"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY OF

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FIELD - DERMATOVENEROLOGY

GENOTYPICAL, PHENOTYPICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH INFLAMMATORY BOWEL DISEASES AND PSORIASIS

- ABSTRACT -

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Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease, with a global prevalence of approximately 2–3% of the world population. Characterized by erythematous-scaly plaques located predominantly on the elbows, knees and scalp, but with possible generalized extension, psoriasis is a pathology with a chronic, relapsing course. Psoriasis is a multisystem inflammatory disease, frequently associated with comorbidities such as psoriatic arthritis, cardiovascular diseases, metabolic syndrome, obesity, psychiatric disorders, inflammatory bowel disease [1]. The prevalence of the disease varies significantly geographically, from 0.09% in Asia to over 11% in Scandinavian countries, while in Romania, the prevalence is estimated at approximately 5%[2]. The pathophysiology of psoriasis involves a complex interaction between genetic factors, immunological disorders (IL-23/Th17 axis), environmental and psychosocial factors. The onset presents two incidental peaks, affecting both sexes relatively equally. Severity is variable and can fluctuate over time. Recent studies have demonstrated immunogenetic overlaps between psoriasis and inflammatory bowel disease[3].

Inflammatory bowel diseases, represented by Crohn's disease (CD) - transmural involvement of any segment of the digestive tract and ulcerative colitis (UC) - inflammation limited to the colonic mucosa, are chronic idiopathic inflammatory pathologies of the digestive tract, with increasing prevalence in urbanizing regions, including Romania[4]. The etiopathogenesis of IBD involves the interaction between genetic predisposition, intestinal dysbiosis, alteration of epithelial barrier function, and dysregulation of the mucosal immune response (the imbalance between Th1 and Th2 lymphocytes plays a central role). IL-4 has an anti-inflammatory, immunomodulatory role, and an inhibitor of IL-1, IL-6, IL-12, and TNF-α. Reduced levels of IL-4 have been reported in patients with Crohn's disease, suggesting a possible protective role of the Th2 response. The IL-4 gene (5q23-31) contains several SNP polymorphisms, including -590C/T (rs2243250), associated with alterations in cytokine expression, but data on their involvement in IBD are limited. Numerous studies have demonstrated a bidirectional association between psoriasis and IBD, common genetic loci (6p21, IL23R, IL12B), immunological overlaps (increased IL-17), and similar inflammatory profile[5]. In addition, anti-TNF biologic therapies used in IBD can induce paradoxical psoriasiform lesions, suggesting convergent immunological mechanisms.

Given the genetic and immunological overlap, the major clinical impact, and the lack of data in the Romanian population, the present work proposes to investigate IL-4 gene polymorphisms in relation to susceptibility to IBD, disease severity, and association with psoriasis.

Chapter 1. Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory dermatosis characterized by a marked acceleration of the keratinocyte life cycle. The keratinization process, which normally lasts approximately 28 days, is reduced to 3–5 days, causing the accumulation of incompletely differentiated keratinocytes on the skin surface (hyperparakeratosis). This epidermal hyperproliferation, associated with a significant inflammatory infiltrate, leads to the appearance of typical lesions – well-demarcated erythematous-squamous plaques, covered by pearly white scales, frequently pruritic. Beyond the skin involvement, psoriasis has a significant impact on the quality of life, being associated with social stigmatization, emotional impairment and an increased risk of comorbidities, especially metabolic syndrome and cardiovascular diseases, which underlines its multisystemic character[6].

The global prevalence of psoriasis is estimated to be approximately 2.5%, with significant geographical variation. The disease is more common in Europe (especially in the Nordic countries) than in Southeast Asia. It affects adults more often than children, with prevalence increasing with age, peaking between 60 and 69 years. There is a strong genetic predisposition, with a family history present in 40–50% of patients. Risk factors include both non-modifiable elements (age, sex, genetic predisposition) and modifiable factors such as smoking, alcohol consumption, obesity, stress or skin trauma[7].

From a pathogenic point of view, psoriasis is the result of a complex interaction between innate and adaptive immunity. T cells, especially the Th1 and Th17 subsets, play a central role by producing pro-inflammatory cytokines. The IL-23/Th17 axis is essential in maintaining inflammation, along with TNF-α, which amplifies the immune response and facilitates the migration of inflammatory cells to the skin.[8] Keratinocytes are not just passive targets, but actively participate in the perpetuation of inflammation through the secretion of cytokines and chemokines. Triggers, such as psychological stress, infections (especially streptococcal), the Koebner

phenomenon, certain drugs, or sunburn, can initiate or worsen the disease in genetically susceptible individuals.[9]

Clinically, the most common form is psoriasis vulgaris (80–90% of cases), characterized by erythematous-squamous plaques located predominantly on the elbows, knees, scalp, and lumbar region.[10] Other forms include guttate (post-infectious) psoriasis, inverse psoriasis (in folds), pustular psoriasis, and the rare erythrodermic form. The disease is often associated with psoriatic arthritis, depression, and inflammatory bowel disease.

Diagnosis is mainly clinical, based on history and objective examination, and skin biopsy is reserved for atypical cases[11]. Severity assessment is performed using standardized scores such as PASI, IGA/sPGA and DLQI, which are essential for establishing therapeutic management and monitoring response to treatment.

Treatment aims to control inflammation, reduce lesion extension and improve quality of life. Mild forms mainly benefit from topical therapy (corticosteroids, vitamin D analogues), while phototherapy (NB-UVB) is an effective option for moderate cases. Moderate–severe forms require systemic therapy, including classic drugs (methotrexate, cyclosporine, retinoids), oral small molecules or biological therapies that specifically target TNF-α, IL-12/23, IL-23 or IL-17. These modern therapies have demonstrated increased efficacy and safety, contributing significantly to improving patient prognosis [12,13].

