Digestive Diseases and Sciences (2025) 70:1467–1476
https://doi.org/10.1007/s10620-025-08868-5

ORIGINAL ARTICLE

Prevalence, Clinical Features, and Extraintestinal Manifestations in Patients with Familial Inflammatory Bowel Diseases

Christina Liava[1] · Danai Chourmouzi[2] · Emmanouil Sinakos[1] · Theodoros Dimitroulas[1] · Christina Navrozidou[3] · Evangelos Akriviadis[3]

Received: 7 May 2024 / Accepted: 13 January 2025 / Published online: 13 February 2025

Abstract

Background A positive family history is considered the strongest recognizable risk factor for developing inflammatory bowel diseases (IBD) and is present in 8–12% of cases.

Aims To determine the prevalence of familial IBD and also to compare the clinical characteristics and extraintestinal manifestations between familial and sporadic cases.

Methods We conducted a cross-sectional study based on retrospectively-prospectively collected data from a cohort of IBD patients followed in daily clinical practice. Patients with biopsy-confirmed familial and sporadic IBD aged 16–90 years old were included in the study. A comprehensive questionnaire was used to collect data on each site visit. Logistic regression analysis and chi-squared test were used.

Results In total, 265 patients with IBD were included. 12.1% had a first-degree relative with IBD present (16.4% in Crohn's disease and 5.7% in the ulcerative colitis group, $P < 0.05$). Familial IBD patients were mainly females, were more frequently diagnosed with Crohn's disease and had a higher risk for hospitalization due to an IBD flare ($P < 0.05$), to undergo a surgical procedure ($P < 0.001$), to require treatment with biologic agents ($P < 0.05$), to develop perianal disease ($P < 0.05$), and extraintestinal manifestations ($P < 0.05$), mainly spine joint complications, erythema nodosum, and anterior uveitis.

Conclusion In this study, a positive family history of IBD was present in 16.4% of Crohn's disease and 5.7% of ulcerative colitis patients and was associated with a greater risk for hospitalization, surgical procedures, occurrence of perianal disease, need for treatment with biologic agents, and development of extraintestinal manifestations.

Keywords Familial inflammatory bowel diseases · Crohn's Disease · Ulcerative Colitis · Positive Family History · Extraintestinal Manifestations

Introduction

Inflammatory bowel diseases (IBD) including Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC), are chronic progressive and disabling diseases often diagnosed in young adulthood. The disease course is heterogeneous, ranging from no or mild symptoms to severe complications requiring hospitalization and/or surgery [1]. Currently, the strongest recognizable risk factor for the development of IBD is a positive family history which is

✉ Christina Liava
christinli@auth.gr

Danai Chourmouzi
dchourmouzi@gmail.com

Emmanouil Sinakos
esinakos@auth.gr

Theodoros Dimitroulas
dimitroul@hotmail.com

Christina Navrozidou
cnavrozidou@gmail.com

Evangelos Akriviadis
akriviev@auth.gr

[1] Fourth Department of Internal Medicine, Hippokration General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Konstantinoupoleos Str. 49, 54642 Thessaloniki, Greece

[2] Radiology Unit, Interbalkan Medical Center of Thessaloniki, Thessaloniki, Greece

[3] Gastroenterology Unit, Interbalkan Medical Center of Thessaloniki, Thessaloniki, Greece

present in 8–12% of cases [2–4]. Higher risk is observed in IBD patients with first-degree relatives (FDRs) diagnosed with IBD, and also in patients with CD compared to those with UC [5–11]. The genetic influence in IBD has been supported by epidemiological, familial, and genome-wide association (GWA) studies. However, it is estimated that only 8.2–13.1% of disease heritability is explained by genetic variation, suggesting that other shared environmental and/or epigenetic factors may be involved [12–14].

Previous studies on differences in clinical phenotypes of IBD between familial and sporadic cases are mainly based on retrospective analyses from hospital registries and results were controversial between existing studies. Data regarding possible differences in the natural history of IBD focused on the development of extraintestinal manifestations (EIMs) between familial and sporadic IBD cases have not been sufficiently documented. Distinguishing those IBD patients who are at risk for developing disease-related complications and EIMs might influence screening and therapeutic approaches in a more individualized management. Therefore, we aimed to determine the prevalence of familial IBD in FDRs and also to compare the clinical features and extraintestinal manifestations (EIMs) between familial and sporadic cases, based on retrospectively-prospectively collected data from a cohort of IBD patients followed in daily clinical practice.

Patients and Methods

Aims and Study Design

We conducted a cross-sectional study based on a retrospective-prospective cohort of patients diagnosed with IBD, who were examined between July 2018 and March 2023 at the Gastroenterology Departments of two tertiary Medical Centers in Thessaloniki, Greece (Hippokration General Hospital of Thessaloniki and Interbalkan Medical Center of Thessaloniki). We aimed to estimate the prevalence of familial IBD patients in FDRs (including parents, siblings, and children) as well as to compare the clinical characteristics and EIMs between patients with a positive family history of IBD in FDRs and those without. All enrolled IBD patients were evaluated at least once in our gastroenterology services and a comprehensive questionnaire (Supplementary 1) was fulfilled by the treating physicians. All enrolled patients signed an informed consent form. The collected medical data were updated at each follow-up visit until study completion. To ensure uniformity across sites we used a standard protocol for follow-up visits. IBD patients who received intravenous treatment with biologic agents were examined at each infusion, patients experiencing flares were examined at least every 1 to 3 months, and patients in remission were examined every 6 to 12 months. Outpatients with refractory UC were considered those failing oral corticosteroids and immunomodulators (azathioprine) and for in-hospital patients those failing intravenous corticosteroids.

Our study was reviewed and approved by the Institutional Review Board of both centers.

