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TESI DI LAUREA

Pulmonary manifestations in inflammatory bowel disease: a single centre observational prospective study.

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ABSTRACT

Background: up to 50% of patients affected by inflammatory bowel disease (IBD) express extra-intestinal manifestations (EIMs) involving potentially every organ. Among these, pulmonary EIMs are one of the most underdiagnosed, given their frequently poor symptomatology.

Aim and methods of the study: the following study aims to deeper understand pulmonary EIMs in IBD from the point of view of epidemiology, clinics, radiology and pulmonary functional tests. In a period of fifteen months, IBD patients attending the Gastroenterology department of the University Hospital of Padua were prospectively enrolled and underwent the ATS-DLD-78-A questionnaire on respiratory symptoms, whose compilation was then followed by an interview with a lung medicine specialist (reserved to only those patients with a confirmed IBD diagnosis and reported respiratory symptoms). Subsequently, patients were invited to undergo chest imaging and pulmonary functional tests when necessary.

Results: 152 people were included in the study: 55 revealed a score of 3 points or more at the ATS-DLD-78-A questionnaire (‘positive’ patients), while 97 patients scored low on the questionnaire with a score of less than 3 (‘negative’ patients). The ‘positive’ patients were younger in comparison with the ‘negative’ patients (median 46 vs. 51 years old, respectively), while no different gender distribution was recorded. The ‘positive’ patients were further categorized into two sub-groups: the poorly symptomatic (n = 25, scoring 3-6 points at the questionnaire) and the very symptomatic group (n = 30, scoring 7 or more points at the questionnaire). These two groups, as well as the entire ‘positive’ population, were tested for a series of demographic, clinical and diagnostic variables. Current smokers were 29% of the entire population. EIMs of IBD were already identified and diagnosed in 24% of the population and comorbidities were highly prevalent (occurring in 71% of the entire population). Also, familiarity for lung diseases was reported by 42% of patients (mostly distributed in the very symptomatic group, 61%). Overall, 15 of ‘positive’ patients show radiological abnormalities either on chest x-ray (in 12 out of 34 people undergoing chest x-ray) or on chest CT scan (10 out of 11 people undergoing CT scan), mostly represented by bronchiectasis and parenchymal thickening. Pulmonary functional tests showed no obstructive or restrictive ventilatory disorders, but small airways obstruction was present in a small group of patients (9 out of 28 patients who underwent pulmonary functional tests). Moreover, DLCO was impaired in 14 out of 24 people.

Conclusions: almost one third of the IBD patients presents respiratory symptoms and most of them are younger adults. Familiarity for pulmonary diseases seems to be more associated with highly symptomatic IBD patients. Almost one third of the IBD population with respiratory symptoms presents radiological findings, mostly bronchiectasis. Reduced DLCO and small airways obstruction are the main functional abnormalities.

Further research, maybe with a multicenter population, is needed to confirm these results.

RIASSUNTO

Introduzione: fino al 50% dei pazienti affetti da malattia infiammatoria cronica intestinale (MICI) presenta manifestazioni extra-intestinali (MEI), le quali possono coinvolgere potenzialmente qualunque organo. Tra queste, le MEI polmonari sono tra quelle maggiormente sottodiagnosticate a causa della loro spesso scarsa sintomatologia.

Scopo e metodo di studio: il seguente studio ha l'obiettivo di comprendere più approfonditamente le MEI delle MICI dal punto di vista epidemiologico, clinico, radiologico e spirometrico. In un periodo di quindici mesi, un gruppo di pazienti affetti da MICI afferenti al reparto di Gastroenterologia dell'Ospedale universitario di Padova è stato reclutato tramite un questionario sui sintomi respiratori, la cui compilazione è stata seguita da un colloquio con uno pneumologo riservato esclusivamente ai pazienti con una diagnosi confermata di MICI e con riferiti sintomi respiratori. Poi, i pazienti sono stati invitati a sottoporsi, quando necessario, ad esami di imaging del torace e a prove spirometriche.

Risultati: 152 persone sono state incluse nello studio: 55 totalizzanti 3 o più punti nel questionario ATS-DLD-78-A (pazienti "positivi") e 97 con un punteggio inferiore a 3 punti (pazienti "positivi"). I pazienti "positivi" erano più giovani rispetto ai pazienti "negativi" (i valori mediani erano rispettivamente 46 anni e 51 anni), mentre non è stata registrata alcuna differente distribuzione del genere. Il gruppo "positivo" è stato ulteriormente classificato in due sottogruppi: il gruppo degli scarsamente sintomatici (n = 25, con 3-6 punti nel questionario) e il gruppo dei fortemente sintomatici (n = 30, con 7 o più punti nel questionario). Questi due gruppi, come anche l'intera popolazione "positiva", sono stati valutati attraverso

una serie di variabili demografiche, cliniche e diagnostiche. I fumatori attivi erano il 29% della popolazione totale. Le MEI delle MICI erano state già individuate e diagnosticate nel 24% della popolazione e le comorbidità erano altamente prevalenti (verificandosi nel 71% dell'intera popolazione). Inoltre, la familiarità per patologie polmonari è stata riportata dal 42% dei pazienti (per lo più distribuiti nel gruppo dei fortemente sintomatici, 61%). Complessivamente, 15 pazienti "positivi" hanno mostrato anomalie radiologiche al rx torace (in 12 delle 34 persone sottoposte al rx torace) o alla TC torace (in 10 delle 11 persone sottoposte alla TC torace), rappresentate soprattutto da bronchiectasie ed addensamenti parenchimali. Le spirometrie non avevano mostrato alcun disordine ventilatorio ostruttivo o restrittivo, bensì un'ostruzione delle piccole vie aeree in un piccolo gruppo di pazienti (9 dei 28 pazienti che si erano sottoposti alla spirometria che includeva il parametro FEF25-75). Inoltre, la DLCO era alterata in 14 pazienti su 24.

Conclusioni: Circa un terzo dei pazienti IBD presenta sintomi respiratori, soprattutto giovani adulti. La familiarità per patologie polmonari sembra più associata a pazienti molto sintomatici. Quasi un terzo dei pazienti IBD con sintomi respiratori presenta dei reperti radiologici, perlopiù bronchiectasie. Le principali alterazioni spirometriche rilevate erano valori ridotti della DLCO e un'ostruzione delle piccole vie aeree.

Ulteriori ricerche, possibilmente con una popolazione multicentrica, sono necessarie per confermare questi risultati.

BACKGROUND

INFLAMMATORY BOWEL DISEASE (IBD) – AN OVERVIEW

Inflammatory bowel disease (IBD) is a group of chronic relapsing-remitting affections, including two major pathological entities: ulcerative colitis (UC) and Crohn's disease (CD). In each of these two clinical varieties, IBD shows phlogistic damages to the gastrointestinal tract, differing in both anatomical extension and depth: while UC is restricted to the colorectal region and it is non-transmural, CD might involve any region from mouth to anus and it is transmural (1).

IBD cases are spread worldwide, not only in the most industrialized countries. Most people with IBD live in the Western world, but the incidence of UC and CD has been increasing rapidly in the newly Western countries in the latest years (2). Nowadays it is estimated that over 3 million people living in the United States are affected by IBD (with UC and CD incidence distributed equally) and projections forecast a prevalence of 4 million people by the year 2030 (2,3). Although the symptomatic onset is typical in young adults (most people get diagnosed in their 20s and 30s), IBD can also be diagnosed in the elderly (3).

Both UC and CD are known to be idiopathic disorders, whose actual cause remains unknown. Nonetheless, plenty of studies have provided evidence of a multifactorial etiopathogenesis. Indeed, IBD is associated with: genetic susceptibility of the host [e.g. nucleotide binding oligomerization domain containing 2 (*NOD2)* mutations in CD, *IL-23R* polymorphisms in CD and UC], composition of gut microbiota (e.g. increase of *Mycobacterium avium* subsp. *paratuberculosis* in CD, decrease of *Faecalibacterium prausnitizii* in CD, increase of *Clostridium difficile* in CD and UC), immunological abnormalities (involving both innate and adaptative responses) and environmental factors (e.g. smoke, appendectomy and fat/sugar-rich foods are risk factors for CD, pollution for both CD and UC) (4).

The clinical presentation in IBDs includes a series of symptoms and signs regarding the involvement of the gastrointestinal tract, sometimes associated with constitutional symptoms. Commonly, patients report abdominal pain, diarrhea (with or without blood), weight loss and fatigue (3). In addition to this, there could be more specific clinical features in the two forms of IBD (given their different gastrointestinal involvement) (5,6). In fact, UC is often associated with rectal bleeding (recorded in more than 90% of patients), tenesmus, urgency and mucus discharge due to inflammation and erosions/ulcers of colorectal mucosa (5,6). Instead, the clinical manifestations of Crohn's disease could be complicated by symptoms of intestinal obstruction (e.g. post-prandial abdominal pain, bloating, nausea and vomiting) and by fistulating disease symptoms (e.g. faecaluria, pneumaturia, perianal fistulae, faecal discharges from the vagina); both strictures and fistulae are typical complications of CD, due to transmural lesions of the gastrointestinal tract (6).

Diagnosis of IBD is based on a combination of clinical, laboratory, endoscopic and histological parameters. High blood concentrations of faecal calprotectin and C-reactive protein (CPR), anemia and leukocytosis are possible findings suggesting a gastrointestinal inflammatory process, but endoscopy with biopsy is the most sensitive and specific tool to confirm diagnosis of IBD (5,6). Endoscopic patterns of UC include a variety of phlogistic findings ranging in severity from erythema and vascular congestion to loss of vascular pattern, mucosal erosion and ulcers and spontaneous bleeding. Colorectal inflammation in UC is extended in a continuous and circumferential manner and it is microscopically reflected in mucosal atrophy, crypt architectural distortion and basal plasmacytosis (5). Endoscopic patterns of CD include a variety of findings: longitudinal ulcerations, erythema, oedema, nodular or cobblestone mucosal lesions, abscesses, fistulae and strictures. Gastrointestinal inflammation in CD (usually located across terminal ileum and proximal colon) is extended in a discontinuous, patchy and segmental manner and it is microscopically reflected in epithelioid granuloma, lymphoid aggregates or focal patchy inflammatory infiltrate. Also, it is recommended to perform MRI enterography, CT enterography or wireless capsule endoscopy to evaluate the entirety of the small intestine (6).

Typically, IBD requires medical management aiming to control the inflammatory process, while surgery can be considered in case of severe complications or drug therapy failure (5,6). Medical treatment for mild-to-moderate active UC includes suppository or oral mesalazine possibly associated with topical or oral corticosteroids; medical treatment for moderate-to-severe active UC includes oral or intravenous corticosteroids, thiopurines (azathioprine, 6-mercaptopurine), anti-TNF (infliximab, adalimumab) and other biologics or small molecules (vedolizumab, ustekinumab, mirikizumab, tofacitinib, filgotinib, upadacitinib, ozanimod); medical treatment for acute severe UC includes intravenous corticosteroids or, in non-responders, ciclosporin or infliximab (5). CD drug therapy has similar protocols, including oral or intravenous corticosteroids (especially for mild and moderate-to-severe active CD), thiopurines, methotrexate, anti-TNF and other biologics or small molecules (6).