Chapter 2. Paradoxical Psoriasis

Paradoxical psoriasis (PP) is an immune-mediated cutaneous adverse event, occurring mainly in patients treated with biological therapies, especially TNF-α inhibitors, for other inflammatory diseases. It is characterized by the development of psoriatic or psoriasiform lesions, clinically similar to idiopathic psoriasis, but with distinct pathogenic mechanisms. Unlike the classic form, PP involves the overproduction of interferon-α (IFN-α) secondary to TNF-α blockade and the absence of persistent T-cell activation, suggesting a specific therapeutically induced immune imbalance. PP has a multifactorial etiology, with genetic predisposition playing an important role, and associations with different genetic polymorphisms involved in the response to anti-TNF therapy have been described. Risk factors include family history of psoriasis, smoking, and psychological stress. Therapeutic management aims to maintain control of the underlying disease and treat skin lesions. In mild-moderate forms, continuation of the biologic and association

with topical therapy is recommended, and in severe cases, systemic treatments can be added or the biologic agent can be changed [14,15].

Most cases are associated with TNF-α inhibitors, and pharmacogenetic data suggest that genetic variations can influence both the efficacy of the treatment and the risk of paradoxical reactions.

Chapter 3. Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD) are a group of chronic, recurrent inflammatory diseases of the digestive tract, determined by an abnormal immune response to the intestinal mucosa. The main clinical entities are Crohn's disease and ulcerative colitis, which share common etiopathogenic mechanisms, but present distinct morphological and clinical features. Crohn's disease is characterized by segmental, asymmetric and transmural involvement, which can affect any segment of the digestive tract, while ulcerative colitis involves continuous inflammation, limited to the mucosa and submucosa, with rectal onset and progressive proximal extension. Both have alternating periods of activity and remission. Clinical phenotyping is performed by the Montreal classification, useful in assessing the prognosis and risk of complications. In Crohn's disease, this includes age at diagnosis, location of lesions and disease behavior (inflammatory, stenotic or penetrating), as well as the presence of perianal involvement. In ulcerative colitis, the classification is based on the extent of the lesions (proctitis, left-sided colitis, extensive colitis)[16].

The global prevalence of IBD is estimated to be approximately 0.3%, with a high incidence in Western Europe and North America, but also expanding in developing countries. The disease can occur at any age, with two peaks of incidence, and the distribution by sex is approximately equal. Risk factors include genetic predisposition, smoking (with different effects in the two entities), oral contraceptive use, urban environment, and increased levels of hygiene in childhood. The etiopathogenesis of IBD is complex and incompletely elucidated, involving the interaction of genetic susceptibility, environmental factors, and intestinal dysbiosis. First-degree relatives have a 4–8-fold increased risk, and over 240 genetic loci have been associated with the disease, many overlapping with other immune disorders, including psoriasis. Genes such as NOD2, ATG16L1 and IRGM, as well as IL-23-related pathways, are frequently implicated in Crohn's disease, while variants of IL-10 and MDR1 are relevant in ulcerative colitis. Immunologically, Crohn's disease is dominated by a Th1/Th17 response, with increased production of IL-12, IL-23, IFN-γ, IL-17

and TNF-α, the latter having a central therapeutic role. Integrins contribute to the recruitment of leukocytes to the intestine. In ulcerative colitis, a Th2/Th9 profile predominates, with the involvement of the cytokines IL-4, IL-5, IL-9 and IL-13, which affect the integrity of the epithelial barrier and increase intestinal permeability. IL-4 has a complex, possibly protective role, and polymorphisms of the IL-4 gene, such as rs2243250, may influence cytokine expression and susceptibility to the disease [17,18].

Diagnosis is based on the correlation of clinical data (diarrhea, often bloody in ulcerative colitis, abdominal pain, weight loss), physical examination and laboratory investigations. Extraintestinal manifestations occur in approximately a quarter of patients and can be ocular, cutaneous, articular or hepatobiliary. Evaluation includes blood and stool tests (fecal calprotectin), imaging (CT, MRI) and colonoscopy with multiple biopsies. Severity is assessed by validated scores: CDAI for Crohn's disease and Mayo score for UC [19,20].

The differential diagnosis between the two entities is based on clinical, endoscopic and histological characteristics: discontinuous, transmural involvement, with "jumping" lesions in Crohn's disease versus continuous, superficial inflammation, with rectal onset in ulcerative colitis.

Therapeutic management aims to induce and maintain remission and prevent complications. Strategies include the "step-up" or "top-down" approach, depending on severity. Treatment includes aminosalicylates (especially in ulcerative colitis), corticosteroids for acute flares, thiopurines for maintenance of remission, and biological therapies (anti-TNF, anti-integrins, anti-IL-12/23) in moderate–severe or refractory forms. [21,22] The choice of therapy is guided by disease severity, phenotype, and individual response, with the primary goal of mucosal healing and improved long-term prognosis.

Chapter 4. Working hypothesis and general objectives

The paper analyzes the relationship between the polymorphism of the interleukin-4 (IL-4) gene and susceptibility to inflammatory bowel disease (IBD) in the Romanian ethnic population, as well as the correlation of the genetic marker with the clinical phenotype of IBD patients. In parallel, the study aims to characterize the epidemiological and phenotypic characteristics of IBD patients who develop psoriatic/psoriasiform skin manifestations, including paradoxical psoriasis, during the course of the disease or as an adverse reaction to treatment.

The working hypothesis is based on the premise that inflammatory bowel diseases occur in genetically predisposed individuals, in whom environmental factors and intestinal dysbiosis trigger an aberrant immune response. Although cytokines involved in inflammation are intensively studied, the role of IL-4 remains controversial, which justifies the evaluation of an IL-4 gene polymorphism in relation to the risk of Crohn's disease, respectively ulcerative colitis, and the clinical expression of the disease.