Inclusion Criteria

Eligible patients were considered those with biopsy-confirmed IBD (CD, UC, and IC) aged 16–90 years old at study entry. IBD patients with missing data about IBD family history in FDRs were excluded from the analysis ($n=41$). Furthermore, those diagnosed with indeterminate colitis were also excluded ($n=4$). The final cohort of interest included 265 IBD patients. In the majority of the enrolled FDRs ($n=28$), IBD was diagnosed in our centers, and the patients were followed up by our team. Only 4 IBD patients had an FDR diagnosed with IBD based on endoscopic and/or histologic findings reported from outside health care facilities.

Data Collection

We collected data on (i) demographic characteristics (age at diagnosis of IBD, age at study entry, gender, and anthropometric measures [height, weight, Body Mass Index (BMI)], (ii) clinical characteristics (IBD type, Montreal classification, hospitalization for IBD flares and/or complications, surgery for IBD, aphthous stomatitis, perianal disease), (iii) colonoscopy findings, (iv) histopathologic findings, (v) extraintestinal manifestations, (vi) extraintestinal complications (osteoporosis related or not with corticosteroids treatment, nephrolithiasis, cholelithiasis), (vii) pharmacologic therapy [mesalamine, sulfasalazine, systemic corticosteroids (prednisone, methylprednisolone) topical corticosteroids (budesonide), methotrexate, thiopurines (azathioprine, 6-mercaptopurine), biologic agents (infliximab, adalimumab, vedolizumab, ustekinumab), Janus Kinase (JAK) inhibitors (tofacitinib) and supplementary diet (Modulen®)], (viii) other coexisting diseases (arterial hypertension, thyroiditis Hashimoto, depression, cardiovascular events, psoriasis, rheumatoid arthritis, diabetes mellitus type II, Takayasu's arteritis), (ix) other surgical procedures (appendectomy), (x) smoking status (patients were categorized as current, past and non-smoker patients), and (xi) family history of IBD in FDRs, as well as other autoimmune diseases (thyroiditis Hashimoto, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, vasculitis, sarcoidosis and Takayasu's arteritis).

Definition of Extraintestinal Manifestations

All EIMs were diagnosed by a physician and were classified according to the most recent published data [15].

Musculoskeletal EIMs (peripheral arthritis, axial spondyloarthropathies) were diagnosed by a rheumatologist in cooperation with the treating gastroenterologist. Peripheral arthritis was defined as pain, swelling, and/or redness in one or more peripheral joints. Axial spondyloarthropathies (ankylosing spondylitis including sacroiliitis based on the most recent rheumatology classification criteria [16]) were diagnosed based on clinical, laboratory, and specific radiologic findings on x-ray examination and magnetic resonance imaging (MRI). Skin manifestations were examined by a dermatologist with or without histologic confirmation and included erythema nodosum, pyoderma gangrenosum, and hydradenitis suppurativa. Ocular manifestations were diagnosed by an ophthalmologist. Furthermore, liver-biliary tract manifestations were comprised by the occurrence of primary sclerosing cholangitis (PSC) based on specific MR cholangiopancreatography (MRCP) features in combination with clinical, laboratory, and/or histologic data. Finally, vascular manifestations were divided into (a) cardiovascular manifestations including myopericarditis and (b) thromboembolic events including deep vein thrombosis, pulmonary embolism, and stroke, based on imaging data. EIMs were updated at each follow-up visit based on a systematic screening (physical examination, laboratory test results, and/or imaging studies) and patient reporting. In case the patient was followed by another physician specialist, such as rheumatologist, appropriate medical records were retrieved and used for update.

Statistical Analysis

Missing data for variables were less than 5% for the final cohort of enrolled IBD patients (n = 265) and were included in the analysis. All patient characteristics (except age, anthropometric measures, and laboratory values) between groups were summarized as frequencies for categorical variables. Comparative data for continuous variables are reported as median (interquartile range [IQR]) or mean (standard deviation). For statistical comparison of the characteristics between patients with familial and sporadic IBD, a *Mann–Whitney U test* was used for variables that are not normally distributed and a *Chi-square test* with or without *Fischer's exact test* was used for categorical variables. Univariate logistic regression analysis was performed to examine the association between a positive family history of IBD in FDRs and all patient characteristics and additionally to investigate the crucial odds ratio (OR) for each factor. The results were reported as OR and 95% confidence intervals (CIs). All reported *P* values were 2-sided, and *P* values less than 0.05 were considered statistically significant. Patients with missing data were excluded from the final analysis. All statistical analyses were performed using IBM SPSS Statistics, version 28.0.

Results

Demographic Characteristics and Gender-Specific Risks

In total, 265 IBD patients were included in the study. The median age at study entry was 46 (16–90) and the median age at diagnosis was 29 (6–81). The median BMI was 24 (17–60). About 53.6% of IBD patients were males and 46.4% females. Female patients had an almost 2.5-fold increased risk of having an FDR diagnosed with IBD (17.1% familial IBD females vs 7.7% familial IBD males, OR 2.45; 95% CI: 1.13–5.32; $P = 0.023$). Furthermore, females of the entire cohort (sporadic and familial) diagnosed with IBD compared to males had a higher risk for developing erythema nodosum (12.3% vs 4.2% males, OR 3.18; 95% CI: 1.19–8.47; $P = 0.021$), isolated sacroiliitis (23% vs 13.4%, OR 1.93; 95% CI: 1.02–3.66; $P = 0.045$) and for colonic location of CD (16.9% vs 5.8%, OR 3.30; 95% CI: 1.10–9.86; $P = 0.033$). A trend was also found for multiple EIMs (47% vs 30.6% males, OR 2.01; 95% CI: 0.97–4.14; $P = 0.060$), perianal disease with abscesses and/or fistulas (27.9% vs 18.3%, OR 1.72; 95% CI: 0.96–3.08; $P = 0.066$), and ulcerative proctitis (15.4% vs 3.6%, OR 4.82; 95% CI: 0.97–23.87; $P = 0.054$). Males with IBD compared to females had a higher risk for left-sided ulcerative colitis (45.5% vs 19.2% females, OR 3.50; 1.47–8.36; $P = 0.005$).

