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THE ROLE OF TRANSITION IN THE CARE OF PEDIATRIC-ONSET INFLAMMATORY BOWEL DISEASE PATIENTS

Ph.D. Thesis

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List of Abbreviations

ASCA	Anti-Saccharomyces cerevisiae Antibodies
AZA	azathioprine
BMI	Body Mass Index
CD	Crohn's Disease; Morbus Crohn
CDAI	Crohn's disease activity index
CDED	Crohn's disease exclusion diet
CI	confidence interval
ECCO	European Crohn's and Colitis Organisation
EEN	exclusive enteral nutrition
E.G.	*exempli gratia*
EIC	extraintestinal complication
EIM	extraintestinal manifestation
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
ESR	erythrocyte sedimentation rate
HLA	human leukocyte antigen
HR	hazard ratio
IBD	inflammatory bowel disease
IBD-SES	inflammatory bowel disease self-efficacy score
IBD-U	inflammatory bowel disease unclassified
IL	interleukin
MTX	methotrexate
NASPGHAN	North American Society For Pediatric Gastroenterology, Hepatology and Nutrition
NF-κB	nuclear factor kappa B
NOD2	nucleotide-binding oligomerization domain-containing protein 2
OR	odds ratio

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P-ANCA	perinuclear anti-neutrophil cytoplasmic antibodies
PC	percentile
PCDAI	pediatric Crohn's disease activity index
PDP	prevalence doubling period
PIBD	pediatric-onset inflammatory bowel disease
PUCAI	pediatric ulcerative colitis activity index
SD	standard deviation
SDS	standard deviation score
TNF-α	tumor necrosis factor alpha
TRAQ	Transmission Risk Assessment Questionnaire
UC	ulcerative colitis
USA	United States of America
VEO-IBD	very early onset inflammatory bowel disease
W	with
W/O	without

Certain sections of this Ph.D. thesis have been published in the Therapeutic Advances in Gastroenterology Journal, under the title *"Transition is associated with lower disease activity, fewer relapses, better medication adherence, and lower lost-to-follow-up rate as opposed to self-transfer in pediatric-onset inflammatory bowel disease patients: results of a longitudinal, follow-up, controlled observational study"*, referred in the "*Bibliography of the candidate's publications - Publications related to the thesis*" section.

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1. Introduction

1.1. INFLAMMATORY BOWEL DISEASE

1.1.1. History and definition

The 1793 book of Matthew Baillie's '*Morbid Anatomy of Some of the Most Important Parts of the Human Body'* marked the first documentation of a disorder consistent with **inflammatory bowel disease** (IBD) [1]. However, it wasn't until 1859 that Samuel Wilks authored the first paper specifically naming a unique, non-infectious gastrointestinal entity [1]. Nearly three decades later, in 1888, William Hale White introduced the term **ulcerative colitis** (UC) in his case series [2]. Subsequently, numerous reports emerged documenting a similar inflammatory disease manifesting beyond the colon. The landmark in classification occurred in 1932 with Crohn et al.'s paper, which established **Crohn's disease** (CD) as a distinct entity from UC, unifying both conditions under the umbrella term of IBD [3].

IBDs are currently defined as chronic, progressive inflammatory disorders of the gastrointestinal tract, with a relapsing-remitting disease course and possible extraintestinal manifestations [4]. The primary subtypes include CD and UC, while cases where definitive differentiation between CD and UC remains uncertain, despite comprehensive diagnostic workup, are classified as **inflammatory bowel disease unclassified** (IBD-U) [5].

1.1.2. Epidemiology

Over the past 250 years, IBD emerged from sporadic cases to a global entity, impacting millions worldwide [1]. This evolution can be divided into four stages. The developing countries currently find themselves in the initial stage, '**Emergence'**, marked by sporadic case reports, while newly industrialised nations have advanced to the second stage, the **'Acceleration in Incidence'**, characterised by a steady rise in incidence over decades, but still with low prevalence [6, 7]. The Western regions of the world have progressed to the third phase, **'Compounding Prevalence'**, witnessing a continuous growth in the population affected by IBD [8]. The fourth stage, '**Prevalence**

Equilibrium' is currently a hypothetical state, where incidence balances mortality, resulting in stabilized or even decreasing prevalence [1]. Key factors influencing this transition include industrialization, urbanization, and westernization [9].