Given that patients with IBD are frequently young and exposed, over time, to extraintestinal manifestations (musculoskeletal, cutaneous, ocular, hepatobiliary), the paper focuses specifically on cutaneous manifestations, with emphasis on psoriatic lesions, psoriasiform lesions, paradoxical psoriasis (in a therapeutic context, especially biological). Against the background of the reported increase in the incidence/prevalence of psoriasis in patients with IBD in the last decade, and considering the genetic and immunological overlap between psoriasis and IBD, the study aims to identify clinical and demographic factors that may predispose to the occurrence of psoriasis in Crohn's disease and ulcerative colitis.

General objectives

1. Investigate the association between the IL-4 gene polymorphism and the susceptibility to develop IBD in patients of Romanian ethnicity.

2. Epidemiological and phenotypic characterization of patients with IBD and psoriasis (psoriatic/psoriasiform/paradoxical).

3. Analysis of the context of the occurrence of paradoxical psoriasis in patients with IBD (disease vs. adverse therapeutic reaction).

Chapter 5. General research methodology

5.1 General description of the study

An analytical, retrospective/descriptive observational study was conducted on a group of 160 patients diagnosed with IBD, conducted in two regional centers in Bucharest, Romania: Gastroenterology Department - Elias University Emergency Hospital and Gastroenterology Department - Fundeni Clinical Institute, the study period being January 2021 - January 2023.

A control group was established consisting of 160 healthy subjects, recruited from the National Institute of Blood Transfusion "Prof. Dr. C. T. Nicolau", with no history of IBD or immune-mediated pathologies, confirmed by a signed questionnaire.

All included patients were Caucasian, of Romanian ethnicity. Participation was conditional on informed consent.

5.2 Inclusion and exclusion criteria

Inclusion criteria:

• histopathologically confirmed diagnosis of Crohn's disease or ulcerative colitis;

• age >18 years at inclusion;

• stable residence in Romania;

• hospitalization during the study period for investigations/procedures related to IBD.

Exclusion criteria:

• refusal to sign informed consent;

• impaired temporal-spatial discernment/orientation;

• incomplete data on personal/hereditary history of psoriasis or anxiety-depressive disorders.

5.3 Study protocol and collected variables

The diagnosis of CD/UC was established according to clinical practice guidelines. A database was built for each patient that included demographic data (current age, age at diagnosis), disease course (duration, number of flares), phenotype (Montreal classification), severity (CDAI - CD and Mayo - UC); disease status at the time of assessment (remission/activity), need for colectomy (elective/emergency), lifestyle (smoking), treatment (topical/systemic/biological - anti-TNF-α, anti-IL-12/23, anti-IL-17) and response to treatment, adverse reactions (including psoriatic/psoriasiform/paradoxical skin manifestations).

Operational definition used in the study - all patients followed treatment ≥3 months; primary non-responder was defined as the need to change treatment 3 months after initiation.

5.4 Phenotypic classification[23]

Montreal classification of Crohn's disease: Age (A): A1 <17 years; A2 17–40 years; A3 >40 years; Location (L): L1 terminal ileum ± cecum; L2 colonic; L3 ileo-colonic; L4 upper

digestive tract; Behavior (B): B1 non-stenosing/non-penetrating; B2 stenosing; B3 penetrating; p – perianal disease

Montreal classification of ulcerative colitis: E1 – proctitis (rectum); E2 – left-sided colitis (up to the splenic flexure); E3 – extensive colitis (beyond the splenic flexure)

5.5 Severity scores

CDAI score (Crohn's disease) – includes clinical parameters (stools, pain, general condition), complications, antidiarrheal use, abdominal mass, hematocrit and weight loss. Interpretation: <150 - remission, 150–200 - mild activity, 200–450 - moderate activity, >450 - severe activity.

Mayo score (ulcerative colitis) – evaluates stool frequency, rectal bleeding, endoscopic appearance of the mucosa and the physician's global assessment. Interpretation: 0–1: remission, 3–6: mild, 7–9: moderate, ≥10: severe flare.

5.6 Statistical analysis

Initial processing and descriptive statistics were performed in Microsoft Excel 2010, using pie/column/bar graphs. Advanced analysis was performed in Python 3.7.4. Contingency tables were constructed for categorical variables; for binary variables, Fisher's exact test was used; for categorical variables with >2 levels, the Chi-square test was used. For numerical variables compared between two groups, Student's t was used, when the application conditions were met. To evaluate the predictive value of numerical parameters, logistic regression models and ROC curves were used, with AUROC calculation and 95% confidence interval. To identify independent factors associated with skin manifestations (psoriatic/psoriasiform) multinomial logistic regression was used. The statistical significance threshold was $p \leq 0.05$, and the strength of significance was conventionally noted (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001).

Chapter 6 - Epidemiological and phenotypic correlations between psoriasis and inflammatory bowel diseases

6.1 Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, immune-mediated diseases, with a relapsing course and a significant impact on the quality of life, frequently affecting the

young population; they are considered systemic pathologies, associated with extraintestinal manifestations, and cutaneous manifestations occur in approximately 10% of patients with IBD.

In the last decade, the association of psoriasis with IBD has been reported more frequently. Psoriasis is a chronic, immune-mediated dermatosis, with genetic and immunological overlaps with IBD; in addition, certain biological therapies can precipitate the appearance of psoriasiform lesions/paradoxical psoriasis. In Romania, amid the increasing incidence of IBD, the identification and characterization of cutaneous manifestations and risk factors becomes clinically relevant, including through the prism of psycho-emotional comorbidities, which can influence the evolution, compliance and therapeutic results.

The specific objectives of the chapter are to characterize the association between IBD and psoriatic/psoriasiform lesions and to identify risk factors for the occurrence of psoriasis in patients with CD/UC.

6.2 Materials and methods

A retrospective observational study was conducted between January 2021 and January 2023, which included 160 patients with IBD hospitalized in two university centers in Bucharest, the diagnosis being established by correlating clinical and paraclinical data, with histopathological confirmation.