Regarding comorbidities, 34.2% of IBD patients had at least one comorbidity. Arterial hypertension was the most common (11.8%) along with thyroiditis Hashimoto (10.6%), and 8.7% of IBD patients received pharmacologic therapy for depression. Cardiovascular events (myocardial infarction, stroke, atrial fibrillation) were reported in 6.8% of IBD patients. Less commonly were observed psoriasis (4.6%), dyslipidemia (3.8%), diabetes mellitus type II (2.3%), rheumatoid arthritis (1.1%), and Takayasu's arteritis (0.4%).

IBD Type

Of the 265 patients included in the study, 159 had CD (60%) and 106 had UC (40%). The prevalence of a positive history of any type of IBD in FDRs of patients included in our cohort study was 12.1% (16.4% in the group of CD patients and 5.7% in UC patients). CD patients had an almost 3.3-fold increased risk of having a FDR diagnosed with IBD, compared to UC patients (OR 3.26; 95% CI: 1.29–8.22; $P = 0.012$). Other autoimmune diseases in FDRs, such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus, sarcoidosis, vasculitis, thyroiditis

Table 1 Prevalence of a Positive Family History in IBD patients

Family History *n (%)*	All IBD *N* = 265	Crohn's Disease *N* = 159	Ulcerative Colitis *N* = 106	Odds Ratio (95% CI)	*P* Value
1st-Degree Relatives with IBD	32 (12.1)	26 (16.4)	6 (5.7)	**3.26 (1.29–8.22)**	**.012**
1st-Degree Relatives with autoimmune diseases	55 (20.8)	31 (19.5)	24 (22.6)	0.83 (0.45–1.51)	.537

Bold values indicate the statistical significant differences

IBD Inflammatory Bowel Disease, *CI* Confidence Interval

Hashimoto, and Takayasu's arteritis, were observed in 20.8% of IBD patients and were similar between the groups of CD and UC patients, as shown in Table 1.

Montreal Classification

Disease phenotype for patients with CD and UC was defined at study entry and was updated after each site visit according to the Montreal classification. The most common age group of CD onset was 17–40 years (56.1%). Ileocolonic location of CD was present in 73.2% of patients, while 40.1% had stricturing behavior and 36.3% had perianal disease (perianal abscesses and fistulas). Familial CD patients had an almost 3.3-fold increased risk for colonic location of the disease, compared to sporadic cases (23.1% vs 8.4% in sporadic, OR 3.27; 95% CI: 1.09–9.85; $P = 0.035$). More than half of UC patients had extensive colitis (57.9%), according to endoscopic findings. About 56.6% of UC patients were in remission and the majority of them were on treatment for UC. Only 5 of UC patients underwent total proctocolectomy with ileal pouch-anal anastomosis (4.7%), of whom all developed pouchitis complicated by abscesses and fistulas.

Clinical Characteristics

Regarding clinical characteristics, we found that familial IBD cases required more often hospitalization due to an IBD flare and/or related complications (65.6% vs 45.9% in sporadic cases, OR 2.25; 95% CI: 1.04–4.87; $P = 0.040$), developed more frequently perianal disease (62.5% vs 39.7%, OR 2.54; 95% CI: 1.18–5.44; $P = 0.017$), and had an almost 3.0-fold greater risk to undergo an IBD-related surgical procedure (46.9% vs 22.7%, OR 3.00; 95% CI: 1.40–6.40; $P = 0.005$), mainly colectomy (40.6% vs 16.3%, OR 3.51; 95% CI: 1.60–7.71; $P = 0.002$) compared to sporadic cases. Development of perianal disease and colectomy refers mostly to CD patients. Further analysis revealed that familial UC patients had an increased risk of undergoing total proctocolectomy with ileal pouch-anal anastomosis, compared to sporadic cases (33.3% vs 1.2% in sporadic UC cases, OR 42.67; 95% CI: 5.53–329.34; $P < 0.001$). Additionally, appendectomy was more frequently conducted in familial CD patients, usually at or before the diagnosis of CD (25% vs 6.8% in sporadic CD patients, OR 4.60; 95% CI: 1.61–13.21; $P = 0.005$). Aphthous stomatitis was observed in 32.8% of IBD patients, as shown in Table 2.

Table 2 Clinical Characteristics of IBD patients

Clinical Characteristics *n/N (%)*	All IBD *N* = 265	Familial IBD *N* = 32	Sporadic IBD *N* = 233	Odds Ratio (95% CI)	*P* Value
Aphthous stomatitis	87 (32.8)	13 (40.6)	74 (31.8)	1.47 (0.69–3.14)	.319
Hospitalization for IBD	128 (48.3)	21 (65.6)	107 (45.9)	**2.25 (1.04–4.87)**	**.040**
Perianal disease	112 (42.3)	20 (62.5)	92 (39.5)	**2.54 (1.18–5.44)**	**.017**
Anal Fissure	108 (40.8)	19 (59.4)	89 (38.2)	**2.35 (1.11–4.99)**	**.026**
Abscess Fistula	60 (22.6)	12 (37.5)	48 (20.6)	**2.30 (1.05–5.03)**	**.037**
Surgical Procedures for IBD	68 (25.7)	15 (46.9)	53 (22.7)	**3.00 (1.40–6.40)**	**.005**
Colectomy	51 (19.2)	13 (40.6)	38 (16.3)	**3.51 (1.60–7.71)**	**.002**
Perianal Area	27 (10.2)	4 (12.5)	23 (9.9)	1.30 (0.42–4.05)	.646
Pouch	5 (1.9)	2 (6.3)	3 (1.3)	5.11 (0.82–31.84)	.080
Appendectomy*	22 (8.4)	7 (23.3)	15 (6.5)	**4.38 (1.62–11.85)**	**.004**

Bold values indicate the statistical significant differences

*4 IBD patients with missing data about appendectomy

IBD Inflammatory Bowel Disease, *CI* Confidence Interval

Smoking Status

About 27.2% of IBD patients were current smokers, 27.2% were past smokers and the majority (45.6%) were non-smokers. Smoking status for familial IBD cases was available for the 28 patients that were followed up in our centers. Current smokers were 25% of familial IBD patients, past smokers 21.4%, and 53.6% were non-smokers. No statistically significant differences were found between familial and sporadic IBD cases.