In 1971, Omran proposed the **Epidemiological Transition Theory**, which correlates shifts in population growth with the primary drivers of mortality across various centuries [10]. IBD serves as a notable exemplification of the final phase, **'Age of Degenerative and Human-Influenced Diseases'**, characterised by the escalation of chronic conditions, where mortality is predominantly attributed to non-infectious diseases influenced by environmental factors, including nutrition and lifestyle [11, 12].

The two longest epidemiological follow-up studies conducted in England and the United States of America (USA) align with these theories: starting around the 1940s, they exhibited a low and consistent incidence of IBD, followed by a notable increase towards the 1980s and a subsequent stabilization phase around the 2000s [13-17]. Similar trends were observed in other parts of the Western world, for instance, in Hungary, the incidence rates of CD and UC rose by 11.1% and 8.9%, respectively, from 1977 to 2001 [18].

The term Prevalence Doubling Period (PDP) is employed to assess the rate at which the prevalence of a disease increases, representing the time required for the prevalence to double within a specified region. This doubling equals an approximate 200% rise in the number of affected patients, owing to the natural population growth. In the Western world currently 0.75% of the population is affected by IBD and with the current 20- to 25-year-long PDP, it is expected to reach 1% by 2030 and 2% by 2050 [1, 15, 19, 20].

Approximately 10% of all IBD patients have a **pediatric-onset** disease (PIBD), of whom 6% are diagnosed before 6 years of age, categorized as very early onset (**VEO-IBD**), and 1% diagnosed within their first year of life (**infantile IBD**) [21-23]. Currently, the incidence of VEO-IBD stands at approximately 4.37 per 100,000, with a prevalence of 14 per 100,000 [22]. The incidence of IBD is having a peak in preschool age, with a second peak for UC between the ages of 10 and 18, and for CD during late adolescence and in young adulthood, up to 25 years of age [24-26].

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1.1.3. Pathogenesis and risk factors

While the exact pathogenesis of IBD is yet unknown, based on our current knowledge it is thought to occur as a result of complex interactions between a dysregulated **immune system** and an altered **intestinal microbiome**, triggered by **environmental factors** in **genetically predisposed** individuals (**Figure 1.**) [27-32].