A database (Microsoft Excel) was established that included demographic and clinical variables: age, age at diagnosis, disease duration, number of flares, phenotype according to the Montreal classification, severity scores, disease status, history of colectomy, smoking, treatments administered, therapeutic response and adverse reactions. Cutaneous manifestations were recorded, and the diagnosis of active psoriatic lesions was confirmed by the dermatologist. Anxiety-depressive disorders were medically documented according to ICD-10 criteria; personal and family history of psoriasis, as well as antidepressant treatment, were noted.

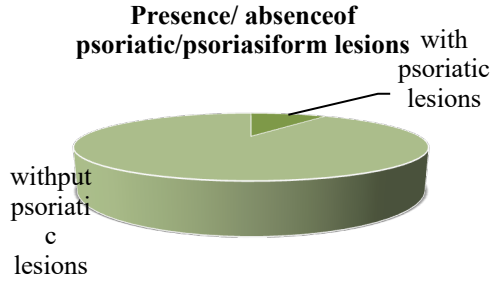
Statistical analysis included descriptive processing (Excel) and advanced analysis (Python 3.7.4), using contingency tables, Fisher exact (binary variables), Chi-square (categorical with >2 levels), Student's t (numeric variables), respectively logistic regression and ROC curves for predictive evaluations.

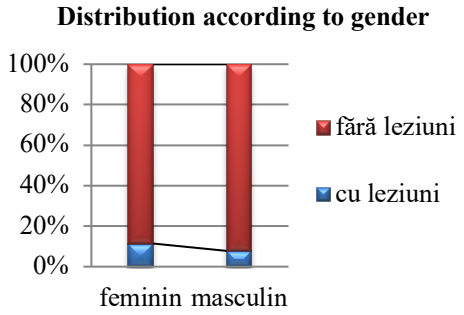
6.3 Results

The group (N=160) was divided into two subgroups, depending on the presence of skin manifestations: BII with psoriatic/psoriasiform lesions (N=15), including both lesions that

appeared “de novo” in the evolution of BII and psoriasiform lesions that appeared in the context of biological therapy (classified in the same subgroup), and BII without psoriatic/psoriasiform lesions (N=145).

In the subgroup with psoriatic/psoriasiform lesions, the gender distribution was relatively balanced, with a slight female predominance, and the mean age was 36.2 years (range 29–43 years). The prevalence of psoriatic/psoriasiform lesions in the group was approximately 9% (15/160), while 91% of the patients did not present these manifestations.

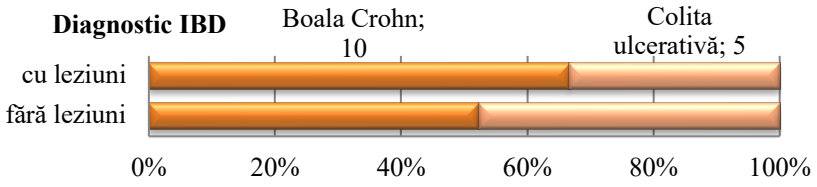




Graph 6.1 Distribution of the group according to the presence of psoriasis

Graph 6.2 Distribution of patients with psoriatic lesions according to gender

It is observed that the majority of patients with psoriatic/psoriasiform lesions were diagnosed with Crohn's disease (66.7%), compared to 33.3% patients with ulcerative colitis. However, the difference between the two subgroups did not reach statistical significance (Chi-square test, p=0.4342). Although the data suggest a higher proportion of psoriatic lesions in patients with Crohn's disease, the statistical result indicates that, within this group, the type of inflammatory bowel disease cannot be considered an independent determining factor for the occurrence of psoriatic-type skin lesions. However, the observed trend is consistent with the literature, which describes a more frequent association between Crohn's disease and psoriasis, a hypothesis that requires validation on larger groups for confirmation.



Graph 6.3 Distribution of patients with psoriasis lesions by diagnosis

Psoriatic lesions occurred predominantly in patients with active disease – moderate in Crohn's disease and severe in ulcerative colitis – and no patients in remission showed such manifestations. The CDAI score had low predictive value (AUROC=0.537), while the Mayo score demonstrated acceptable predictive capacity (AUROC=0.701). Overall, disease severity appears to be associated with the risk of developing psoriasis.

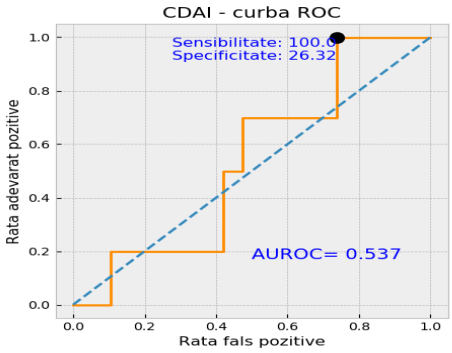


Figure 6.1 ROC curve of the CDAI severity score in predicting the occurrence of psoriatic lesions in patients with Crohn's disease

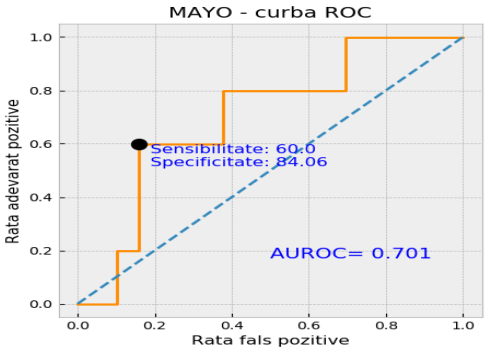


Figure 6.2 ROC curve on the role of the Mayo severity score in predicting the occurrence of psoriatic lesions in patients with ulcerative colitis

Approximately 57.5% of patients with IBD received biological treatment, and of these, approximately 15% developed psoriatic lesions (p=0.0001). In the subgroup with psoriasis, the majority were treated with anti-TNF-α (73%), and the rest with anti-IL-12/23 (27%), suggesting a possible association between biological therapy and the occurrence of paradoxical psoriasis.

Although the majority of patients with IBD and psoriasis responded favorably to biological treatment (86.7%), 80% experienced adverse reactions ($p<0.0001$), an aspect that should be interpreted with caution, since skin lesions themselves can represent adverse reactions.