Treatment Regimens

Pharmacologic treatment for IBD patients was defined at study entry and was updated after each site visit. About 26.9% of IBD patients were on current treatment with anti-tumor necrosis factors (anti-TNFs) at the time of study completion. The most common used anti-TNF agent was Infliximab, mainly used to treat CD patients (24.8% vs 5.7% in UC, $P < 0.001$). Further analysis revealed that familial IBD patients had a threefold greater risk to receive therapy with anti-TNFs, compared to sporadic cases (45.2% vs 24.5% in sporadic, OR 3.04; 95% CI: 1.30–7.09; $P = 0.010$) and especially infliximab (29% vs 15.5% in sporadic, OR 3.23; 95% CI: 1.27–8.24; $P = 0.014$).

Extraintestinal Manifestations

All EIMs were diagnosed by a physician and were observed in 48.9% of IBD patients (Table 3). Familial IBD patients had a 2.4-fold increased risk for developing EIMs, compared to sporadic cases (67.7% vs 46.4% in sporadic, OR 2.43; 95% CI: 1.10–5.39; $P = 0.029$). In the majority of IBD patients, the first EIM was diagnosed at disease onset and/or after IBD diagnosis (76.7% vs 23.3% before IBD diagnosis). The musculoskeletal system was commonly affected (40.2% in the entire cohort), with an almost 2.3-fold increased risk for developing spine joint-related complications in familial IBD patients, compared to sporadic (58.1% in familial vs. 37.8% in sporadic, OR 2.28; 95% CI: 1.07–4.88; $P = 0.034$). Peripheral arthritis was the most frequent EIM observed in the entire IBD cohort (30.7% of IBD patients), with a 2.3-fold elevated risk of affecting familial cases, compared to sporadic (48.4% vs 28.3% in sporadic, OR 2.37; 95% CI: 1.11–5.07; $P = 0.026$). A higher risk for developing axial spondyloarthropathies (ankylosing spondylitis and sacroiliitis) was also found in familial IBD cases (35.5% vs 18.9% in sporadic, OR 2.36; 95% CI: 1.06–5.29; $P = 0.036$).

The second most commonly affected system was the integumentary (13.6% of IBD patients). Familial IBD patients had an almost 3.8-fold greater risk for developing skin complications (OR 3.79; 95% CI: 1.61–8.93; $P = 0.002$), mainly erythema nodosum (22.6% vs 6% in sporadic, OR 4.56; 95% CI: 1.68–12.41; $P = 0.003$). The ocular system was affected in 3.4% of IBD patients, with

Table 3 Prevalence of Extraintestinal Manifestations between Familial and Sporadic IBD Cases

Manifestations *n (%)*	All IBD $N = 264$ *	Familial IBD $N = 31$	Sporadic IBD $N = 233$	Odds Ratio (95% CI)	*p* value
Extraintestinal Manifestations	129 (48.9)	21 (67.7)	108 (46.4)	**2.43 (1.10–5.39)**	**.029**
Musculoskeletal	106 (40.2)	18 (58.1)	88 (37.8)	**2.28 (1.07–4.88)**	**.034**
Peripheral Arthritis	81 (30.7)	15 (48.4)	66 (28.3)	**2.37 (1.11–5.07)**	**.026**
Ankylosing Spondylitis	55 (20.8)	11 (35.5)	44 (18.9)	**2.36 (1.06–5.29)**	**.036**
Skin	36 (13.6)	10 (32.3)	26 (11.2)	**3.79 (1.61–8.93)**	**.002**
Erythema Nodosum	21 (8.0)	7 (22.6)	14 (6.0)	**4.56 (1.68–12.41)**	**.003**
Hidradenitis Suppurativa	12 (4.5)	2 (6.5)	10 (4.3)	1.54 (0.32–7.37)	.590
Pyoderma Gangrenosum	3 (1.1)	1 (3.2)	2 (0.9)	3.85 (0.34–43.75)	.277
Liver-Biliary					
Primary sclerosing cholangitis	5 (1.9)	0 (0.0)	5 (2.1)		.999
Ocular	9 (3.4)	3 (9.7)	6 (2.6)	4.05 (0.96–17.12)	.057
Anterior Uveitis	5 (1.9)	3 (9.7)	2 (0.9)	**12.38 (1.98–77.27)**	**.007**
Vascular	14 (5.3)	1 (3.2)	13 (5.6)	0.56 (0.07–4.47)	.588
Cardiovascular (Myopericarditis)	3 (1.1)	0 (0.0)	3 (1.3)		.999
Thromboembolism	11 (4.2)	1 (3.2)	10 (4.3)	0.74 (0.09–6.01)	.781