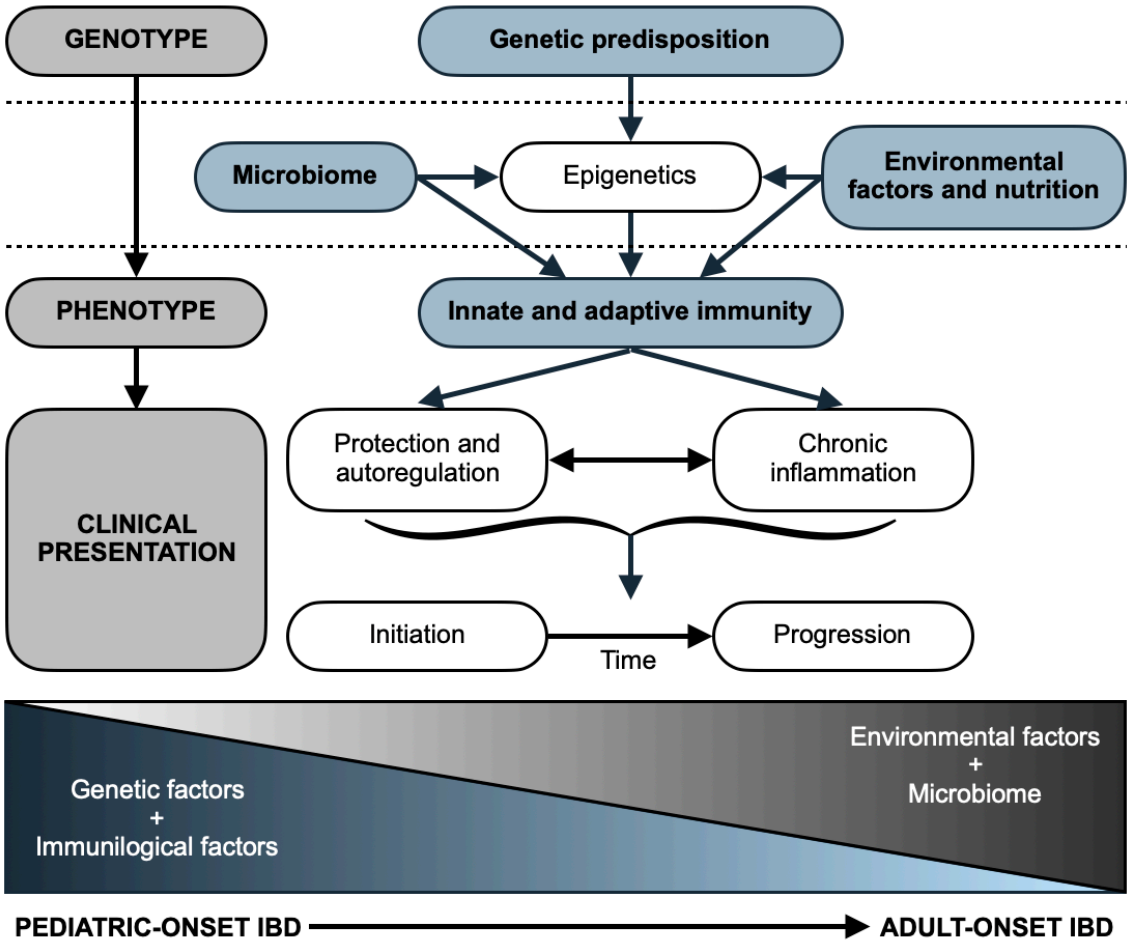

Figure 1. | Factors that play a rule in the development of inflammatory bowel disease, based of our current knowledge

own figure, based on: [32, 33] (IBD - inflammatory bowel disease)

Early twin studies, demonstrating greater concordance in monogenic compared to dizygotic twins with CD provided initial evidence for the role of **genetic predisposition** in the pathogenesis of IBD (20 to 50% vs. 10%) [33, 34]. Subsequent research has

identified over 230 genetic variants associated with IBD, including mutations in genes such as HLA-DRB1 and HLA-DQB predisposing individuals to ulcerative UC, and NOD2 mutations linked to CD [35, 36]. Remarkably, in up to 90% of these identified loci, the mechanism of action involves alterations in gene expression rather than changes in the gene product [37].

In the normal mucosa, a complex and dynamic interplay between the intestinal flora and gut immune mechanisms facilitates appropriate immune responses and regulatory functions. Disruption of this delicate balance leads to defective barrier function, mucosal injury, and inflammation [38, 39]. **Dysbiosis** is a commonly seen microbial pathology in IBD, resulting in a shift from a balanced flora towards pathogenic bacteria, resulting in reduced microbiome gene diversity and bacterial richness, ultimately contributing to functional impairment [40, 41].

Based on our current knowledge, the most important **environmental factors** that can either negatively or positively influence the development of IBD are smoking and passive smoke exposure, appendectomy, diet, industrialisation, antibiotic usage, hygiene status, breastfeeding, vitamin D, gastrointestinal infections, and air pollution [29, 42]. Antibiotic usage is shown to play a bigger role in the development of IBD among the pediatric population than in adults, particularly when administered during early childhood [41, 43-45]. The so-called Western diet, with its high refined sugar, fat, and low fiber content, as well as the use of food additives and conservatives, are the most prominent nutrient risk factors in the pathogenesis of IBD [46].