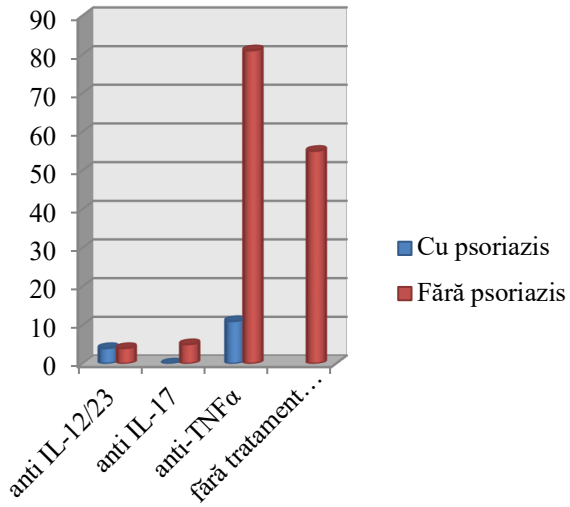
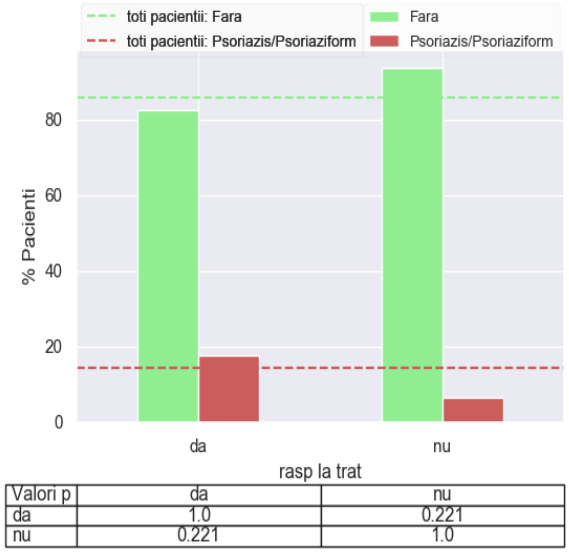


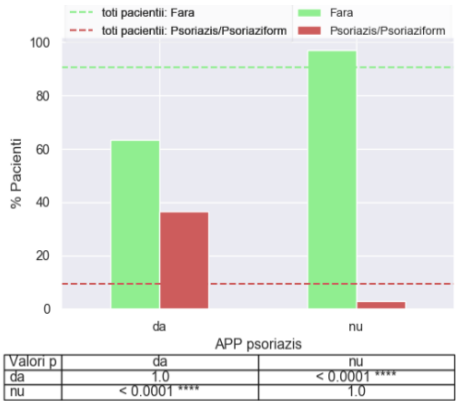
Figure 6.4 Patients with psoriatic lesions and biological treatment



Valori p	da	nu
da	1.0	0.221
nu	0.221	1.0

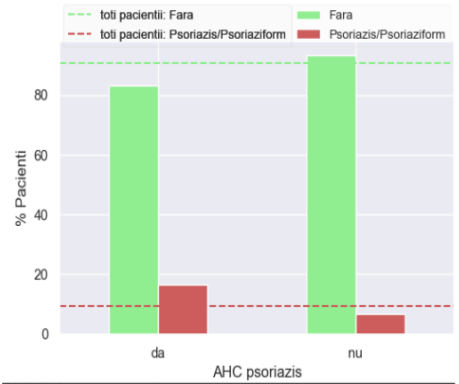
Figure 6.3 Fisher analysis biological treatment – psoriatic lesions

In the group of 160 patients with IBD, 18.8% had a personal history of psoriasis, which was more common in patients with Crohn's disease (70%) compared to ulcerative colitis (30%). In the subgroup with active psoriatic lesions, 73.3% had a personal history of psoriasis, the association being statistically significant ($p<0.0001$), suggesting that personal history is an important predictive factor. A family history of psoriasis was present in 26.3% of patients, with a slight predominance in Crohn's disease. In the subgroup with psoriatic lesions, 46.7% reported a family history, but the association did not reach statistical significance ($p=0.07$), suggesting only a possible trend.



Valori p	da	nu
da	1.0	< 0.0001 ****
nu	< 0.0001 ****	1.0

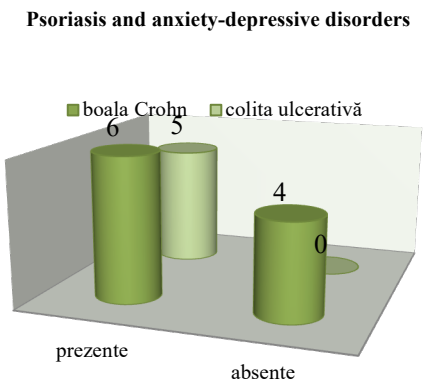
Figure 6.4 Fisher analysis APP psoriasis – BII



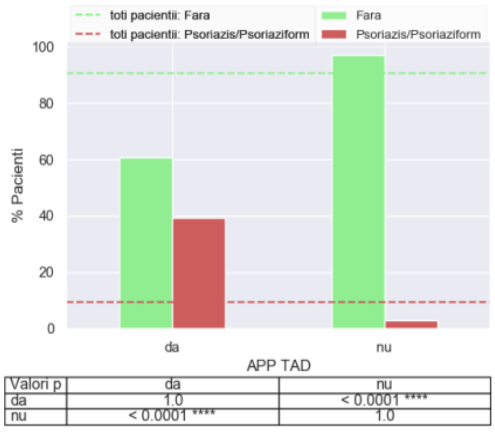
Valori p	da	nu
da	1.0	0.07
nu	0.07	1.0

Figure 6.5 Fisher analysis AHC psoriasis - BII

In the studied group, 17.5% of patients with BII had a history of anxiety-depressive disorders. In the subgroup with psoriatic/psoriasiform lesions, 73.3% had a history of anxiety-depressive disorders, the association being statistically significant ($p<0.0001$), which suggests a possible role of psycho-emotional vulnerability in the occurrence of skin manifestations. In patients with associated psoriasis, 40% were undergoing antidepressant treatment, compared to 13% of those without skin lesions. However, the majority of patients with psoriasis (60%) were not under active treatment, suggesting that the relationship between therapy and skin manifestations is complex and requires cautious interpretation.