EXTRAINTESTINAL MANIFESTATIONS (EIMs) - INTRODUCTION

Apart from gastrointestinal inflammation, IBD is known to be responsible for affecting other organs (7). In fact, IBD is considered a systemic disease, occurring up to almost 50% of patients and being a significant cause of morbidity and mortality (8).

The prevalence of EIMs ranges from 6% up to 47% depending on the definition we consider (7). For example, in 2018 the European Crohn's and Colitis Organization (ECCO) gave a stringent definition of EIMs, including those diseases located outside the gut and either caused by the translocation of inflammatory response from the intestine or triggered by common environmental or genetic predisposition shared with IBD (9). This definition only matches a portion of the entirety of concurrent diseases in IBD patients, which ECCO categorize as "classical EIMs" (9,10) (Table I). The non-classical EIMs are sorted into three other groups: consequences of systemic inflammation, consequences of IBD treatment and manifestations associated with IBD whose pathogenesis is uncertain (Table II) (10).

Potentially, almost any organ can be affected in IBD. Most commonly, EIMs target: the musculoskeletal system (e.g. peripheral and axial arthritis), eyes (episcleritis, anterior uveitis and iritis), skin (e.g. pyoderma gangrenosum, erythema nodosum and Sweet syndrome) and the hepatobiliary system (e.g. primary sclerosing cholangitis) (7).

Both UC and CD can develop EIMs, but, as visible in Table I, complications have a different prevalence in the two forms of IBD (7,11): for example, ocular manifestations are more frequent in CD (7,11), while primary sclerosing cholangitis is more frequent in UC (7,12).

Finally, Table II and Figure 1 show a schematic yet complete overview of the main EIMs, including their categorization suggested by ECCO (9,10).

Organ system	Manifestations	Prevalence
Gastrointestinal	PSC Autoimmune pancreatitis Autoimmune hepatitis	UC: up to 5%; CD: rare Rare Rare (< 1%)
Mucocutaneous	EN PG Oral aphthous ulcers Sweet syndrome Orofacial granulomatosis	5%–15% in CD; 2%–10% in UC 0.4%–2.6% in IBD 5%–50% in CD Rare Rare
Musculoskeletal	IBD-related arthritis Peripheral arthritis Axial arthritis Enthesitis	CD: 10%–20% ; UC: 4%–14% Up to 50% in CD (asymptomatic)
Ocular	Episcleritis and scleritis Anterior uveitis	Scleritis: up to 1%; CD: 5%–12%; UC: 3.5%–4.1%
Pulmonary	Pneumonitis	Rare
Vascular	Cardiovascular disease Thromboembolism Portal vein thrombosis	NA 3- to 4-fold increase Rare

Table I – Extraintestinal Manifestations of Inflammatory Bowel Disease (7). Focus on some of the most described complications in IBD with reference to their prevalence.
PSC: primary sclerosing cholangitis, UC: ulcerative colitis, CD: Crohn's disease, EN: erythema nodosum, PG: pyoderma gangrenosum, NA: not available.

System	A. Extraintestinal manifestations [multifocal inflammation]	B. Complications of IBD and its treatment	C. Associated conditions with uncertain mechanism
Joints and bones	Spondyloarthritis	Metabolic bone disease/ osteoporosis—[drug or nutritionally induced]	Non-inflammatory arthralgia
Eye	Uveitis Episcleritis Scleritis	Drug-induced cataracts and other drug-induced and nutritional eye disease [see supplementary Figure 4]	
Oral, aural and nasal	Oral CD Orofacial granulomatosis Metastatic CD		Sensorineural hearing loss
Skin	Erythema nodosum Pyoderma gangrenosum Sweet syndrome Metastatic CD	Drug-induced skin disease [e.g. anti-TNF–induced psoriasis, DILE] Drug-induced skin cancer Drug hypersensitivity	Vitiligo Psoriasis Eczema Epidermolysis bullosa acquisita Cutaneous polyarteritis nodosa Hidradenitis suppurativa
Urogenital	Metastatic CD	Nephrolithiasis Amyloidosis Drug-induced tubulo-interstitial nephritis	
Hepato-pancreato-biliary	PSC	Portal vein thrombosis Hepatic amyloidosis DILI Drug-induced pancreatitis	Autoimmune hepatitis Granulomatous hepatitis Autoimmune pancreatitis
Neurological		Peripheral neuropathy [drug or nutritionally induced] Venous sinus thrombosis Stroke	Central demyelination
Cardiovascular		Ischaemic heart disease Cerebrovascular accident Mesenteric ischaemia	
Pulmonary		Drug-induced lung fibrosis	Inflammatory bronchial and parenchymal lung disease, including asthma, bronchiectasis, and interstitial pneumonias
Coagulopathy		Venous thromboembolism	
Endocrine		Drug-induced Cushing's and Addison syndromes Drug-induced diabetes	Type 1 diabetes Autoimmune thyroid disease
Infection		Infections including systemic and local secondary to immunosuppression; septic complications of IBD or surgery	

Table II – Suggested categorization of 'non classical' **extraintestinal conditions in IBD patients** (9). Overview of 'non classical' EIMs in relation to their three categories suggested by ECCO. Note that "B." includes two categories formerly described.

DILE: drug-induced lupus erythematosus, PSC: primary sclerosing cholangitis, DILI: drug-induced liver injury.

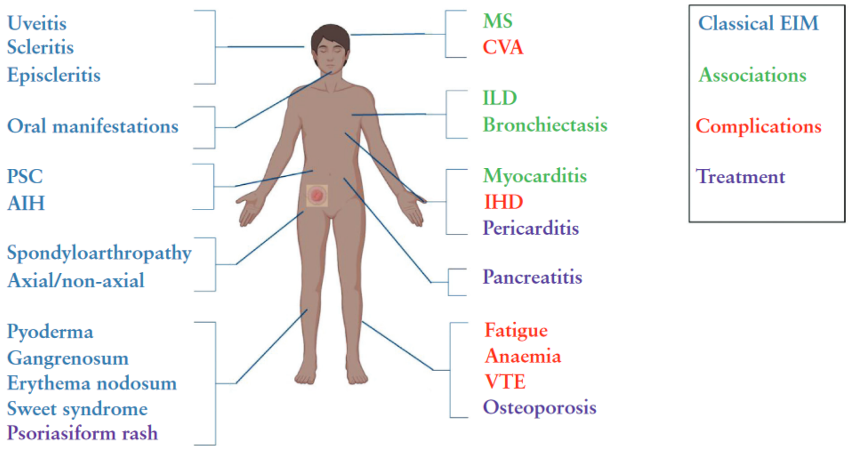

Figure 1 – Extraintestinal Manifestations in IBD (10). Graphic overview of EIMs in relation to their four categories suggested by ECCO: "Classical EIM" (IBD's inflammatory process occurring at distant sites), "Associations" (other immune-mediated disorders associated with IBD), "Complications" (complications of IBD's inflammation extended systemically), "Treatment" (side effects of IBD therapy).

PSC: primary sclerosis cholangitis, AIH: autoimmune hepatitis, MS: multiple sclerosis, CVA: cerebrovascular accident, ILD: interstitial lung disease, VTE: thromboembolic event.

EXTRAINTESTINAL MANIFESTATIONS (EIMs) – PATHOGENESIS

Pathogenesis of EIMs is not fully understood because of their intrinsic complexity and multifactorial nature (8). In general, it is clear that most of the EIMs take place either from an antigen-specific immune reaction (originated in the gut and extended outside the gastrointestinal tract) or from an independent inflammatory process (13).

Possible risk factors are:

- genetics. IBD and many diseases included in EIMs share common genetic risk factors, such as *NOD2* gene variants (present in CD, sacroiliitis and uveitis), many *HLA* genes polymorphisms (linking some forms of UC and CD to musculoskeletal disease), *SOCS1*, *JAK2* and *STAT3* genes variants (associating primary sclerosis cholangitis and IBD) (7,9). Also, it is interesting to note that *Arg381Gln* variant of IL23R has a protective effect on the development of both CD and ankylosing spondylitis (14), reinforcing the theory of a genetic bond between IBD and EIMs;
- environmental factors. Patients with CD and history of active smoking are more likely to present EIMs compared to nonsmokers CD patients (7,15). In this case, EIMs are mainly cutaneous and articular, but an association with pulmonary complications is equally possible (16). Also, it appears that smoking cessation contributes to EIMs' prevalence reduction (17);
- activation of the immune system. It is possible that IBD patients express ectopically gut-specific chemokine and adhesion molecules (7,8). Among these molecules, MAdCAM-1 and CCL25 are the main players: both are expressed in the gut endothelium and are fundamental for the attraction of T cells to the gut (8,18). In particular, T cells bind MAdCAM-1 and CCL25 by means of $\alpha4\beta7$ integrin and CCR9 receptor respectively (18). In patients with IBD an altered lymphocytes homing occurs, facilitating the upregulation of the expression of both MAdCAM-1 and CCL25 in the liver. This event enhances the migration of gut-tropic T cells to the liver and the development of hepatobiliary inflammation (8,19,20).

Lastly, it is important to specify that this model can be applied to liver EIMs only, since it is a phenomenon limited to this organ (7,8).

In addition to this, it is possible that a cross-reactivity mechanism participates to EIMs pathogenesis (8,9). Indeed, both enteric bacteria and host major histocompatibility complex (MHC) molecules have shared peptide sequences (18), meaning that the activated immune response towards the gastrointestinal tract could be hijacked to non-intestinal sites (8,9). Yet, further studies are needed to validate this mimicry hypothesis (9);

- microbiota and dysbiosis. Gut microbiota might have a role in EIMs pathogenesis, even though it is not fully understood (8). First of all, specific microbiota products may cause the disruption of the gut mucosal barrier, creating a leaky intestinal barrier. Because of this, microbiota components (e.g. lipopolysaccharides) and metabolites (e.g. short chain fatty acids) can easily translocate from the intestinal to the extraintestinal site, raising the risk of EIMs and systemic inflammatory responses (9). On the other hand, an altered microbiota (i.e. dysbiosis) could promote intestinal immune cell populations to migrate to other organs (7). This theory seems to be reinforced by studies showing a recurrent pattern of microbiota in patients with both IBD and EIMs (9). For example, patients with psoriatic arthritis often present decreased faecal microbial diversity, resembling dysbiosis in IBD (21) and the same situation is met in patients with primary sclerosing cholangitis (22).

PULMONARY EIMs – INTRODUCTION

As mentioned before, IBD can be complicated by EIMs affecting likely any organ and system, airways and lung parenchyma included. In fact, there is a large consensus on the acknowledgement of an actual connection between IBD and lung disease, as stated by recent ECCO Guidelines on EIMs (10).

Pulmonary complications in IBD are usually underdiagnosed, being in most of cases mildly symptomatic or completely asymptomatic (10,16,23). This justifies the common consideration of pulmonary EIMs as rare complications of IBD (16). In contrast, studies confirm that 37% - 55% of patients with IBD present abnormalities on chest imaging or pulmonary function tests; in many cases these alterations are found incidentally, with no symptom or pathological sign associated (24–26). However, one large retrospective study (25) has observed respiratory symptoms in approximately 10% of people with IBD. These numbers seem to suggest that pulmonary EIMs of IBD might be more common than expected, but their actual prevalence remains relatively unknown (10).