Bold values indicate the statistical significant differences

*1 IBD patient with missing data about extraintestinal manifestations

IBD Inflammatory Bowel Disease, *CI* Confidence Interval

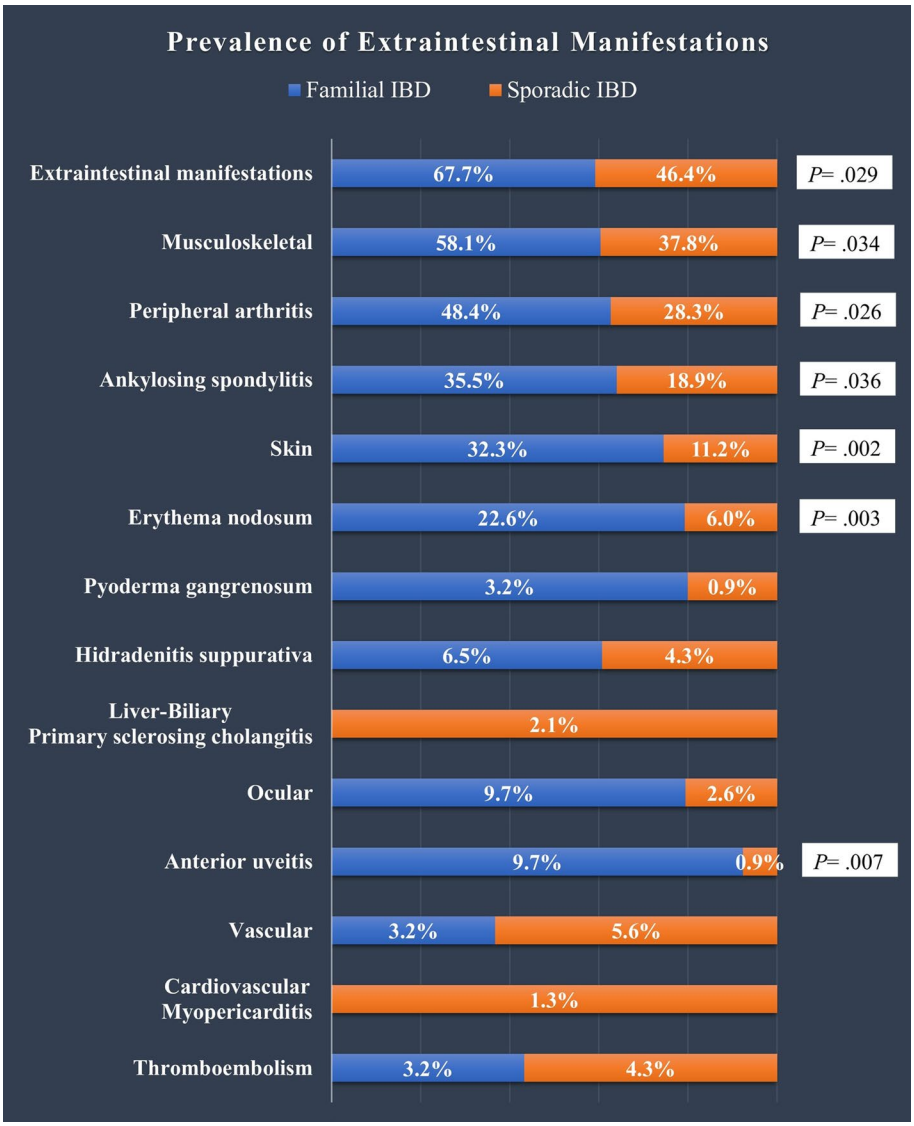

Fig. 1 Frequency of extraintestinal manifestations between familial and sporadic IBD cases. *IBD: Inflammatory Bowel Disease*

a 12.5-fold increased risk for developing anterior uveitis in familial IBD patients, compared to sporadic (9.7% vs 0.9%, OR 12.38; 95% CI: 1.98–77.27; $P = 0.007$, Fig. 1).

Extraintestinal Complications

Extraintestinal complications were observed in 14.8% of IBD patients (7.2% nephrolithiasis, 6.1% cholelithiasis, and 4.9% osteoporosis, including osteoporosis related to the use of corticosteroids). Familial IBD patients had a trend for developing extraintestinal complications, compared to sporadic cases (25.8% vs 13.3% in sporadic, OR 2.27; 95% CI: 0.93–5.52; $P = 0.071$) (Fig. 2).

Discussion

We analyzed a cohort of 265 IBD patients who were clinically evaluated on multiple occasions in two referral centers specialized in the care of IBD patients. We performed an analytical cross-sectional study assessing the prevalence of familial IBD patients, as well as the clinical features and EIMs between familial and sporadic cases. Of the 265 IBD patients, we found that 32 (12.1%) had a positive family history of any type of IBD in FDRs. In patients with CD, the prevalence of a positive family history in FDRs was higher (16.4%) compared to patients