Graph 6.5 Distribution of patients with psoriatic manifestations and APP of anxiety-depressive disorders



Valori p	da	nu
da	1.0	< 0.0001 ****
nu	< 0.0001 ****	1.0

Figure 6.6. Fisher Psoriasis Analysis – APP of Anxiety-Depressive Disorders

6.4 Discussion

Crohn's disease, ulcerative colitis and psoriasis are chronic, immune-mediated conditions that share common pathogenic mechanisms, including overlapping genetic susceptibility, epithelial barrier dysfunction and activation of similar inflammatory pathways, particularly those mediated by T-helper lymphocytes and proinflammatory cytokines [24,25]. This immunological convergence explains both the bidirectional epidemiological association reported in the international literature and the therapeutic overlap through the use of TNF-α and IL-12/23 inhibitors[26].

In the analyzed group (N=160), the prevalence of psoriasis/psoriasiform lesions was approximately 9.37%, a value 3–4 times higher than the estimated prevalence in the general population. The occurrence of skin manifestations was more frequent in patients with Crohn's disease compared with ulcerative colitis, consistent with data from European cohorts and recent genetic studies [27,28]. More severe forms of activity were associated with an increased risk of developing psoriatic lesions. The CDAI score has the highest sensitivity (100%) in predicting psoriasis, but low specificity (26.32%), so it identifies patients at risk well, but with many false positive results, while the MAYO score has the highest specificity (84.06%), suggesting that severe forms are strongly associated with the development of psoriatic lesions. A central element of the analysis is biological therapy. The majority of patients with psoriatic manifestations were exposed to TNF-α inhibitors and IL-12/23 inhibitors, supporting the concept of paradoxical psoriasis as an immunological adverse reaction[29]. In addition, the increased frequency of psycho-emotional comorbidities[30] suggests the involvement of stress factors and the gut-brain axis in modulating the inflammatory response and clinical cutaneous expression.

Clinical factors associated with increased risk were female gender, age >35 years, disease duration >5 years, diagnosis of Crohn's disease (vs. ulcerative colitis), and the best statistical predictors were personal history of psoriasis (Youden J=0.60), history of anxiety-depressive disorders (Youden J=0.61) and biological treatment and associated adverse reactions (Youden J=0.77 – the highest), suggesting an important role in the occurrence of psoriasis, including paradoxical forms.

6.5 Conclusions

Overall, the results highlight the multifactorial nature of the association between IBD and psoriasis, in which the severity and duration of the disease, the genetic and psychological

background of the patient and exposure to biological therapies act synergistically. Although most of the findings are aligned with the international literature, the relatively small size of the subgroup with psoriatic lesions requires cautious interpretation of some results and the need for validation in prospective studies with larger cohorts.

Chapter 7. IL-4 gene polymorphism in patients with inflammatory bowel diseases – disease risk and clinical manifestations

7.1 Introduction

Inflammatory bowel diseases represent a major public health problem, whose etiopathogenesis involves the complex interaction between environmental factors, intestinal dysbiosis and genetic susceptibility, leading to a dysregulated immune response and the perpetuation of chronic inflammation. Although the role of proinflammatory cytokines is well documented, the contribution of interleukin-4 (IL-4) remains insufficiently elucidated. In this context, the present study aims to evaluate the association between IL-4 gene polymorphisms and phenotypic characteristics of patients diagnosed with Crohn's disease and ulcerative colitis.

7.2 Materials and methods

A prospective observational study was conducted between January 2021 and January 2022, which included 160 patients with inflammatory bowel disease and 160 healthy subjects as a control group. The diagnosis was established according to current guidelines, by correlating clinical, paraclinical and histopathological data. Relevant clinical variables were collected and analyzed, including the type of disease, location and evolutionary pattern in Crohn's disease, extension in ulcerative colitis, severity scores (CDAI and MAYO), smoking status, extraintestinal manifestations, need for colectomy, anti-TNF alpha biological treatment and therapeutic response.

Genetic analysis targeted two single nucleotide polymorphisms (rs2243250 and rs2070874) of the IL-4 gene, selected based on data from the literature and the dbSNP database, with a minor allele frequency >10% in the European population. Genotyping was performed by real-time polymerase chain reaction using TaqMan assays. Statistical analysis included non-parametric tests (Mann-Whitney U), the χ^2 test for categorical variables and for assessing Hardy-Weinberg equilibrium, as well as haplotype and linkage disequilibrium analysis using SPSS and

PLINK programs. The statistical significance threshold was set at $p \leq 0.05$, with the Bonferroni correction for multiple comparisons.