1.1.4. Differences between pediatric- and adult-onset IBD

PIBD is thought to be more **complex** and **extensive** compared to the adult-onset form, often exhibiting a more **severe phenotype** and **rapid progression** [47]. Over 80% of pediatric UC patients present with extensive disease or pancolitis, a proportion significantly higher than the reported 50% among adults. Furthermore, pediatric CD patients are more prone to upper gastrointestinal involvement than adult patients [34, 48]. In a study by Vernier-Massouille et al., involving 404 pediatric-onset CD patients over a 2-year follow-up period, disease progression was observed in 31% of the

children. Complicated disease behavior was evident in 29% of patients at diagnosis, increasing to 59% by the end of the follow-up period. [49].

In pediatric populations, males have a predilection for CD, while females tend to present more often with UC. However, these gender disparities tend to equalize by the end of adolescence, with a subsequent shift towards female predominance among CD patients in adulthood [25, 26, 34].

Pediatric-onset, particularly VEO-IBD patients are more likely to have a positive **family history** of IBD compared to adult patients, due to the significant role of genetic predisposition in the initial manifestation of PIBD [50, 51].

Up to 20% of patients with VEO-IBD are reported to have a **monogenic disease**, whereas adult-onset IBD typically has a polygenic involvement [22, 52, 53]. More than 60 monogenic mutations have been identified to play a role in the development of VEO-IBD, including loss-of-function mutations in IL-10 and its receptor, as well as dysregulation in the NF-κB pathway [54-56]. Furthermore, VEO-IBD patients tend to have **colonic involvement** with a highly heterogenous clinical presentation, resulting in 20% to 35% of initial diagnoses being categorized as IBD-U [6, 22, 52, 57-59].

1.1.5. Diagnosis and classification of IBD subtypes

The diagnosis of PIBD relies on the Porto criteria, established by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2005 and revised in 2014. PIBD is classified into **UC**, **CD**, or **IBD-U**, with UC further categorized into *typical* and *atypical* forms based on the phenotype present at the time of the diagnosis. The diagnostic algorithm includes oesophagogastroduodenoscopy and colonoscopy with multiple histological examinations, magnetic resonance enterography, laboratory tests (eg. complete blood count, at least two inflammatory markers, albumin, transaminases, and γGT), and fecal examination (eg. calprotectin, stool culture) [60].

PIBD is further categorized based on the **Paris classification**, which is a pediatric modification of the Montreal classification, published by the *North American Society for Pediatric Gastroenterology, Hepatology and Nutrition* (NASPGHAN) in 2011. It

examines the disease extent and severity in UC, whereas the age at the time of diagnosis, the localisation and behaviour of the disease, and growth failure in CD [61].

Serological marker positivity increases the likelihood of IBD in atypical cases and can help in distinguishing between CD and UC in patients with an IBD-U diagnosis. **ASCA** positivity is observed in 50% to 70% of CD, in contrast to only 10% to 15% of UC patients, and less than 5% of the general population [62, 63]. Conversely, **P-ANCA** positivity is reported in 60% to 70% of UC and just 20% to 25% of CD patients [64].

The most common **presentational symptom** in UC is bloody diarrhoea, whereas CD is more likely to present with abdominal pain, non-bloody diarrhoea, unexplained anemia, fever, weight loss, or growth retardation. The so-called "*classic triad"* of abdominal pain, diarrhoea, and weight loss occurs in only 25% of CD patients [65].

1.1.6. Activity indexes

To assess disease activity and therapeutic efficacy in IBD patients, age-appropriate, validated, and disease-subtype-specific scores are employed. For the evaluation of patients younger than 19 years of age **PCDAI** and **PUCAI** are used, from which **CDAI** and **Mayo score**, details and abbreviations can be seen in **Table 1**. [66-73].