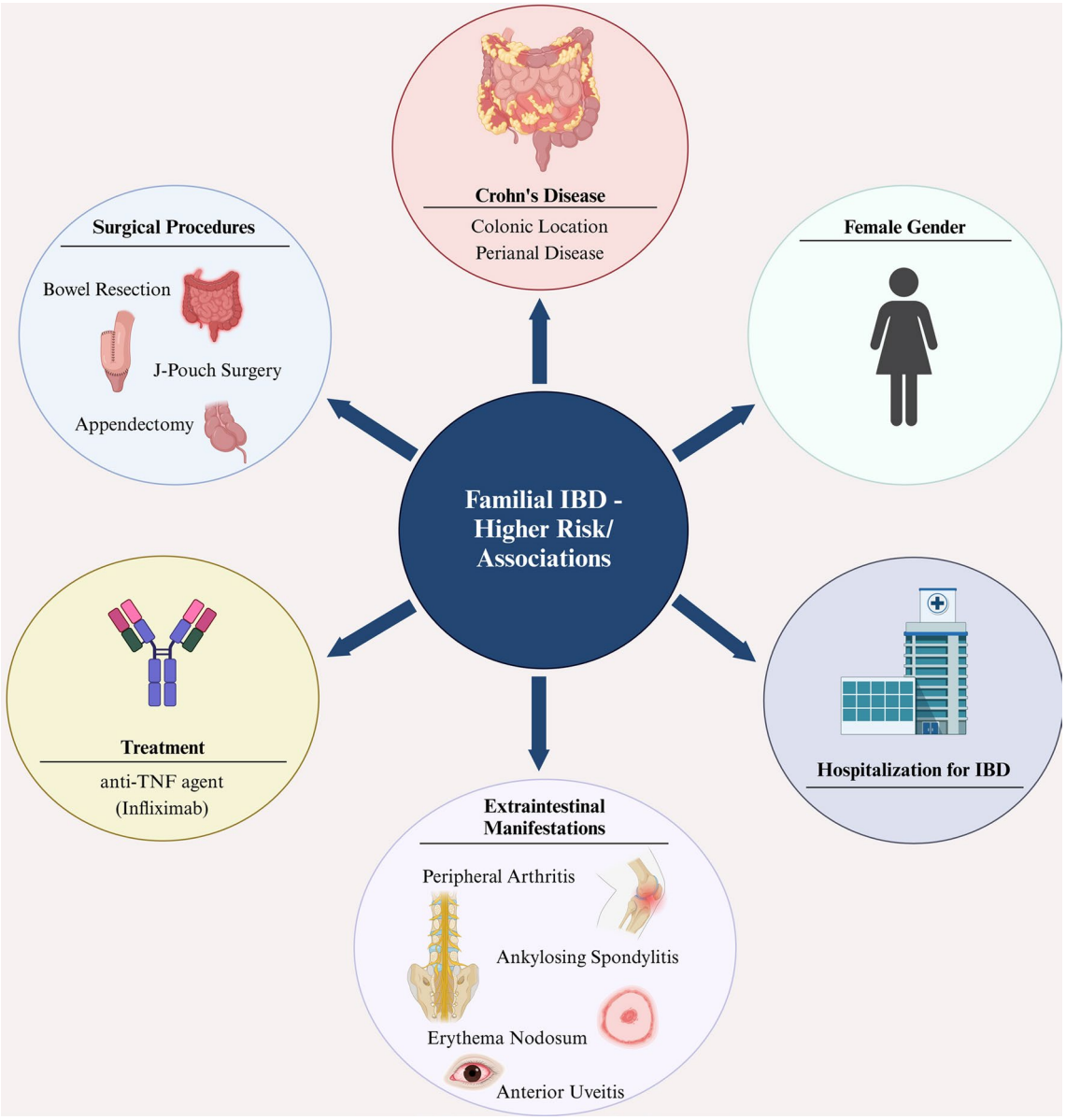

Fig. 2 Associated clinical risk factors of familial IBD patients

with UC (5.7%). The risk for familial IBD was also higher in female patients in the entire IBD cohort.

Epidemiological studies across the globe have shown that the prevalence of familial CD in FDRs ranges from a low rate of 2.5% in Korea, to a high of 39.3% in the USA; prevalence in European studies stands somewhere in between [3, 9, 14, 17–21]. These variations in the prevalence of familial IBD cases could be attributed to differences in the study design and the definition of a positive family history; genetic and environmental variations among geographic areas could also play a role. Compared to a large cohort study conducted in Southern Europe (Spain), we identified similar clinical risk factors; however, a lower prevalence of familial CD (8.4%) and a higher prevalence of familial UC (6.8%) in FDRs were observed in this study [3].

The importance of early age at disease onset has been reported in many population-based studies [3, 11, 17, 19] and also in a systematic review and meta-analysis [18]. In some studies, early age onset was associated with a more severe disease course [22–25]. Median age at diagnosis was similar in our cohort compared to those other studies. However, we found no difference regarding the age of disease onset between familial and sporadic cases and this discrepant result could be attributed to the small sample size of familial IBD cases in our cohort compared to other cohort studies. Additionally, it has to be mentioned that the age of IBD

diagnosis is not an objective measure and for various reasons (mild clinical course, social, and economic circumstances), a delay in diagnosis occurs not infrequently.

Colombel et al. reported a higher frequency of both small bowel and colonic involvement in familial CD cases, compared to sporadic cases [26], and similar results were also reported in a study by Carbonnel et al. [27]. A more recent large cohort study conducted in Spain found that familial CD patients had a higher percentage of ileocolonic location [3]. However, our study revealed only a higher frequency for colonic involvement in familial CD patients. It should be emphasized that the Montreal classification, which reflects the disease behavior, can dynamically change during the disease course and may be influenced by the length of the follow-up period of individual IBD patients. This may explain differences between study results, regarding the disease location of familial IBD patients. Data on possible aggressive disease course in familial IBD cases are also conflicting between different countries across the globe. Studies conducted in the USA and Korea have concluded that familial CD patients have a more aggressive disease course (higher frequency of complications, intestinal resection, and use of anti-TNFs) compared to sporadic cases [3, 11, 17, 26–28]. Additionally, data from Spain showed that familial CD were more severe with a higher percentage of penetrating behavior and perianal disease than sporadic disease [3], findings that were also supported by earlier studies conducted by Colombel et al. and Carbonnel et al. [26, 27].

Contrary to these reports, studies from Scandinavia (Norway) and Asia (Iran) have found no association between a positive IBD family history and disease phenotype, course, or outcomes [19, 21], though, in the Scandinavian cohort, relapse was more frequent in UC patients with familial IBD than sporadic cases [19]. Results not supporting an aggressive course in familial IBD cases have also been provided by a systematic review and meta-analysis published in 2014, which found no differences in disease location, need for surgery, or EIMs between familial and sporadic IBD cases, although very few studies included in the meta-analysis reported these outcomes [18]. Our study clearly reveals that familial IBD follows a more aggressive clinical course since we found not only a higher proportion of familial CD patients with complicated disease course (development of perianal disease, treatment with anti-TNFs, and increased risk to undergo a surgical procedure), as shown in many previous studies but also an increased risk of familial UC patients to develop chronic refractory colitis and require total proctocolectomy with ileal pouch-anal anastomosis.