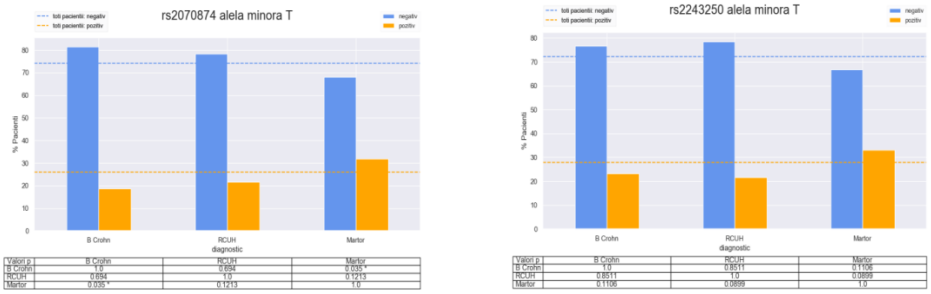
7.3 Results

The analyzed group included 160 patients diagnosed with inflammatory bowel disease, of which 86 (53.75%) with Crohn's disease and 74 (46.25%) with ulcerative colitis. The gender distribution was relatively balanced, with a slight male predominance, more pronounced in ulcerative colitis than in Crohn's disease. The mean age of the patients was similar between genders and diagnoses, ranging around 35–36 years. The duration of the disease was most frequently between 1 and 5 years in both pathologies. According to the Montreal classification, in Crohn's disease the ileal location predominated, followed by the colonic and ileo-colonic. In ulcerative colitis, the left form was the most frequent, followed by extensive colitis and proctitis. In terms of severity, moderate forms were predominant in Crohn's disease, while in ulcerative colitis a relatively balanced distribution between mild and moderate forms was observed. Most patients underwent biological treatment, especially anti-TNF alpha, with a favorable response in over two thirds of cases and a low rate of adverse reactions. Extraintestinal manifestations were absent in most patients; the most frequent were cutaneous and joint ones. An increased prevalence of a history of psoriasis and anxiety-depressive disorders was also noted, without significant differences between the two diseases.

Analysis of IL-4 gene polymorphisms (rs2243250 and rs2070874) suggests a possible protective effect of the minor T allele in inflammatory bowel diseases (IBD). In Crohn's disease, the frequency of the T allele was significantly lower in patients compared to controls for both SNPs, indicating a lower risk of disease (OR < 1). Also, carriers of genotypes containing the T allele (CT + TT) had a significantly reduced risk of developing Crohn's disease ($p=0.04$). In ulcerative colitis, the distribution of alleles followed the same pattern, but the differences were not statistically significant in the allelic analysis. However, the analysis of genotypes (CT + TT) revealed a significantly lower risk for carriers of the T allele ($p = 0.04$ for rs2243250 and $p = 0.03$ for rs2070874).

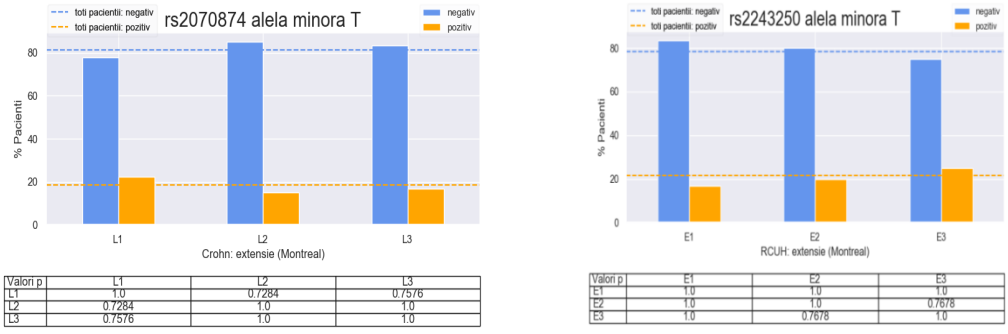
The pooled analysis of all IBD patients confirmed the lower frequency of the T allele compared to the control group, supporting its protective role ((corrected $p \approx 0.02$). Carriers of the CT + TT genotypes also presented a reduced overall risk of disease. Haplotype analysis showed that the CC haplotype is associated with an increased risk of IBD ($p=0.003$). The moderate linkage

disequilibrium between the two SNPs suggests a relevant genetic correlation between the studied variants ($r^2 = 0.72$ in the control group).



Charts 7.1 (a, b) Analysis of the relative frequency of positivity of the rs2243250 (right) and rs2070784 (left) alleles in patients with IBD versus control patients

Analysis of the association of IL-4 polymorphisms (rs2243250 and rs2070874) with the extent of the disease, according to the Montreal classification, highlighted the following: In Crohn's disease, the ileal location (L1) showed a lower frequency of the minor T allele for both SNPs, with subunit OR values, suggesting a possible protective effect; however, the results did not reach statistical significance ($p \approx 0.06–0.07$). For the L2 and L3 locations, no relevant differences were identified, and in ulcerative colitis, the allelic analysis did not demonstrate significant associations according to extent. However, in the pancolitis subgroup (E3), the genotype distribution for rs2243250 revealed significant differences compared to the control group, suggesting a possible influence of the genetic variant on the extensive phenotype of the disease.



Valori p	L1	L2	L3
L1	1.0	0.7284	0.7576
L2	0.7284	1.0	1.0
L3	0.7576	1.0	1.0

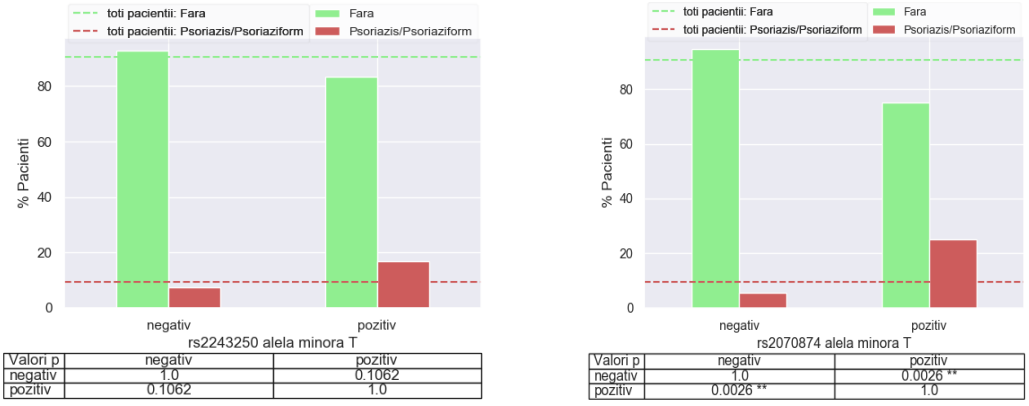
Valori p	E1	E2	E3
E1	1.0	1.0	1.0
E2	1.0	1.0	0.7678
E3	1.0	0.7678	1.0

Graph 7.2 IL-4 polymorphism in IBD according to the extent of the disease

IL-4 polymorphisms (rs2243250 and rs2070874) were significantly associated with extraintestinal manifestations in patients with inflammatory bowel disease. The minor T allele was

more common in patients with IBD, and the CT + TT genotypes were associated with an approximately 3-fold increased risk of developing these complications.