In fact, it seems that this intestine – lung relationship may be biunivocal: some studies have found increased risk of development of gastrointestinal disorders in patients with chronic lung diseases (e.g. asthma and chronic obstructive pulmonary disease) (27,28).

Finally, the results of a British study that collected and analyzed UK data on causes of death among IBD patients (29), might further suggest a underlying bond between IBD and lung disease: indeed, heart and respiratory diseases were the most common causes (responsible for 41.3% of deaths in CD and for 42.9% of deaths in UC, when globally considered), followed by lung cancer, whose association has been proven only with CD (16).

PULMONARY EIMs – PATHOGENESIS

Overall, respiratory EIMs include a wide range of diseases affecting airways, lung interstitium, pulmonary vasculature and pleura (24). Even though their pathophysiology is still unclear, pulmonary manifestations of IBD seems to be the result of a multifactorial etiopathogenesis, including a series of risk factors shared with other EIMs, such as host genetics, environmental factors, immune system dysregulation and dysbiosis (4,16,30). In addition to this, many hypotheses have been brought out to spotlight specific pathogenic mechanisms at the base of pulmonary EIMs, all of which reunited under an umbrella term: the "lung-gut axis".

Since 1968, year of publication of the first article on a possible lung-gut crosstalk (31), studies have gathered data in support of the idea of a relationship between gut and lung alterations, eventually focusing on IBD and associated pulmonary complications (32). In the first place, lung and gut have biological features in common: deriving both from the same embryological structure (the foregut region of the endoderm), the two organs present a similar epithelium (with columnar cells and goblet cells) as well as a shared submucosal lymphoid tissue (33,34). Hence, lungs and gut might be susceptible to the same antigens (e.g. smoke, microorganisms, drugs, diet) and develop a similar inflammatory reaction against them (16,24,35).

After an extended study of literature, Cavalli et al. (16) suggested a possible co-presence of various molecular and cellular processes underling the "lung-gut axis":

- the evidence of leaky intestinal barrier in IBD patients (9,16). This phenomenon leads gut antigens to translocate to systemic circulation, activating dendritic cells, macrophages and neutrophils (16). The consequent expression of pro-inflammatory cytokines (IL-6, TNF-α, IFN-γ, VEGF) increases lungs' vasculature permeability and the extravasation of neutrophils (16,36–38), letting gut's inflammation extend systemically, hence to the lungs (16). This process compromises lungs function of regulating neutrophils homeostasis, resulting in an excessive neutrophil migration to the pulmonary mucosa (16);
- a dysregulation of matrix metalloproteinase (MMP) activity (16,39,40) produced by leukocytes. In fact, increased expression of MMP has been found both in IBD and in chronic obstructive pulmonary disease (COPD) (39,41);
- the presence of *NOD2* gene polymorphisms in both CD and COPD (4,16,42), resulting in a reduced expression of α-definsins and in leaky intestinal and pulmonary mucosal barriers (16,39). This phenomenon might suggest a possible shared genetic susceptibility between pulmonary diseases and CD (16), hypothesis further supported by common gene loci *DENND1B*, *SMAD3*, *SLC22A4/5* (5q31/IBD5) found in both asthma and CD and by *ORMDL3* gene variants observed in both IBD and childhood-onset asthma (16,33,43).

Another evidence of lung-gut relationship consists in the increased risk of respiratory infectious complications in IBD patients due to both systemic inflammation and immunosuppressive therapy (10,44).

Additionally, it is interesting to note that it is not only possible for gastrointestinal inflammation to migrate to the lungs during IBD pathological activity, but also after its suppression: this theory is supported by the evidence of a connection between curative surgery in UC and the subsequent onset of bronchiectasis (registered in 50% of IBD-bronchiectasis patients). There are few explanations at the base of bronchiectasis and their post-colectomy diagnosis: it could be either possible that – given a common embryological origin – the former colic inflammation shifts to the lungs or that – given the suspension of immunomodulant therapy after surgery – latent lung immune reactions emerge in the post-operative period (45–47). Also, it has been reported that other patients had experienced relapses of respiratory symptomatology after surgical procedures (e.g. ileostomy, proctectomy, colectomy), supporting the inflammation shift theory (16,24,48).

So far, it has only been discussed the possible pathogenesis of pulmonary diseases as a direct consequence of IBD itself. The main non-infectious cause of pulmonary disease in IBD patients is not a EIM per se, but it is a lung injury induced by IBD medications (e.g. sulfasalazine, mesalamine, azathioprine, 6-mercaptopurine, methotrexate, anti-TNF monoclonal antibody) (16,24,44).

PULMONARY EIMs – CLINICAL FEATURES

Overview

In 90% of patients with IBD airways diseases occur from months to years after the gastroenterological diagnosis, meaning that there is almost 10% of IBD patients who present a respiratory tract involvement before IBD diagnosis (16,44,45). Also, it seems that airways EIMs are not related to IBD activity (16,47,48). Clinically significant respiratory diseases are less common than asymptomatic conditions, which can be recognized by alterations in functional tests and thoracic imaging (16,24).

Airways diseases

Airway inflammation is the most common respiratory EIM, involving 40-63% of all IBD patients with respiratory symptoms (16,45).

Large airways are more frequently damaged than small airways and are mainly found within UC female patients (34). Diseases of this region may be clinically significant, showing dyspnea, wheezing, productive cough, phlegm, stridor, hoarseness or chest pain (16,48). In most cases, large airways affections consist in bronchiectasis (2/3 of IBD patients with large airways involvement) (34), often diagnosed after a curative surgery (47). Asthma, despite being the main pulmonary comorbidity in both UC and CD, has no clear pathophysiological association with IBD: they could be either two manifestations of a common systemic inflammation or a risk factor one to another (16,49). Moreover, the coexistence of IBD and asthma increases the risk of death (16). COPD is another important respiratory EIM of IBD: in fact, in a review by Raftery et al. it is stated that both UC and CD are more frequent among COPD patients and, vice versa, that COPD occurs more frequently in IBD patients. This biunivocal relationship is probably due to smoke exposure, which is a common risk factor in both COPD and CD (50). Ultimately, it seems that CD increases the risk for patients of dying from COPD (51). Other large airways diseases may involve ENT-tract and trachea (e.g. glottic and subglottic oedema/stenosis, tracheitis) (16).

Small airways diseases associated with IBD manifest as bronchiolitis with poor clinical features. Usually, pulmonary function tests show abnormalities and typical radiological patterns (chest x-ray, high resolution CT scan) in earlier disease course, sometimes even before IBD onset (16,24,33).

Interstitial lung diseases

Interstitial lung diseases (ILDs) are uncommon EIMs of IBD (24), but can be diagnosed in patients with exertional dyspnea, dry or productive cough, fever and pleuritic chest pain (52). Usually, the development of ILDs is parallel to IBD and/or other EIMs activity (44,53) and occurs more frequently in UC female patients (34). The most diagnosed ILD is cryptogenic organizing pneumonia (50% of cases) (24), followed by: non-specific interstitial pneumonia, granulomatous interstitial diseases, pulmonary necrobiotic or granulomatous nodules, eosinophilic interstitial pneumonia (16). It is important to keep in mind that ILDs might be the expression of infections or drug-mediated lung injury (45,54).

Pulmonary embolism

IBD patients have a two-/three-fold risk of venous thromboembolism (VTE), hence, a higher risk of pulmonary embolism. IBD is a risk factor for two reasons: its potential to induce systemic inflammation and its treatment (e.g. corticosteroids, hospitalization, surgery) (16).

Vasculitis

Only few cases of granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and other forms of vasculitis have been reported in literature. In these case reports patients were predominantly female, and IBD diagnosis usually preceded vasculitis onset (16).

<u>Respiratory tract infections</u>

IBD inflammatory activity, immunosuppressive therapy, bowel surgery and malnutrition are critical risk factors for respiratory tract infections (16). There is a two-/three-fold higher risk of invasive pneumococcal disease (e.g. pneumonia, meningitidis) in patients with IBD starting years in advance compared to IBD diagnosis (55). Community-acquired pneumoniae caused by *Legionella pneumophila* are primarily encountered while in therapy with anti-TNF monoclonal antibodies (56). Other microorganisms have been isolated in immunosuppressed IBD patients affected by pneumonia: *Mycobacterium tuberculosis*, influenza virus, herpes simplex virus, measles virus and *Pneumocystis jirovecii* (16).

<u>Lung cancer</u>

There is a higher risk of lung cancer in CD patients, especially in female smokers, but no evidence of association with UC has been found (16,57,58). CD phenotype, severity of intestinal disease and immunomodulator use appear to correlate to an increased risk of lung cancer (59).

<u>Drug-mediated lung diseases</u>

Given an IBD patient with respiratory symptoms it is important to consider the possibility of a drugs-induced lung injury (being this the main noninfectious cause of lung disease in IBD) (24,44). In Table III it is shown a schematic comparison between medication-induced lung injuries and IBD-related lung disease, useful for running a correct differential diagnosis (24).

Each drug used in IBD patients presents affections of either small airways or lung interstitium as pulmonary adverse effects (16,24), but in case of medication-induced lung injuries lung parenchyma is more frequently involved compared to IBD-related lung disease. Symptoms frequently occurring in these conditions are dyspnea, non-productive cough, fever and hypoxemia (24).

Mesalazine and sulfasalazine are responsible for many sorts of acute lung injury, ranging from affections of small airways (e.g. bronchiolitis obliterans, hypereosinophilic obliterative bronchiolitis, lymphocytic alveolitis) to interstitial lung diseases (e.g. eosinophilic pneumonia, organizing pneumonia) (16,24). Symptoms usually begin from five days to many years after drugs administration (60).

Azathioprine and 6-mercaptopurine are responsible for mainly interstitial pneumonitis and organizing pneumonia (16,24). Symptoms usually begin from one month to two years after drugs administration (61).

Methotrexate is responsible for pulmonary fibrosis or hypersensitivity pneumonitis (16). Symptoms often begin several months after drugs administration (62).

Anti-TNF monoclonal antibodies are responsible for infections, exacerbations of underlying lung disease and various other interstitial lung diseases. Symptoms tend to begin within the first doses of medication (63).

Features	Medication-Induced Lung Injury	IBD-Related Lung Disease
Triggers	New medication in recent weeks-months	Active IBD or no triggers
Symptoms	Dyspnea, fever, cough, chest pain	Dyspnea, fever, cough, chest pain
Involved areas	Parenchyma > airways	Airways > parenchyma
Management	Hold medication, consider steroids	Steroids (inhaled vs systemic)
Prognosis	Risk for permanent lung damage (azathioprine, 6-mercaptopurine, methotrexate > mesalamine, sulfasalazine, TNF antagonists)	Chronic pulmonary dysfunction common, significant chronic symptoms are uncommon

IBD= inflammatory bowel disease; TNF = tumor necrosis factor.