However, there are also conflicting results on the risk of developing EIMs in familial IBD patients. Some studies have shown a higher prevalence of EIMs in the familial group [3, 29, 30]. Other studies however have found no difference between familial and sporadic IBD cases [18, 31, 34]. Nevertheless, most studies did not categorize EIMs according to the affected organ system. Our study not only found an association between familial IBD and the occurrence of EIMs but also categorized the EIMs according to the affected organ system, thus providing specific results on the type of EIMs in familial IBD cases. We found that familial IBD patients had a greater risk to develop spine joint complications, erythema nodosum, and anterior uveitis, compared to sporadic cases. Swiss cohort studies revealed that a positive IBD family history was associated with ongoing EIMs, including peripheral arthritis, axial spondyloarthropathies, and cutaneous manifestations, but only in patients with CD [32, 33]. The higher prevalence of EIMs in familial IBD patients compared to sporadic cases contributes to a more severe clinical phenotype and aggressive behavior of the disease with disabling effects on various system organs. Additionally, it plays also an important role in a more targeted treatment selection and individualized approach of these patients.

Mechanisms linking to a more aggressive disease course include specific genetic variants that are shared by CD and UC and other disease-specific variants, such as NOD2/CARD15 gene, which is associated with CD. Associations have been reported between methylation of specific region of the genome and CD, which might imply that environmental factors could influence the IBD clinical phenotype by epigenetic alterations of the genome [35]. However, patients with a genetic predisposition to IBD may require less environmental exposures prior to disease occurrence. Altered genes might also affect the interaction between intestinal cells and the bacteria, which predisposes to increased inflammatory responses. These conditions, along with the loss of function of the immune system to destroy inappropriately responding cells, results in a chronic inflammatory state of the gut [36]. Genetic counselors could play an important role in identifying at-risk individuals for developing IBD. Early genetic screening would be useful to prevent or modify disease development and to manage the patient in a more individualized approach. In already diagnosed patients with IBD, genetic testing might offer information about the disease course, such as the development of IBD-related complications, EIMs, response to treatment, and prognosis. However, further studies are needed to better understand the genetics of IBD in conjunction with environmental exposures, changes in the microbiome, and epigenetic alterations.

The strengths of our study refer to the fact that, unlike many previous studies that analyzed electronic databases or hospital registries, all enrolled IBD patients and their FDRs were diagnosed and clinically evaluated at our two referral centers by the same group of expert physicians, and a positive family history was considered only when one or more FDRs had histologically confirmed IBD (either CD or UC). Most data were prospectively collected through March 2023,

and the information of the patients enrolled in the study has been updated after each outpatient visit or hospital event; therefore, the data of the disease follow-up are mostly prospective. All IBD patients and their FDRs included in our study had histologic confirmation of IBD. Finally, collected data regarding EIMs were prospectively updated and further categorized into different affected organ systems, according to published data [31].

However, the study has some limitations not to be ignored. First, this is not a true population-based study. Our cohort of IBD patients includes IBD patients referred to specialized centers, commonly with more aggressive disease courses that may require hospital admission and/or surgery, compared to those who are followed in outpatient private practice. This could explain the distribution of cases with UC and CD in our cohort which differs from that observed in population-based studies, where the prevalence of UC cases may be higher than CD. The population of patients enrolled in the current study could also contain an overrepresentation of IBD patients with a positive family history or with a more severe disease course compared to true population-based studies. However, due to the open access of patients to referral centers, and the advocacy of patient groups, care of IBD patients in Greece (severe and non-severe) is highly concentrated in the hospital setting; thus, data reported by the present study is probably typical of the general population of IBD patients in our country.

Conclusion

The study demonstrated that a positive IBD family history in FDRs of IBD patients is associated with an increased risk for hospitalization, perianal disease, surgical treatment, occurrence of EIMs, and need for treatment with anti-TNF agents. In addition, females of the entire IBD cohort and CD patients of both sexes were at greater risk of having offsprings diagnosed with IBD and/or siblings and parents with IBD. These results should be taken into account when consulting patients with IBD. However, large multicenter prospective cohort studies should confirm these clinical associations, which may have practical implications for patient care when the predictive ability of family aggregation is gauged relative to other predictors, particularly at the time of initial diagnosis, when information on disease characteristics is commonly limited.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-025-08868-5.

Author Contributions Christina Liava contributed to the conception and design of the study, acquisition, analysis, and interpretation of data. She drafted the article, made critical revisions related to the important intellectual content of the manuscript, and approved the final version of the article to be published. Danai Chourmouzi contributed to the conception and design of the study, acquisition, analysis, and interpretation of data. They also contributed to the preparation of the article and approved the final version. Sinakos Emmanouil, Theodoros Dimitroulas, and Navrozidou Christina helped in the acquisition of data, made critical revisions related to the important intellectual content of the manuscript, and then approved the final version of the article to be published. Evangelos Akriviadis contributed to the conception and design of the manuscript, he made critical revisions related to important intellectual content and approved the final version of the manuscript.

Funding No funding sources.

Data Availability The data underlying this article are available in [Zenodo] at https://doi.org/https://doi.org/10.5281/zenodo.8366603.

Declarations

Conflict of interest No potential conflicts of interest.

STROBE statement The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

References

1. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007;369:1641–1657.
2. Annese V, Andreoli A, Astegiano M et al. Clinical features in familial cases of Crohn's disease and ulcerative colitis in Italy: a GISC study. Italian study group for the disease of colon and rectum. *Am J Gastroenterol* 2001;96:2939–2945.
3. Andreu M, Márquez L, Domènech E et al. Disease severity in familial cases of IBD. *J Crohns Colitis* 2014;8:234–239.
4. Lewkonia RM, McConnell RB. Progress report. Familial inflammatory bowel disease–heredity or environment? *Gut* 1976;17:235–243.
5. Colombel JF, Grandbastien B, Gower-Rousseau C et al. Clinical characteristics of Crohn's disease in 72 families. *Gastroenterology* 1996;111:604–607.
6. Peeters M, Nevens H, Baert F et al. Familial aggregation in Crohn's disease: increased age-adjusted risk and concordance in clinical characteristics. *Gastroenterology* 1996;111:597–603.
7. Park SH, Hwang SW, Ye BD et al. Concordance regarding disease type and phenotypic characteristics among patients with familial inflammatory bowel disease. *J Gastroenterol Hepatol* 2020;35:988–993.