Analysis of psoriatic skin manifestations in patients with inflammatory bowel disease revealed significant associations with IL-4 polymorphisms. Positivity for rs2243250 was significantly more common in patients with psoriasis compared to those without skin lesions, but in detailed subgroup analysis the association did not maintain statistical significance, suggesting only a possible trend. In contrast, for rs2070874, the association with psoriatic manifestations was strong and statistically significant. The absence of the minor T allele and the presence of the CC genotype were more common in patients without skin lesions, indicating the involvement of this genetic variant in the susceptibility to psoriatic manifestations. Overall, the results suggest that although the minor T allele may have a protective role in the overall susceptibility to IBD, it seems associated with an increased risk of extraintestinal manifestations, especially cutaneous. Analysis of the rs2243250/rs2070874 haplotype did not demonstrate a significant association with the presence of psoriasis, although the CC haplotype was more frequent in patients without lesions.



Valori p	negativ	pozitiv
negativ	1.0	0.1062
pozitiv	0.1062	1.0

Valori p	negativ	pozitiv
negativ	1.0	0.0026 **
pozitiv	0.0026 **	1.0

Figure 7.3 IL-4 polymorphism in patients with psoriatic lesions and IBD

Multinomial logistic regression analysis identified several independent risk factors associated with the development of skin manifestations in patients with inflammatory bowel disease. Severity of the disease (assessed by CDAI scores for Crohn's disease and MAYO scores for ulcerative colitis), personal history of anxiety-depressive disorders, and the presence of the minor T allele of the rs2070874 polymorphism were independently associated with the development of skin lesions.

Regarding the specific prediction of psoriatic/psoriasiform lesions, multivariate analysis revealed as independent risk factors: personal history of psoriasis, family history of psoriasis,

personal history of anxiety-depressive disorders, active treatment with antidepressants, and the presence of the minor T allele of rs2070874.

Based on these variables, a prediction score was developed that integrated disease severity, genetic status for rs2070874, and personal and family history of psoriasis. Evaluation of the score's performance by ROC curve analysis demonstrated high predictive capacity (AUROC = 0.899), with a sensitivity of 93.33% and a specificity of 82.07%. These results suggest that integrating clinical and genetic parameters into a composite model may represent a useful tool for identifying IBD patients at high risk of developing psoriatic lesions.

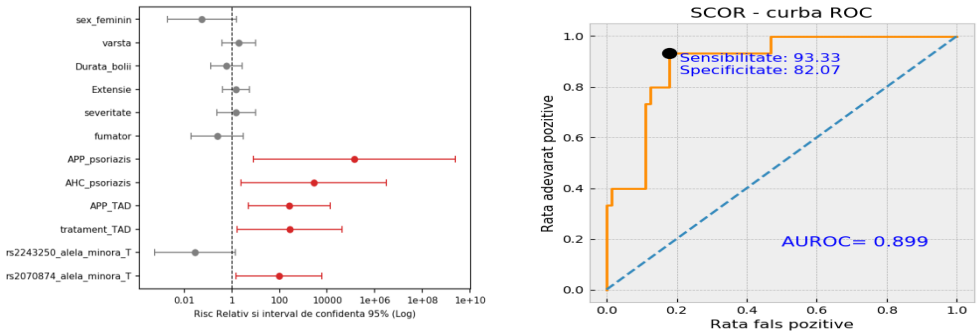


Figure 7.4 Prediction score for the development of psoriatic lesions in patients with inflammatory bowel disease

7.4 Discussion

The role of Th2-type immunity in the pathogenesis of IBD is less elucidated compared to the Th1 and Th17 axes, but experimental and clinical data suggest the involvement of IL-4 and IL-13 cytokines in the processes of epithelial healing and modulation of inflammation. Genetic variability in the IL-4 gene, located in the 5q23–31 region, may influence cytokine expression, susceptibility and clinical phenotype of IBD [31,32,33,34]. The present study demonstrated a protective effect of the minor T allele for the rs2243250 (−590C/T) and rs2070874 (−34C/T) polymorphisms, both in Crohn's disease and in the entire IBD group, evidenced by its significantly lower frequencies in patients compared to the control group. In contrast, the rs2243250/rs2070874 CC haplotype was associated with an increased risk of developing the disease. In terms of phenotypic expression, the presence of the minor T allele of rs2070874 was significantly associated with extraintestinal manifestations, especially psoriatic skin lesions, as well as with lack of response to anti-TNF alpha therapy, and the rs2243250 genotypes were implicated in the extensive pancolitis

model in ulcerative colitis, suggesting a differential role of IL-4 polymorphisms both in disease susceptibility and in modulating severity and systemic complications [35,36].

7.5 Conclusions

Based on the identified independent risk factors (disease severity, psoriasis APP and AHC, anxiety-depressive disorders and the presence of the T allele of rs2070874), a predictive score with high diagnostic performance (AUROC = 0.899) was proposed, suggesting the utility of genetic and clinical markers in a personalized model. The main limitations of the study are the relatively small sample size and the strict definition of non-response to anti-TNF therapy. Confirmation of these results in larger cohorts in ethnically different populations is necessary to validate the clinical implications of IL-4 polymorphisms in IBD.

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List of abbreviations

IBD – inflammatory bowel disease

CD – Crohn’s disease, UC – ulcerative colitis

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1. Andrei Ovidiu Olteanu et al, *Paradoxical Psoriasis induced by Ustekinumab: A Comprehensive review and Case Report, Medicina*, 2025 – chapter 6, pages 39-73. https://doi.org/10.3390/medicina60010106

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