Table III – Features of Medication-Induced Lung Injury vs. IBD-Related Lung Disease (24). Note that exceptions to this scheme are possible in clinical practice.

PULMONARY EIMs – DIAGNOSIS

Diagnosis of pulmonary EIMs requires:

- pulmonary function tests (PFTs), which are frequently altered in both symptomatic and subclinical pulmonary conditions (16). The most common finding is the reduction of diffusing capacity for carbon monoxide (DLCO) (64), whose relation to IBD activity has been reported in some studies (16). Also, IBD patients with active disease often present significantly reduced forced expiratory volume in one second (FEV1), indicating pulmonary obstruction, and maximal expiratory flow at 25%, 50% and 75% (MEF 75-25), indicating peripheral airway obstruction (65). Other PTFs abnormalities can be found in IBD patients (even if asymptomatic): high values of RV, TLC and RV/TLC ratio (especially when intestinal inflammation is more active), positive bronchoprovocation challenge with methacholine and increased exhaled nitric oxide (NO) measurement, suggesting small airways inflammation (16);
- chest x-ray, which is not much informative in large airways disease, but can suggest the presence of small airways involvement (e.g. with air trapping, ground-glass opacities) or interstitial involvement (e.g. with focal/diffuse peripheral opacities and air bronchograms) (16);
- high resolution CT (HRCT), which better characterize the involvement of large airways (showing thickening of tracheobronchial wall, bronchiectasis, sputum plugs, tree-in-bud pattern, ...), small airways (defining bronchiolar wall thickening, mucoid plugs, centrolobular ground-glass nodules, tree-in-bud pattern, mosaic pattern, ...), lung interstitium (displaying variously distributed consolidations, ground-glass

opacities and nodules) (16). HRCT is the most reliable imaging technique to detect alterations in IBD patients with subclinical pulmonary inflammation, whose main findings are: peribronchial thickness, air trapping, fibrosis, emphysema, bronchiectasis, alveolitis (16,66,67).

- bronchoscopy with bronchoalveolar lavage or lung biopsy (16), which can be useful in order to get a definitive diagnosis. Macroscopically, mucosal airways and intestinal inflammatory lesions appear alike (46).

In their review (24), Massart and Hunt suggested a diagnostic workup to apply to those IBD patients presenting with respiratory symptoms and abnormal chest imaging. The first step consists in ruling out ongoing bacterial, viral and fungal infections (depending on patients' clinical presentation, severity of immunosuppression) or pulmonary embolism (mainly in patients experiencing dyspnea and chest pain). Next, it is important to assess medications used throughout the entire IBD course (because of the frequent delay between administration and symptoms onset). Once medication etiologies are excluded (e.g. no regression of symptoms after drug suspension), it is possible to consider the pulmonary process as a consequence of the underlying inflammatory bowel disease. At this point, high resolution CT and bronchoscopy or video-assisted thoracoscopic surgery for biopsy are strongly recommended for a definitive diagnosis.

Finally, Cavalli et al. (16) propose regular PFT screening in IBD patients in order to early detect respiratory inflammation, which is often subclinical. However, available literature shows no clear benefit regarding PTFs screening in IBD patients (10).

PULMONARY EIMs – TREATMENT

As already discussed, pulmonary EIMs may occur concomitantly to IBD activity (and possibly respond to its immunosuppressive treatment) or may be independent from them (7). Usually, asymptomatic patients do not need specific treatment for lung manifestations. In the other hand, symptomatic patients often require specific treatments (i.e. drugs for IBD are not enough alone). While the first choice of treatment are steroids (inhaled or systemic), intravenous therapy is required for life-threatening critical manifestations, such as subglottic stenosis (68–70).

A severe complication of untreated airway inflammation is tracheal stenosis, which can be either treated with steroids or with an invasive approach (when refractory to medicaments); invasive therapies include interventional rigid bronchoscopy (e.g. dilatation, stent placement, laser beam) and surgery (71,72).

Airway diseases (asthma, COPD, bronchiolitis) are treated with inhaled/systemic steroids and bronchodilators, but they can also benefit from immunomodulating therapy (e.g. anti-TNF monoclonal antibodies) (46).

Other pulmonary EIMs of IBD can be treated with specific drugs or procedures: for example, pulmonary embolism requires anticoagulant therapy, while respiratory infections could be treated with antibiotics and prevented with vaccination (e.g. pneumococcal vaccination, given the higher risk of invasive pneumococcal infections in IBD patients) (16).

Finally, in medicament-related pulmonary manifestations it is fundamental to withdraw the drug inducing lung injury. Also, in case of severe pulmonary involvement, it is possible to associate steroids to the therapy (16).

RATIONALE OF THE STUDY

Regardless of their predominant intestinal involvement, IBD should be considered as a systemic disease. Given the wide range of organs potentially affected by IBD inflammation and the increasing number of IBD diagnosis worldwide, it is desirable to better understand EIMs' prevalence and clinical features. Studying IBD from this perspective might help physicians to raise awareness of the actual epidemiology of less common, maybe still subclinical, extraintestinal affections in IBD patients. Among these, respiratory affections seem to be one of the most underdiagnosed EIMs, likely due to their heterogeneous presentation, including their onset (i.e. preceding or succeeding IBD diagnosis), the region of the respiratory system involved (i.e. upper airways, trachea, bronchi, lung parenchyma), their pathophysiological pattern (i.e. inflammatory activity-related it-self or drug-related mechanisms) and their clinical manifestation (i.e. subclinical, mildly or highly symptomatic).

Based on these considerations, this study aims to reinforce the existing literature about epidemiological, clinical, radiological and functional tests features of respiratory EIMs of IBD.

STUDY DESIGN AND METHODS

TARGET POPULATION AND DATA COLLECTION

This study is an observational prospective study, which means that patients would be recruited in the present and then followed during time, in order to spotlight potential clinical associations. IBD patients attending regular follow-up visits at the Gastroenterology IBD department of the University Hospital of Padua between January 2024 and April 2025 were consecutively and prospectively enrolled. IBD patients have been recruited by handing out or mailing a questionnaire corresponding to the Italian translation of the first five questions of the Pulmonary ATS-DLD-78-A (American Thoracic Society Division of Lung Disease) standardized questionnaire on respiratory symptoms (cough, phlegm, wheezing and breathlessness). Each question included a total of twenty-eight sub-questions: some of them allowed a ‘yes’ or ‘no’ answer, some others needed a brief alphanumeric answer.

Once a patient handed in or sent back his answers, lung medicine specialists reviewed the questionnaire in its entirety and gave one point to each ‘yes’ answer, obtaining a final score ranging from one to twenty-two points. Afterwards, it has been set a cut-off score (3 out of twenty-two points) since many IBD patients may present with some respiratory symptoms of little clinical significance. Therefore, questionnaires were considered ‘positive’ for respiratory symptoms if three or more sub-questions were answered ‘yes’, negative in case of fewer ‘yes’ answers.

Patients who did not have a confirmed diagnosis of IBD, or who did not fully answer all the questions, or who were not willing to participate in the study were excluded.

Figures 2 and 3 show questions one to five of the Pulmonary ATS-DLD-78-A questionnaire and Figures 4, 5 and 6 show their translation to Italian (used for our survey).

After this first phase of recruitment, patients with 'positive' questionnaire and confirmed IBD diagnosis have been interviewed by respiratory clinicians in order to better assess their respiratory medical history and clinical examination. Note that in some cases practitioners could only visit patients by telemedicine, which resulted in just an anamnestic evaluation, collecting data such as age, sex, smoking history, exposition to pneumo-toxic agents, familiarity for lung disease, vaccinations, comorbidities, respiratory symptoms (cough, sputum, dyspnea, wheezing and their exacerbations) and IBD history and IBD treatment (both medical and surgical). Also, laboratory exams, such as blood count, autoimmunity tests, immunoglobulin E blood title and fecal calprotectin have been collected, when available. At the end of each interview, lung medicine specialists evaluated patients' clinics and prescribed respiratory function tests and chest x-ray, if not yet performed. In a few cases, when both respiratory function tests and chest x-ray could not give clear information about pathological findings, patients underwent second line diagnostic exams, such as high-resolution CT scan.

Finally, for study purposes, it has been decided to sort the population with positive questionnaires into two groups, based on total scores from ATS-DLD-78-A questionnaire: a 'poorly symptomatic patients' group (formed by people who total up three to six points) and a 'very symptomatic patients' group (formed by people who total up seven or more points).

Participant ID (affix ID label here)	**LIFE** Acrostic: ☐☐☐☐☐ Interviewer: ☐☐☐☐☐ Visit Code: ☐☐☐ Date of Visit: ☐☐ month ☐☐ day ☐☐☐☐ year

Pulmonary ATS-DLD-78-A Form (Baseline)

"We would like to ask you some questions that pertain mainly to your chest. Please answer yes or no if possible. (*Interviewer Note: If the participant is in doubt about whether his/her answer is 'Yes' or 'No', record 'No'.*")

Question 1 – Cough		
A. Do you usually have a cough? *{count a cough with first smoke or on first going out-of doors. Exclude clearing of throat}*	☐ Yes	☐ No (Skip to C)
B. Do you usually cough as much as 4 to 6 times a day, 4 or more days of the week?	☐ Yes	☐ No
C. Do you usually cough at all on getting up, or first thing in the morning?	☐ Yes	☐ No
D. Do you usually cough at all during the rest of the day or at night?	☐ Yes	☐ No
If 'Yes' to any of the above (A, B, C, or D), answer the following. If 'No' to ALL, skip to Question 2.		
E. Do you usually cough like this on most days for 5 consecutive months or more during the year?	☐ Yes	☐ No
F. For how many years have you had this cough?	Number of Years ☐☐	
Question 2 – Phlegm		
A. Do you usually bring up phlegm from your chest? *{Count phlegm with the first smoke or on first going out-of-doors. Exclude phlegm from the nose. Count swallowed phlegm.}*	☐ Yes	☐ No (Skip to C)
B. Do you usually bring up phlegm like as much as twice a day, 4 or more days of the week?	☐ Yes	☐ No
C. Do you usually bring up phlegm at all on getting up, or first thing in the morning?	☐ Yes	☐ No
D. Do you usually bring up phlegm at all during the rest of the day or at night?	☐ Yes	☐ No
If 'Yes' to any of the above (A, B, C, or D), answer the following. If 'No' to ALL, skip to Question 3.		
E. Do you usually bring up phlegm like this on most days for 3 consecutive months or more during the year?	☐ Yes	☐ No
F. For how many years have you had trouble with phlegm?	Number of Years ☐☐	

Figure 2 – Questions 1-2 from ATS-DLD-78-A questionnaire.

