disease, a different clinical presentation compared with males could be the cause of delay in diagnosis in women.[20] Another factor that could be implicated in this delay is the overlap in clinical presentation between IBD and functional gastrointestinal disorders and the frequent assumption that functional pathology is much more common in women.[21,22] This may lead to increased misdiagnosis of functional gastrointestinal disorders in women with IBD. Also gynecological symptoms can be confused with IBD.

Most previous studies assessing risk factors associated with diagnostic delay have found no difference in diagnosis times between women and men.[3,5,8,9,11] However, these studies have important limitations, as they are carried out in databases that were not specifically designed for studying diagnostic delay[5] by reviewing medical records without evaluating patients[3] or by conducting long-term retrospective questionnaires that make it difficult to adequately identify factors related with delays in diagnosis of IBD.[8,9,11] Studies showing gender differences must have a more refined methodology, using protocolized questionnaires for physicians and patients,[1,7] specifically aimed at looking for differences related to the sex of patients or reviewing electronic medical records that are linked to the different levels of health care.[10]

There are several points that differentiate our study from previous studies. First, detection of gender bias in diagnostic delay was the primary outcome being evaluated. Second, our analysis was performed separately between CD and UC, eliminating the known differences in diagnostic delay in both diseases.[3,5,9,10] Third, our data consistently showed that men have more misdiagnoses, which supports a more complex diagnostic process. Finally, our study was carried out in patients with a recent diagnosis of IBD (within 6 months of diagnosis), and with the use of electronic health record systems, patient recall bias and technological errors were minimized.

In CD and UC, the median time from symptom onset to consultation with the first doctor was less than 1 month, and we detected no gender differences. Universal access to the health system in Spain is probably why this interval is shorter than in other countries.[3,5,7,10] As we performed a personalized case-by-case search, we were able to actively follow the diagnostic process of each patient. We found that the diagnostic process was not linear between symptoms, primary care, and secondary care. One-fifth of patients initiated their medical contact through the emergency department, and 17% of patients were diagnosed without being evaluated by primary care. Diagnosis through urgent hospital admission, often without contact with primary care, has already been described in previous studies and should be considered when assessing the overall diagnostic delay and strategies to minimize it.[10,23] It is important to remark that women had more misdiagnoses at all levels of health care, including the emergency department, primary care, gastroenterology secondary care, and even in hospitalized patients. It is also important to remark that the delay in onset of symptoms to diagnosis is entirely in the delay from presentation to a health care profession to diagnosis and not because of delay in seeking evaluation for the symptoms. This result could mean the existence of a systematic diagnostic bias regarding digestive symptoms and gender, with more frequent attribution of symptoms to functional rather than organic disorders. Our results are consistent with those reported by Walker et al, who evaluated different levels of the health care system in the delay of IBD

diagnosis, showing a negative association of male gender with diagnostic delay in secondary care.[10]

We found only small differences in the clinical presentation between sexes, ruling out that diagnostic delay in women could be secondary to differences in the characteristics of symptoms, suggesting that gender bias is mainly due to differences in the attribution of symptoms between health professionals. A potential cause of the diagnostic delay could be the low rates of fecal biomarker use during the prediagnostic study. The use of fecal calprotectin has been shown to be useful in the diagnosis of IBD in primary and secondary care.[24–26] Therefore, the use of this objective parameter as a screening method in patients with gastrointestinal symptoms could combat gender bias in medical assessment.

We also analyzed which diagnoses were made erroneously before the final diagnosis of IBD. The most frequent misdiagnosis was gastrointestinal infections, for which no gender inequities were observed. However, functional gastrointestinal disorders were more common in women than in men. This gender bias in diagnosis is probably due to 2 reasons: the assumption that functional gastrointestinal pathology is more common in women, and as seen in our study, women are more frequently presenting with asthenia and arthralgias, which may be confused with functional disorders.[21,22] It is important to remark that misdiagnosis is found even with significantly higher rates of anemia and personal history of IBD, which should make the diagnosis of IBD even more preeminent for clinicians. Population studies have not shown sex differences in the incidence of IBD. Only for UC is there a slight male predominance, whereas in CD, especially in Western countries, there is a female predominance.[27]

Our study has some important strengths. First, we directly assessed diagnostic delay in patients with a recent diagnosis of IBD, minimizing recall bias. Second, we assessed prediagnostic clinical symptoms and biomarkers, which increases our knowledge of the factors that occur during diagnostic delay. Moreover, the study was carried out in a universal health care system with gender parity in primary and secondary care medical professionals, minimizing the socioeconomic factors of the patients and gender-related biases of the medical professionals carrying out the diagnostic study. Finally, an investigation of gender bias was the primary aim of our study, allowing adequate measurement of this effect and study of its potential causes.

A limitation of our study is that the sample size was too small to assess gender inequities in misdiagnoses stratified by type of IBD because the sample size was calculated to observe global differences in diagnostic delay in IBD between men and women. Another limitation of our study is that, although it is a multicenter study, it was carried out in one region of Spain. Although we have taken the first step towards visualizing the diagnostic delay in women, studies with a similar methodology but larger population and different health systems are needed to expand the knowledge base and confirm our results.

In summary, we have demonstrated a longer delay in the diagnosis of IBD in women compared with men for both CD and UC. These differences were observed at all levels of the health care system. Misdiagnosis is also more common in women, with a more frequent diagnosis of functional gastrointestinal disorder. This diagnostic delay could provoke deficiencies in clinical care. Our results must be taken into account by clinicians, health care workers, and policy-makers in order to effectively reduce these gender inequities.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Ethical Considerations

The Ethics Committee of HGUA-ISABIAL approved the study (PI 2018/047). All patients signed informed consent.

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Conflicts of Interest

The authors have no financial disclosures or conflicts of interest to declare.

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