8. Cabré E, Mañosa M, García-Sánchez V et al. Phenotypic concordance in familial inflammatory bowel disease (IBD). Results of a nationwide IBD Spanish database. *J Crohns Colitis* 2014;8:654–661.
9. Halme L, Turunen U, Heliö T et al. Familial and sporadic inflammatory bowel disease: comparison of clinical features and serological markers in a genetically homogeneous population. *Scand J Gastroenterol* 2002;37:692–698.
10. Probert CS, Jayanthi V, Hughes AO et al. Prevalence and family risk of ulcerative colitis and Crohn's disease: an epidemiological study among Europeans and south Asians in Leicestershire. *Gut* 1993;34:1547–1551.
11. Borren NZ, Conway G, Garber JJ et al. Differences in clinical course, genetics, and the microbiome between familial and sporadic inflammatory bowel diseases. *J Crohns Colitis* 2018;12:525–531.
12. Momozawa Y, Dmitrieva J, Théâtre E et al. IBD risk loci are enriched in multigenic regulatory modules encompassing putative causative genes. *Nat Commun* 2018;9:2427.
13. Crowley E, Warner N, Pan J et al. Prevalence and clinical features of inflammatory bowel diseases associated with monogenic variants, identified by whole-exome sequencing in 1000 children at a single center. *Gastroenterology* 2020;158:2208–2220.
14. Santos MPC, Gomes C, Torres J. Familial and ethnic risk in inflammatory bowel disease. *Ann Gastroenterol.* 2018;31:14–23.
15. Rogler G, Singh A, Kavanaugh A et al. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. *Gastroenterology* 2021;161:1118–1132.
16. Rudwaleit M, van der Heijde D, Landewé R et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis.* 2011;70:25–31.
17. Hwang SW, Kwak MS, Kim WS et al. Influence of a positive family history on the clinical course of inflammatory bowel disease. *J Crohns Colitis* 2016;10:1024–1032.
18. Childers RE, Eluri S, Vazquez C et al. Family history of inflammatory bowel disease among patients with ulcerative colitis: a systematic review and meta-analysis. *J Crohns Colitis* 2014;8:1480–1497.
19. Henriksen M, Jahnsen J, Lygren I et al. Are there any differences in phenotype or disease course between familial and sporadic cases of inflammatory bowel disease? Results of a population-based follow-up study. *Am J Gastroenterol* 2007;102:1955–1963.
20. Moller FT, Andersen V, Wohlfahrt J et al. Familial risk of inflammatory bowel disease: a population-based cohort study 1977–2011. *Am J Gastroenterol* 2015;110:564–571.
21. Saberzadeh-Ardestani B, Anushiravani A, Mansour-Ghanaei F et al. Clinical Phenotype and Disease Course of Inflammatory Bowel Disease: A Comparison Between Sporadic and Familial Cases. *Inflamm Bowel Dis* 2022;28:1004–1011.
22. Vernier-Massouille G, Balde M, Salleron J et al. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008;135:1106–1113.
23. Chouraki V, Savoye G, Dauchet L et al. The changing pattern of Crohn's disease incidence in northern France: a continuing increase in the 10- to 19-year-old age bracket (1988–2007). *Aliment Pharmacol Ther* 2011;33:1133–1142.
24. Pigneur B, Seksik P, Viola S et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis* 2010;16:953–961.
25. Gower-Rousseau C, Dauchet L, Vernier-Massouille G et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 2009;104:2080–2088.
26. Laharie D, Debeugny S, Peeters M et al. Inflammatory bowel disease in spouses and their offspring. *Gastroenterology* 2001;120:816–819.
27. Carbonnel F, Macaigne G, Beaugerie L et al. Crohn's disease severity in familial and sporadic cases. *Gut* 1999;44:91–95.
28. Chung SH, Park SJ, Lee HS et al. Similar clinical characteristics of familial and sporadic inflammatory bowel disease in South Korea. *World J Gastroenterol* 2014;20:17120–17126.
29. Satsangi J, Grootscholten C, Holt H et al. Clinical patterns of familial inflammatory bowel disease. *Gut* 1996;38:738–741.
30. Karmiris K, Avgerinos A, Tavernaraki A et al. Prevalence and characteristics of extra-intestinal manifestations in a large cohort of Greek patients with inflammatory bowel disease. *J Crohns Colitis* 2016;10:429–436.
31. Ricart E, Panaccione R, Loftus EV Jr et al. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis* 2004;10:207–214.
32. Vavricka SR, Brun L, Ballabeni P et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol* 2011;106:110–119.
33. Roth N, Biedermann L, Fournier N et al. Occurrence of skin manifestations in patients of the Swiss Inflammatory Bowel Disease Cohort Study. *PLoS One* 2019;14:e0210436.
34. Ampuero J, Rojas-Feria M, Castro-Fernández M et al. Predictive factors for erythema nodosum and pyoderma gangrenosum in inflammatory bowel disease. *J Gastroenterol Hepatol* 2014;29:291–295.
35. Ek WE, D'Amato M, Halfvarson J. The history of genetics in inflammatory bowel disease. *Ann Gastroenterol.* 2014;27:294–303.
36. Cummings SA, Rubin DT. The complexity and challenges of genetic counseling and testing for inflammatory bowel disease. *J Genet Couns.* 2006;15:465–476.