Participant ID (affix ID label here)	***LIFE***	Acrostic ☐☐☐☐☐ Visit Code ☐☐☐

Question 3 – Cough		
A. Have you had episodes of (increased*) cough and phlegm lasting for 3 weeks or more each year? *{*for individuals who usually have cough and/or phlegm}*	☐ Yes	☐ No (Skip to Q4)
B. For how long have you had at least 1 such episode per year?	Number of Years ☐☐	
Question 4 – Wheezing		
A. Does your chest ever sound wheezy or whistling:		
1) When you have a cold?	☐ Yes	☐ No
2) Occasionally apart from colds?	☐ Yes	☐ No
3) Most days or nights?	☐ Yes	☐ No
If 'Yes' to any of the above (1, 2, or 3), answer the following. If 'No' to ALL, skip to Question 5.		
B. For how many years has this been present?	Number of Years ☐☐	
C. Have you ever has an ATTACK of wheezing that has made you feel short of breath?	☐ Yes	☐ No (Skip to Q5)
D. How old were you when you had your first such attack?	Age in Years ☐☐	
E. Have you had 2 or more such episodes?	☐ Yes	☐ No
F. Have you ever required medicine or treatment for the(se) attack(s)?	☐ Yes	☐ No
Question 5 – Breathlessness		
A. If disabled from walking by an condition other than heart or lung disease, please describe and proceed to Q6. ***Nature of condition(s):***		
B. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?	☐ Yes	☐ No (Skip to Q6)
C. Do you have to walk slower than people of your age on level because of breathlessness?	☐ Yes	☐ No
D. Do you ever have to stop for breath when walking at your own pace on the level?	☐ Yes	☐ No
E. Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on the level?	☐ Yes	☐ No
F. Are you too breathless to leave the house or breathless on dressing or undressing?	☐ Yes	☐ No

Figure 3 – Questions 3-5 from ATS-DLD-78-A questionnaire.

NOME:

COGNOME:

DATA DI NASCITA:

TELEFONO:

PATOLOGIA INTESTINALE DIAGNOSTICATA:
- Morbo di Crohn
- Colite Ulcerosa
- Nessuna delle precedenti

Questionario sui sintomi respiratori (ATS-DLD-78-A)

Vorremmo porle alcune domande che riguardano principalmente i suoi sintomi respiratori. La preghiamo di rispondere **SI** o **NO** (se è in dubbio tra "SI" e "NO", segni "NO").

Domanda 1 – Tosse

A. Di solito ha la tosse? (Escluso lo schiarimento della gola): SI NO

*Se la risposta è **NO**, passi a C.*

B. Di solito tossisce da 4 a 6 volte al giorno, per 4 o più giorni alla settimana? SI NO

C. Di solito tossisce appena si alza o come prima cosa al mattino? SI NO

D. Di solito tossisce durante il resto della giornata o di notte? SI NO

*Se ha risposto **SI** a una delle domande precedenti (A, B, C o D), risponda a quanto segue. Se ha risposto **NO** a tutte, passi alla "Domanda 2 – Catarro".*

E. Ha la tosse nella maggior parte dei giorni per almeno 5 mesi consecutivi all'anno? SI NO

F. Da quanti anni ha questa tosse? Numero di anni

Domanda 2 – Catarro

A. Di solito espettora? (anche dopo aver fumato o se esce all'aperto; non consideri il catarro dal naso; consideri il catarro inghiottito) SI NO

*Se la risposta è **NO**, passi a C.*

B. Di solito espettora almeno due volte al giorno, 4 o più giorni alla settimana? SI NO

Figure 4 – Questionnaire administered for this study (page 1 of 3).

C. C. Di solito il catarro viene fuori appena si alza o come prima cosa al mattino? ◯ SI ◯ NO

D. D. Di solito il catarro si presenta durante il resto della giornata o di notte? ◯ SI ◯ NO

*Se ha risposto **SI** a una delle domande precedenti (A, B, C o D), risponda a quanto segue. Se ha risposto **NO** a <u>tutte</u>, passi alla "Domanda 3 – Tosse".*

E. Ha il catarro nella maggior parte dei giorni per almeno 3 mesi consecutivi all'anno? ◯ SI ◯ NO

F. Da quanti anni ha problemi di catarro? Numero di anni ☐

Domanda 3 – Tosse

A. Ha avuto episodi di aumento della tosse e del catarro che durano per 3 o più settimane all'anno? (Per gli individui che hanno abitualmente tosse e/o catarro) ◯ SI ◯ NO

*Se la risposta è **NO**, passi alla "Domanda 4 – Respiro sibilante".*

B. Per quanto tempo ha avuto almeno 1 episodio di questo tipo all'anno? Numero di anni ☐

Domanda 4 – Respiro sibilante

A. Ha mai un respiro affannoso o sibilante:

I) Quando è raffreddato? ◯ SI ◯ NO

II) Occasionalmente, a parte il raffreddore? ◯ SI ◯ NO

III) La maggior parte dei giorni o delle notti? ◯ SI ◯ NO

*Se ha risposto **SI** a una delle domande precedenti (I, II o III), risponda a quanto segue. Se ha risposto **NO** a <u>tutte</u> le precedenti (I, II, III), passi alla "Domanda 5 – Mancanza di respiro".*

B. Da quanti anni è presente questa situazione (respiro sibilante)? Numero di anni ☐

C. Ha mai avuto un attacco di respiro sibilante che le ha fatto mancare il respiro? ◯ SI ◯ NO

*Se la risposta è **NO** passare alla "Domanda 5 – Mancanza di respiro".*

D. Quanti anni aveva quando ha avuto il primo attacco di questo tipo? Età in anni ☐

E. Ha avuto 2 o più episodi di questo tipo? ◯ SI ◯ NO

F. Ha mai avuto bisogno di medicine o di trattamenti per gli attacchi? ◯ SI ◯ NO

Figure 5 – Questionnaire administered for this study (page 2 of 3).

Domanda 5 - Mancanza di respiro

A. Se non può camminare per una condizione diversa da una malattia cardiaca o polmonare, scriva qui di seguito la patologia/il motivo ______ e non risponda alle domande successive.

B. Ha problemi di mancanza di fiato quando cammina di fretta in piano o in leggera salita?
○ SI ○ NO

C. Deve camminare più lentamente dei coetanei in piano a causa della mancanza di fiato?
○ SI ○ NO

D. Deve mai fermarsi per respirare quando cammina al suo ritmo in piano? ○ SI ○ NO

E. Le capita mai di doversi fermare per respirare dopo aver camminato per circa 100 metri (o dopo qualche minuto)? ○ SI ○ NO

F. Le manca il fiato per uscire di casa o le manca il fiato nel vestirsi o nello svestirsi? ○ SI ○ NO

Figure 6 – Questionnaire administered for this study (page 3 of 3).

<u>DATA ANALYSIS</u>

Anamnestic and clinical features, radiological exams and functional tests performed by patients were first evaluated by lung medicine clinicians and then collected in a database. Categorical variables are described as absolute numbers (n) and relative values (%), while continuous variables are described by median and minimum-maximum values. Data analysis was made by the application of Chi square test or Fisher’s exact test (for categorical variables) and Mann-Witney U test (for continuous variables), supported by GraphPad Prism version 10.4.1 for Windows (GraphPad Software, Boston, Massachusetts USA, www.graphpad.com).

P-values <0.05 were considered statistically significant.

RESULTS

ENTIRE STUDY POPULATION

Two hundred and fifty-three IBD patients have been contacted by telephone and email or in person (when they came to their scheduled follow-up at the Gastroenterology department). While ten people did not agree to be included in the project, two hundred and forty-three people showed interest in the study and collected the above-mentioned questionnaire, which was answered by one hundred and seventy-eight IBD patients (while sixty-five patients did not hand in or send back by email their filled in copy of the questionnaire). Seventeen people were further excluded from the study population because they did not present a confirmed IBD diagnosis. Of the resulting group of one hundred and sixty-one IBD patients, ninety-seven were included in the study population as 'negative patients' (scoring <3 points in the questionnaire, as previously described), fifty-five were included in the study population as 'positive patients' (scoring ≥3 points in the questionnaire) and nine were excluded from the study population because of either a respiratory symptomatology related to a non-airways disease – e.g. anemia and gastroesophageal reflux disease – (three people) or a subsequent voluntary withdraw from the study (six people). In Figure 7 a schematic yet complete version of the study population recruitment process is displayed.

In Table IV there is a focus on demographic data of the IBD patients included in this study (n = 152). In particular, male gender was the most represented in each group of people (52% of the entire population, 52% of the negative population and 53% of the positive population) (p value = 0.89) and the median age was 50 years old (range 19-83) for the entire population, 51 years old (range 19-83) for the negative population and 46 years old (range 19-78) for the positive population (p value = 0.038).

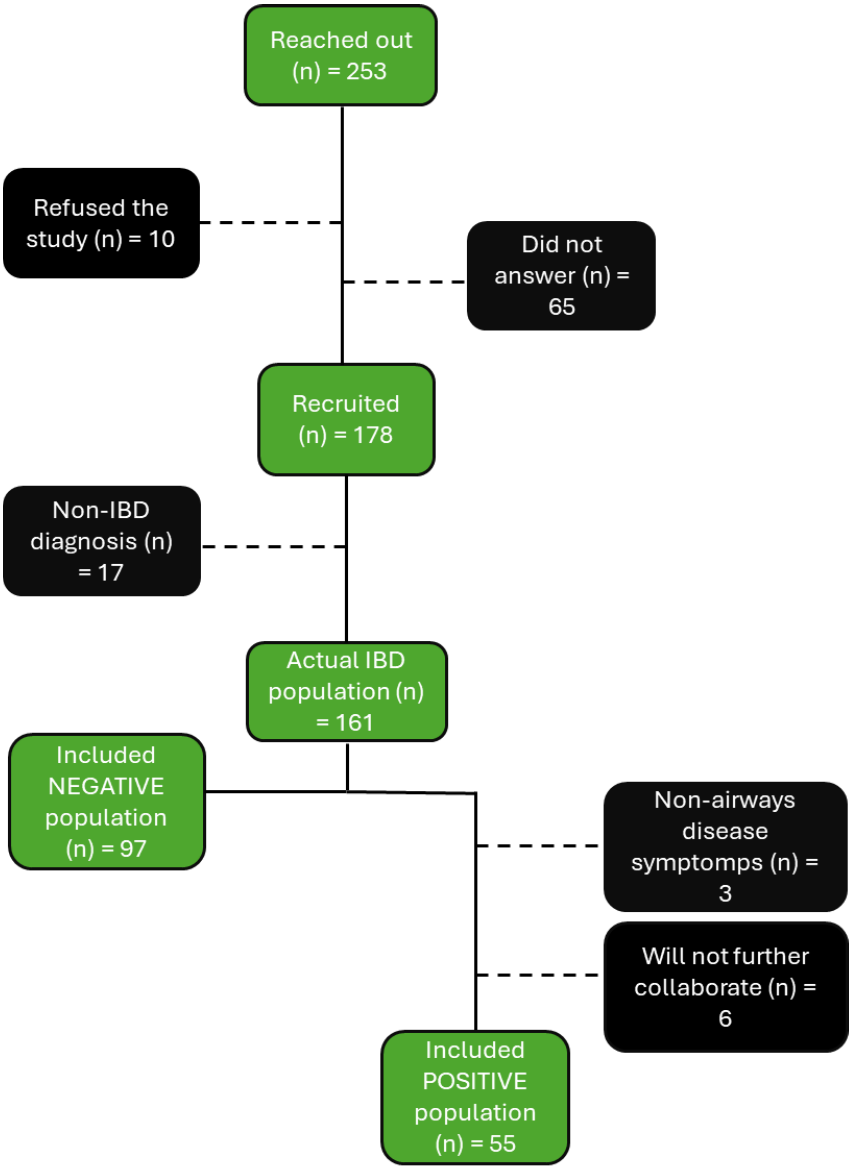

Figure 7 – The recruitment process.

	Entire Population (n = 152)	Negative (n = 97)	Positive (n = 55)	p value
Male – n (%)	79 (52)	50 (52)	29 (53)	0.89
Age – years	50 (19 - 83)	51 (19-83)	46 (19-78)	**0.038**

Table IV – Demographic data of the entire population and of negative (score <3) and positive (score ≥3) patients. Values for 'Male' variable are expressed as numbers and percentages, values for 'Age' variable are expressed as median and ranges as appropriate. Chi square test (for categorical variables) and Mann-Whitney U test (for continuous variables) were used to compare demographic data and baseline clinical characteristics between the negative and positive groups.

POPULATION TESTED POSITIVE FOR THE QUESTIONNAIRE

Patients with positive questionnaires (3 points or more at questionnaire) have been subsequently sorted in two groups: 30 (55%) poorly symptomatic group scoring 3-6 points in the questionnaire and 25 (45%) very symptomatic group scoring 7-22 points in the questionnaire (Table V).

Group	Score	n (%)
Poorly symptomatic	3-6	30 (55)
Very symptomatic	7-10	10 (18)
	11-14	10 (18)
	15-18	5 (9)
	19-22	0 (0)

Table V – Patients grouped by score of the questionnaire administered to the study population. The numerosity of both groups is expressed as numbers and percentages.

Demographic data of the entire positive population, then categorized in poorly and very symptomatic groups were presented in Table VI.

Male patients were present in 53% of the entire positive population, with equal distribution among the poorly symptomatic and very symptomatic groups (53% vs. 52%; p value = 0.92).

The median age of the entire population was 46 years old (range 19-78), also equally represented between the two groups [47 (19-78) and 46 years old (20-75), p value = 0.94].

Focusing on smoking habits among positive patients, it resulted that 16 people from the entire population (29%) were current smokers, 16 (29%) former smokers and 23 (42%) nonsmokers; from group 1 there were 7 (23%) current smokers, 9 (30%) former smokers and 14 (47%) nonsmokers; from group 2 there were 9 (36%) current smokers, 7 (28%) former smokers and 9 (36%) nonsmokers (p value = 0.57).

20 people from the entire population (37%) had a positive history of occupational exposure, with an equal distribution among both groups (37% of the whole group 1 and 38% of the whole group 2) (p value > 0.99). People claimed to be exposed to a wide range of potentially toxic inhalants: passive smoke, asbestos, industrial pollution, plaster dust, sheet metal, paints, solvents, ammonia, lacquer, glues, rubbers, immunomodulant drugs, therapeutic gases and molds.

Most positive people denied a history of allergy to both inhalants and non-inhalants (29 out of 55 people, 53% of the total), of which 18 were from poorly symptomatic (60%) and 11 from very symptomatic group (36%) (p value = 0.24). The remaining 26 people confirmed to be allergic to at least one inhalant, food or drug, with the following distribution: 9 were allergic only to inhalants (16%), 7 were allergic only to non-inhalants molecules found in food or drugs (13%) [with a statistically significantly higher proportion in very symptomatic compared to poorly symptomatic group (28% vs. 0%, p value = 0.0024)] and 10 (18%) of the entire positive population were allergic to both inhalants and non-inhalants.

42% of total positive patients had familiarity for lung disease, with a higher frequency in very symptomatic compared to poorly symptomatic groups: 14 (61%) vs. 8 (27%) (p value = 0.012). The majority of patients referred familiar history for asthma (mentioned in 9 interviews), lung cancer (mentioned in 9 interviews) or chronic obstructive pulmonary disease (mentioned in 4 interviews).

Comorbidities were highly prevalent in both groups but equally distributed [22 (73%) and 17 (68%), p value = 0.66], reaching a total of 39 people (71%) in the entire positive population. Comorbidities were extremely heterogeneous (arterial hypertension, chronic rhinitis, gastroesophageal reflux disease, dyslipidemia, etc.).

15 (27%) patients from the entire population presented an already diagnosis chronic lung disease at the moment of our screening (asthma in 14 cases, parenchymal nodule in 1 case), with such distribution: 5 people from poorly symptomatic (17%) and 10 people from very symptomatic (40%) (p value = 0.071). This variable did not consider respiratory infections, which have been studied separately.

Of positive IBD patients, 44% suffered from Crohn's disease (CD) (14 from poorly symptomatic and 10 from very symptomatic) and 56% suffered from ulcerative colitis (UC) (31 people in total, 16 from poorly symptomatic and 15 from very symptomatic) (p value = 0.62).

Extraintestinal manifestations of IBD (EIMs) have been identified in 13 people (24%), 8 from poorly symptomatic (27%), 5 from very symptomatic (21%) (p value = 0.75). Some patients suffering from EIMs reported diseases such as primary sclerosing cholangitis, arthritis (for example, seronegative spondylarthritis), erythema nodosum and other cutaneous lesions.

Focusing on medical treatment, Mesalamine (5-ASA) and its derivatives (such as Sulfasalazine) have been administered to

43 people in total (78%), 26 from poorly symptomatic (87%) and 17 from poorly symptomatic (68%) (p value = 0.11). Systemic steroids have been administered to 31 people in total (56%), 15 from poorly symptomatic (50%) and 16 from very symptomatic (64%) (p value = 0.30). Monoclonal antibodies (MAb) have been administered to 39 people in total (71%), 19 from poorly symptomatic (63%) and 20 from very symptomatic (80%) (p value = 0.18).

	Entire positive population (n = 55)	**Poorly symptomatic (n = 30)**	**Very symptomatic (n = 25)**	**p value**
Male – n (%)	29 (53)	16 (53)	13 (52)	0.92
Age – years	46 (19-78)	47 (19-78)	46 (20-75)	0.94
Smoking history				
• **Current – n (%)**	16 (29)	7 (23)	9 (36)	0.57
• **Former – n (%)**	16 (29)	9 (30)	7 (28)	
• **Nonsmokers – n (%)**	23 (42)	14 (47)	9 (36)	
Occupational exposure – n (%)	20 (37)	11 (37)	9 (38)	>0.99
Allergies – n (%)				
• **Inhalant only – n (%)**	9 (16)	7 (23)	2 (8.0)	0.16
• **Non-inhalant only – n (%)**	7 (13)	0 (0.0)	7 (28)	**0.0024**
• **Both – n (%)**	10 (18)	5 (17)	5 (20)	>0.99
• **None – n (%)**	29 (53)	18 (60)	11 (44)	0.24
Familiarity - n (%)	22 (42)	8 (27)	14 (61)	**0.012**

Comorbidities - n (%)	39 (71)	22 (73)	17 (68)	0.66
Previous diagnosis of lung disease – n (%)	15 (27)	5 (17)	10 (40)	0.071
Crohn's disease – n (%)	24 (44)	14 (47)	10 (40)	0.62
Ulcerative colitis – n (%)	31 (56)	16 (53)	15 (60)	
Extraintestinal manifestations – n (%)	13 (24)	8 (27)	5 (21)	0.75
Treatment				
• **Steroids – n (%)**	31 (56)	15 (50)	16 (64)	0.30
• **5-ASA – n (%)**	43 (78)	26 (87)	17 (68)	0.11
• **MAb – n (%)**	39 (71)	19 (63)	20 (80)	0.18

Table VI – Demographic features and clinical history of the entire positive population (≥3 points), the poorly symptomatic group (3-6 points) and the very symptomatic group (>6 points). Values for categorical variables are expressed as numbers and percentages, values for continuous variables are expressed as median and ranges as appropriate. Chi square test (for categorical variables), Fisher's exact test (for categorical variables, if n <5) and Mann-Whitney U test (for continuous variables) were used to compare demographic data and baseline clinical characteristics between the poorly symptomatic group and the very symptomatic group.
5-ASA: Mesalamine (and derivatives), MAb: monoclonal antibodies.

Laboratory exams have been considered, too: blood count, autoimmunity tests, immunoglobulin E blood title and fecal calprotectin. Of these, only the leukocyte formula has been analyzed, as shown in Table VII: 17 data were collected from poorly symptomatic and 20 from very symptomatic, for a total of 37 data representing the entire population. The following analyses were made with the most recently available blood counts.

Neutrophils' median value was 3.80 cells*10^9/L (1.6-16.03) for the entire population, varying from 3.58 cells*10^9/L (2.13-6.99) for poorly symptomatic to 4.21 cells*10^9/L (1.60-16.03) for very symptomatic (p value = 0.30).

Lymphocytes' median value was 2.40 cells*10^9/L (0.81-4.25) for the entire population, varying from 1.16 cells*10^9/L (0.81-3.79) for poorly symptomatic to 2.40 cells*10^9/L (1.68-4.25) for very symptomatic (p value = 0.24).

Eosinophils' median value was 0.16 cells*10^9/L (0.00-1.92) for the entire population, varying from 0.17 cells*10^9/L (0.01-1.96) for poorly symptomatic to 0.16 cells*10^9/L (0.00-1.96) for very symptomatic (p value = 0.77).

Monocytes' median value was 0.61 cells*10^9/L (0.21-1.45) for the entire population, varying from 0.58 cells*10^9/L (0.26-0.88) for poorly symptomatic to 0.61 cells*10^9/L (0.21-1.45) for very symptomatic (p value = 0.66).

	Entire positive population (n = 37)	**Poorly symptomatic (n = 17)**	**Very symptomatic (n = 20)**	**p value**
Neutrophils - n cell*10^9/L	3.80 (1.6-16.03)	3.58 (2.13-6.99)	4.21 (1.60-16.03)	0.30
Eosinophils - n cell*10^9/L	0.16 (0.00-1.92)	0.17 (0.01-0.530)	0.16 (0.00-1.96)	0.77

Lymphocytes - n cell*10^9/L	2.40 (0.81-4.25)	2.16 (0.81-3.79)	2.40 (1.68-4.25)	0.24
Monocytes - n cell*10^9/L	0.61 (0.21-1.45)	0.58 (0.26-0.88)	0.61 (0.21-1.45)	0.66

Table VII – Leukocyte formula of the entire positive population (≥3 points), the poorly symptomatic group (3-6 points) and the very symptomatic group (>6 points). The considered variables are all continuous variables, hence expressed as median and ranges as appropriate. Mann-Whitney U test was used to compare leukocytes formula between the poorly symptomatic group and the very symptomatic group.

The clinical presentation of IBD patients tested positive for the ATS-DLD-78-A questionnaire has been evaluated as well (Table VIII). The answers of 54 patients (30 from group 1, 24 from group 2) have been considered for the following analyses.

33 people from the entire positive population (61%) reported cough as one of their current symptoms, with a higher prevalence (even not statistically significant) among very symptomatic compared to poorly symptomatic group (75 vs. 50%, p value = 0.061).

32 (59%) people from the entire positive population reported sputum as one of their current symptoms: 17 of them were from group 1 (57%), 15 from group 2 (63%) (p value = 0.66).

26 (48%) people from the entire positive population reported dyspnea as one of their current symptoms, with a higher prevalence among very symptomatic compared to poorly symptomatic group (63% vs. 37%, p value = 0.05).

19 people from the entire positive population (35%) reported wheezing as one of their current symptoms: 15 of them were from group 1 (50%), 18 from group 2 (75%) (p value = 0.75).

	Entire positive population (n = 54)	**Poorly symptomatic (n = 30)**	**Very symptomatic (n = 24)**	**p value**
Cough – n (%)	33 (61)	15 (50)	18 (75)	0.061
Sputum – n (%)	32 (59)	17 (57)	15 (63)	0.66
Wheezing – n (%)	19 (35)	10 (33)	9 (38)	0.75
Dyspnea – n (%)	26 (48)	11 (37)	15 (63)	0.05

Table VIII – Main respiratory symptoms of the entire positive population (≥3 points), the poorly symptomatic group (3-6 points) and the very symptomatic group (>6 points). The considered variables are all categorical variables, hence expressed as numbers and percentages. Chi square test was used to compare the numbers of symptoms reported by the poorly symptomatic group and the very symptomatic group.

Moreover, positive patients have been asked whether they had a positive history of recurrent airways infections or one episode of clinically significant airways infection (or rather, infections that implied the admission to the hospital or the persistence/exacerbation of respiratory symptoms in the aftermath), as shown in Table IX. A total of 52 IBD patients were asked about this topic: 28 from poorly symptomatic, 24 from very symptomatic. Note that not all of these 52 patients could clearly state if their reported infectious episodes involved exclusively the lower respiratory system (trachea, bronchi, lungs).

Most patients claimed a negative history of infective respiratory disease (40 out of 52 people, corresponding to 77% of the whole): 23 people from poorly symptomatic, 17 people from very symptomatic. Recurrent infections were reported by 2 people from poorly symptomatic (7.1%) and 5 people from very symptomatic (21%), for a total of 7 people (13%) referring to those events. One severe infectious episode was reported by 3 people from poorly symptomatic (11%) and 2 people from very symptomatic (8.3%), for a total of 5 people (9.6%) referring to that event. There was no statistically significant difference between the two groups (p value = 0.39).

	Entire positive population (n = 52)	**Poorly symptomatic (n = 28)**	**Very symptomatic (n = 24)**	**p value**
Airways infections history				
• **Negative history – n (%)**	40 (77)	23 (82)	17 (71)	0.39
• **Recurrent infections – n (%)**	7 (13)	2 (7.1)	5 (21)	
• **Severe infectious episode – n (%)**	5 (9.6)	3 (11)	2 (8.3)	

Table IX – Airways infections history of the entire positive population (≥3 points), the poorly symptomatic group (3-6

points) and the very symptomatic group (>6 points). The considered variables are all categorical variables, hence expressed as numbers and percentages. Chi square test and Fisher's exact test (if n <5) were used to compare variables between the poorly symptomatic group and the very symptomatic group.

During the period of observation, a group of positive IBD patients underwent radiological exams.

34 people (16 from poorly symptomatic, 18 from very symptomatic) performed a chest x-ray (Table X), that was positive for radiological abnormalities in the 35% of cases (12 of 34 people from the entire population). The difference in radiographical positivity among the two groups (7 people from poorly symptomatic, 5 people from very symptomatic) was not considered statistically significant (p value = 0.49).

Also, a total of 11 people (4 from poorly symptomatic, 7 from very symptomatic underwent a high-resolution CT scan, which showed radiological abnormalities in 10 cases (i.e. 4 findings from poorly symptomatic, 6 from very symptomatic).

Considering the total number of radiological exams (either x-rays or high-resolution CT scans), we found eight cases of bronchiectasis, three cases of parenchymal thickening, two cases of bronchial walls inflammation, two cases of emphysema, one case of organizing pneumonia, one case of pleural thickening, one case of interstitial thickening and one case of lymphadenopathy.

Figures 8-9 show some of the most resounding findings at high resolution CT-scan.

	Entire positive population (n = 34)	Poorly symptomatic (n = 16)	Very symptomatic (n = 18)	p value
X-ray – n (%)	12 (35)	7 (44)	5 (28)	0.49

Table X – X-ray alterations of the entire positive population (≥3 points), the poorly symptomatic group (3-6 points) and the very symptomatic group (>6 points). The categorical variable considered here is expressed as numbers and percentages. Chi square test and Fisher's exact test (if n <5) were used to compare variables between the poorly symptomatic group and the very symptomatic group.

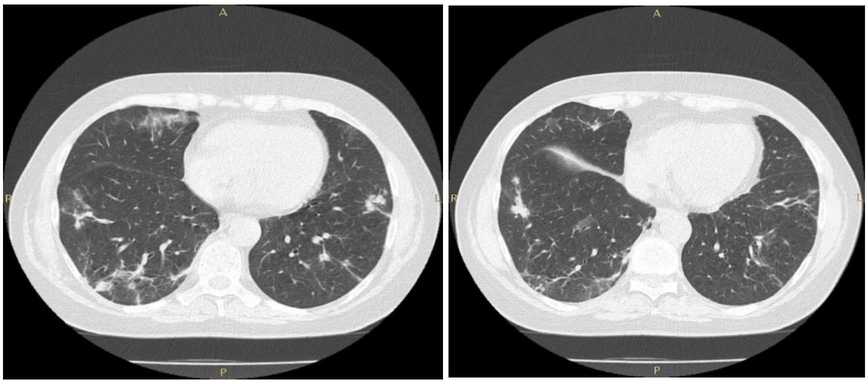

Figure 8 – Axial high-resolution CT scan images of a 60 years old female Crohn's disease patient included in the very symptomatic group. She referred chronic cough and sputum, but had no previous lung disease diagnosis.

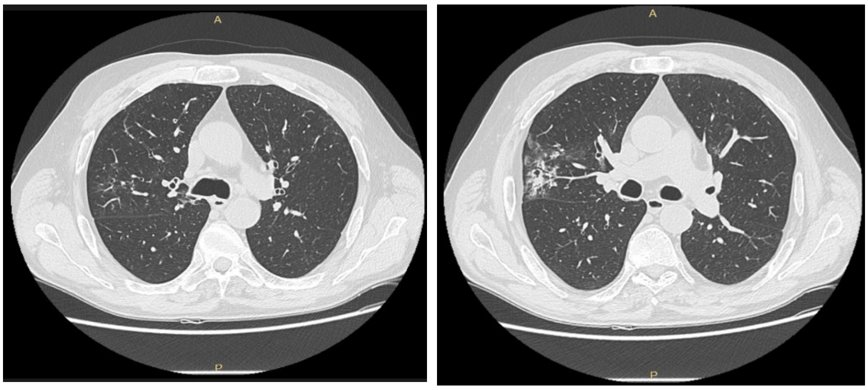

Figure 9 – Axial high-resolution CT scan images of a 75 years old male Crohn's disease patient included in the very symptomatic group. He referred chronic cough, sputum, wheezing and dyspnea. He also had a previous diagnosis asthma and slowly resolving pneumonia.

32 positive IBD patients underwent functional tests (Table XI): 18 from poorly symptomatic, 14 from very symptomatic group.
FEV1 median value was 3.56 L (1.45-5.82) for the entire population, varying from 3.46 L (1.45-5.10) for poorly symptomatic and 3.61 L (1.26-5.82) for very symptomatic (p value = 0.54). The corresponding percentage volumes show no median reduction (FEV1 <80%) with a non-statistical significance between groups.
FVC median value was 4.08 L (1.78-7.12) for the entire population, varying from 3.81 L (1.83-5.16) for poorly symptomatic and 4.34 L (1.78-7.12) for very symptomatic (p value = 0.36).
Tiffeneau index (FEV1 to FVC ratio) had a median value of 0.83 (0.70-0.95) for the entire population, varying from 0.86 (0.73-0.95) for poorly symptomatic and 0.82 (0.70-0.87) for very symptomatic (p value = 0.059). Being median and ranges values >0.70, the entire positive population did not have an obstructive disease.
FEF25-75 median value was 89% (33-146) for the entire population, varying from 90% (62-146) for poorly symptomatic and 89% (33-141) for very symptomatic (p value = 0.43). 9 out 28 patients presented a reduction in FEF25-75 (< 80%) meaning a small airways disease, resulting in values (Table XII).
TLC median value was 6.18 L (3.23-8.78) for the entire population, varying from 5.82 L (3.23-8.01) for poorly symptomatic and 6.90 L (3.71-8.78) in very symptomatic (p

value = 0.24). The corresponding percentage volumes showed no median reduction in TLC <80%.

DLCO median value was 76% (42-107) for the entire population, varying from 74% (51-107) for poorly symptomatic and 86% (42-93) for very symptomatic (p value = 0.28). 14 out 24 cases DLCO was pathologically reduced (<80%) (Table XIII).

	Entire Positive population (n = 32)	Poorly symptomatic (n = 18)	Very symptomatic (n = 14)	p value
FEV1 - L	3.56 (1.45-5.82)	3.46 (1.45-5.10)	3.61 (1.26-5.82)	0.54
FEV1 - %pred.	105 (47-132)	107 (86-132)	105 (47-129)	0.83
FVC – L	4.08 (1.78-7.12)	3.81 (1.83-5.16)	4.34 (1.78-7.12)	0.36
FVC – %pred.	107 (85-141)	108 (85-141)	106 (92-133)	0.93
FEV1/FVC	0.83 (0.70-0.95)	0.86 (0.73-0.95)	0.82 (0.70-0.87)	0.059
FEF25-75 - %pred	89 (33-146)	90 (62-146)	89 (33-141)	0.43
TLC - L	6.18 (3.23-8.78)	5.82 (3.23-8.01)	6.90 (3.71-8.78)	0.24
TLC - %pred.	104 (57-118)	105 (73-117)	103 (57-118)	0.77
DL_{CO} – %pred.	76 (42-107)	74 (51-107)	86 (42-93)	0.28

Table XI – Functional data of the entire positive population (≥3 points), the poorly symptomatic group (3-6 points) and the very symptomatic group (>6 points). The considered variables are all continuous variables, hence expressed as median and ranges as appropriate. Mann-Whitney U test was used to compare functional data between the poorly symptomatic group and the very symptomatic group.

	Entire positive population (n = 9)	**Poorly symptomatic (n = 5)**	**Very symptomatic (n = 4)**	**p value**
FEF25-75 <80% - %pred	67 (33-79)	67 (62-79)	65 (33-75)	0.61

Table XII – Analysis of FEF25-75 <80% population. This functional variable has been studied in each population: the entire positive population (≥3 points), the poorly symptomatic group (3-6 points) and the very symptomatic group (>6 points). FEF25-75 is a continuous variable, hence expressed as median and ranges as appropriate. Mann-Whitney U test was used to compare this functional data between the poorly symptomatic group and the very symptomatic group.

	Entire positive population (n = 14)	**Poorly symptomatic (n = 11)**	**very symptomatic (n = 3)**	**p value**
DL_{CO} <80% - %pred	72 (42-79)	72 (51-79)	74 (42-75)	>0.99

Table XIII – Analysis of DLCO <80% population. This functional variable has been studied in each population: the entire positive population (≥3 points), the poorly symptomatic group (3-6 points) and the very symptomatic group (>6 points). DLCO is a continuous variable, hence expressed as median and ranges as appropriate. Mann-

Whitney U test was used to compare this functional data between the poorly symptomatic group and the very symptomatic group.

DISCUSSION

Even though the prevalence of pulmonary extraintestinal manifestations (EIMs) of IBD is still partially unknown (10), literature shows that approximately 10% of people with IBD presents respiratory symptoms (25), suggesting that pulmonary EIMs of IBD could be more common than what it is perceived. Regarding that point, this study showed that roughly one third of the IBD patients (55 out of 152 people, 36%) reported respiratory symptoms (i.e. positivity at the ATS-DLD-78-A questionnaire). Also, it seemed that those people who resulted 'positive' at the questionnaire were younger than patients without respiratory symptoms [46 vs. 51 years old (19-83), p value = 0.038]. Instead, male and female patients were equally distributed in both 'negative' and 'positive' groups.

Those 55 patients who tested positive for the questionnaire were the main source of information for this study. People with IBD and respiratory symptoms were further stratified into two sub-groups based on the scores at the questionnaire: the poorly symptomatic group (points: 3-6) and the very symptomatic group (points: >6).

Focusing on epidemiology, among this group of people with IBD and respiratory symptoms, ages and genders were evenly distributed in poorly symptomatic and very symptomatic groups.

More than half of patients have never smoked or have in the past (71% of the entire population), with a predominance of data regarding nonsmokers (42% of the entire population) over the former smokers population (29% of the entire population). Also, in poorly symptomatic group there was a higher prevalence of nonsmokers (47%) over both former and current smokers, in very symptomatic there was a higher prevalence of nonsmokers and current smokers (36% each) over former smokers. These results are not clearly coherent to what it is found in literature: smoke is an acknowledged risk factor for both lung diseases and EIMs of IBD (7,15,16). Instead, this study shows the lowest prevalence of active smokers of the entire study in poorly symptomatic group and a comparable distribution of data among 'active smokers', former smokers' and 'nonsmokers' categories in very symptomatic group.

Roughly one third of the entire population was exposed to lung-injuring substances in working environments. In addition, there was no different distribution of data among poorly and very symptomatic groups. These results might suggest that pulmonary EIMs do not primely correlate to occupational exposure.

Most of IBD patients with respiratory symptoms have a negative history of allergies to both inhalants and non-inhalants (53% of the entire population), accompanied by a similar distribution in prevalences for allergies to inhalants (16%), non-inhalants (13%) and both (18%). Non-allergic patients are the main population in both groups, with a difference in distribution (60% of group 1, 44% of very symptomatic group). Allergic people to only inhalants seemed to be concentrated mainly in poorly symptomatic group, while allergic people to only non-inhalants seemed to be concentrated mainly in very symptomatic group [0 people (0%) vs. 7 people (28%), p value = 0.0024]. Also, allergies to both inhalants and non-inhalants had a similar distribution among the two groups (17% of group 1, 20% of group 2). From this data it seems that allergies might not clearly associate with an increase of pulmonary EIMs prevalence. Though, data tell that very symptomatic patients might have a higher probability of suffering from an allergy (in fact, very symptomatic group has the lowest prevalence of non-allergic patients in this study). In addition, it is interesting to note that allergy to only non-inhalants resulted in a statistically significant difference between the two groups. This evidence's meaning is still doubtful, suggesting either an association between allergies to food/drugs and clinically relevant respiratory symptoms or a mere coincidence.

Familiarity for lung diseases was differently distributed among poorly and very symptomatic group [8 out of 30 people (27%) vs. 14 out of 23 people (61%), p value = 0.012], suggesting that very symptomatic people might have a predisposition to develop airways diseases.

Comorbidities were highly prevalent in IBD patients with respiratory symptoms (71%), showing a similar distribution among poorly and very symptomatic groups. Interestingly, only a few IBD patients from the entire population had previously diagnosed lung diseases (27% of the entire population, most of which were asthmatic), with a different distribution of data among groups. This data seems to support this method of recruitment (i.e. the administration of a questionnaire on respiratory symptoms) as a potential screening test. In fact, the vast majority of IBD patients with respiratory symptoms (60% of the very symptomatic group and 83% of the poorly symptomatic group) had no previous lung disease diagnosis, perhaps meaning that their symptomatology was first evaluated by lung medicine clinicians through this study.

Ulcerative colitis diagnosis was slightly more prevalent than Crohn's disease diagnosis both in the entire population (56% and 44% respectively) and in poorly and very symptomatic group. These data might match the equity in prevalence of ulcerative colitis and Crohn's disease found in literature (3). Also, the study showed a similar distribution of EIMs both in the entire population (24%) and in poorly and very symptomatic group showing an under recognition of the phenomenon, whose prevalence corresponds to approximately the 50% of IBD patients (8).

Regarding the medical therapies patients have been taking throughout their IBD history, three groups of drugs were the most administered: mesalazine and its derivatives, systemic corticosteroids and monoclonal antibodies. Within the entire population mesalazine was the most extensively used drug (78%), followed by monoclonal antibodies (71%) and systemic corticosteroids (56%). Focusing on the comparison between poorly and very symptomatic group, it resulted that mesalazine was mainly used by less symptomatic patients (87% of group 1 vs. 68% of group 2), while both corticosteroids and monoclonal antibodies had a higher prevalence among more symptomatic patients (corticosteroids: 50% of poorly symptomatic group and 64% of very symptomatic group, monoclonal antibodies: 63% of poorly symptomatic group and 80% of very symptomatic group). This data might suggest a role of immunosuppressive therapy – especially the anti-TNF monoclonal antibodies – in the onset or exacerbation of respiratory symptoms, given their acknowledged role in drug-induced lung injury (24,63). Also, being monoclonal antibodies typically administered to patients with a moderate-to-severe IBD activity (5,6), it is possible that a broadly usage of these medications in very symptomatic IBD patients confirms the association between gut inflammation and airways disease (i.e. the 'lung-gut axis' theory) (16,24).

Regarding the clinical features of the entire population, cough (61%) and sputum (59%) were the main reported symptoms, followed by dyspnea (48%) and wheezing (35%). As expected, each symptom's prevalence was higher in very symptomatic than in poorly symptomatic. Also, roughly 23% of the entire population had a remarkable history of respiratory infections (including recurrent infections or a single clinically severe episode of airways infection), mainly distributed in very symptomatic: in fact, almost 30% of very symptomatic had a positive history of respiratory infective disease compared to a rough 18% of poorly symptomatic. This data distribution seems coherent to the former categorization of the entire population in poorly and very symptomatic groups. Also, very symptomatic IBD patients could be more susceptible to infections since their group presented a higher prevalence of administered immunosuppressive therapies (i.e. monoclonal antibodies and corticosteroids), which are known to be risk factors for infectious diseases.

Regarding the leukocyte formula, both neutrophils and lymphocytes median values were in-range and appeared to be slightly higher in very symptomatic than in poorly symptomatic group, but no statistically significant difference was found. Also, both monocytes and eosinophils median values appeared to be similar and in-range.

Among IBD patients with respiratory symptoms who performed a chest x-ray (34 people), 12 people (35% of the population) had radiographical alterations, mainly distributed in poorly symptomatic than in very symptomatic (44% vs. 28%). It is not clear why these counterintuitive results occurred (or rather, a higher prevalence of radiographical findings among poorly symptomatic patients), but it is reasonable to assume that the lower numerosity of the entire population might have falsified the analysis. Also, the low sensibility of chest x-ray in the identification of radiological alterations could have contributed to this. In addition to this, a little group of IBD patients (11 people) underwent a high-resolution CT scan, showing radiological findings in 91% of cases (data perhaps supporting the evidence of higher sensitivity of chest CT scan in comparison to chest x-ray). Considering the total number of radiological exams, the two most reported findings consisted of 15 patients presenting radiological abnormalities (either on chest x-ray or CT scan) of which eight cases of bronchiectasis and three cases of parenchymal thickening; these results are in line with the main alteration reported in literature (16).

Regarding respiratory function tests, data gathered from 32 IBD patients showed neither obstructive nor restrictive ventilatory disorders, given normal median values of FEV1, FVC, FEV1/FVC and TLC volumes both in the entire population of patients and in poorly and very symptomatic groups. However, o32% of cases presented reduced FEF25-75, suggesting the presence of small airways obstruction. The presented data do not clearly correspond to the evidence found in literature: in fact, IBD patients with active disease often perform positive pulmonary function tests, resulting in reduced FEV1 and FEF25-75 (65). This mismatch could be explained by the presence of an IBD population with different stages of intestinal disease: perhaps, some patients underwent the tests while in clinical remission. The most relevant alteration regarding pulmonary function tests was the reduction of DLCO <80% in more than half of IBD patients that underwent this test (58%). Interestingly, when analyzing data from poorly and very symptomatic groups separately, it resulted that DLCO impaired values were much more prevalent in poorly symptomatic compared to very symptomatic (69% 38%). Although non-statistically significant (p value >0.99), these results show agreement with the existing literature: in fact, the reduction in DLCO is the most common alteration in pulmonary function tests performed by IBD patients (73–75). Also, studies show that abnormalities of DLCO (as well as of other pulmonary function tests variables) can be met in asymptomatic patients, too (75,76). This implies, on the one hand, that finding a higher number of impaired DLCO values in poorly symptomatic patients is fully coherent with what reported in literature, but, on the other hand, that this study might have underestimated the prevalence of pulmonary functional changes in IBD population, since IBD patients without respiratory symptoms (i.e. people with 0-2 questionnaire scores) were excluded.

CONCLUSIONS

Over one third of IBD patients included in this study reported chronic respiratory symptoms, with higher prevalence among the youngest and no gender predominance. Actively smoking habit was a prerogative of barely one quarter of IBD patients with respiratory symptoms and just one third of this population reported occupational exposure. Also, familiarity for lung diseases was predominant among the group of highly symptomatic patients, which suggested an underlying predisposition to develop airways diseases. In addition to this, very symptomatic IBD patients were associated with a more extensive administration of immunosuppressive drugs (monoclonal antibodies and corticosteroids) and with higher numbers of airways infections. Finally, regarding diagnostic exams, bronchiectasis was the main radiological finding (both in chest x-rays and high-resolution CT scans) and DLCO was the most widely reported alteration in pulmonary functional tests, involving more than half of patients who have undergone this exam.

In conclusion, with the intent of better understanding respiratory EIMs of IBD, this observational prospective study has gathered a series of epidemiological, clinical, radiological and functional tests data whose meaning does not have univocal interpretations. In fact, while some analyses seem to find confirmation in existing literature, others appear to be discordant. However, it is important to notice a low amount of statistically significant results, meaning that further analysis is advised to deepen (or resize) the relevance of these data.

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