Table 1. | Inflammatory bowel disease activity scoring systems

Score	Symptoms	Physical examination	Laboratory tests / Endoscopy	Range	Significant change
PCDAI	abdominal pain, stool count, general well being	height, weight, abdominal and perirectal state, EIMs	hematocrit, ESR, albumin	0 - 100 points	12.5 points
PUCAI	activity level, abdominal pain, rectal bleeding, stool number, consistency, nocturnality	-	-	0 - 85 points	20 points
CDAI	liquid stools, abdominal pain, general well-being, use of antidiarrhoeal drugs	abdominal mass, weight	hematocrit	0 - 600 points	20 points
Mayo score	stool frequency, rectal bleeding, physicians rating of the disease activity		mucosal appearance	0 - 12 points	3 points

PCDAI - pediatric Crohn's disease activity index, PUCAI - pediatric ulcerative colitis activity index, CDAI - Crohn's disease activity index, EIM - extraintestinal manifestation, ESR - erythrocyte sedimentation rate
based on: [64 - 71]

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1.1.7. Extraintestinal manifestations and complications

The extraintestinal symptoms of IBD can be categorized into two main groups: **extraintestinal manifestations** (EIM) or **complications** (EIC). EIMs are conditions that appear outside the gastrointestinal tract are more prevalent among IBD patients, while EICs are those caused by the loss of intestinal function or the treatment of IBD (**Figure 2.**) [74]. The appearance and activity of the EIMs may parallel the disease activity (e.g. *erythema nodosum*, *arthritis*, *episcleritis*), or may be independent (e.g. *pyoderma gangrenosum*, *sclerosing cholangitis*).

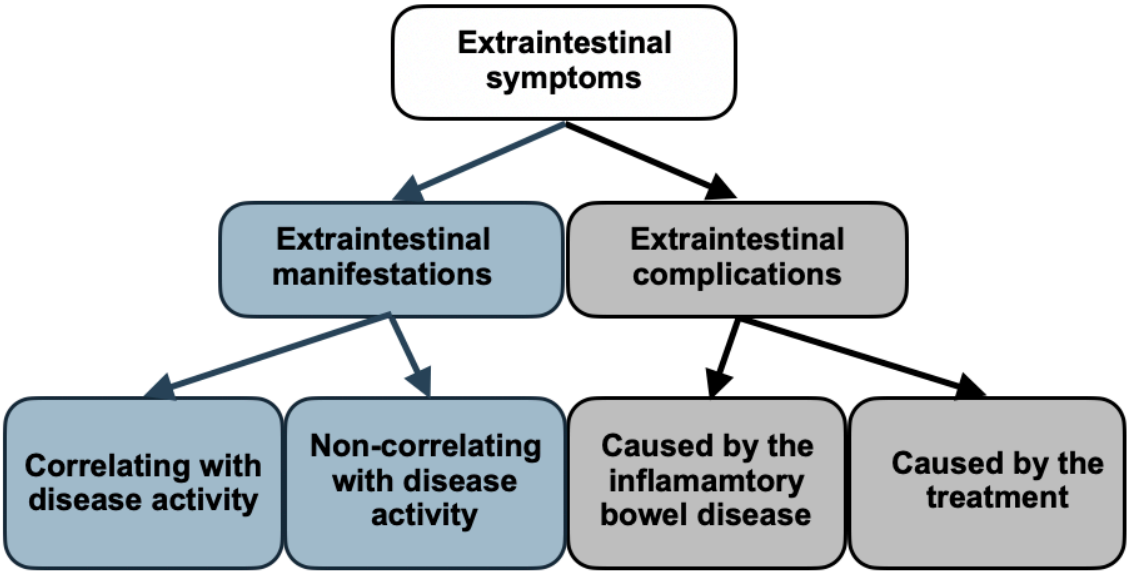

Figure 2. | The classification of the extraintestinal symptoms of inflammatory bowel disease *(own figure)*

The most common EIMs are **musculoskeletal** (e.g. *arthritis*), **dermatologic** (e.g. *erythema nodosum*, *pyoderma gangrenosum*), **hepatobiliary** (e.g. *pancreatitis*, *sclerosing cholangitis*), **ophthalmologic** (e.g. *uveitis*, *scleritis*, *episcleritis*) and **hematologic** (e.g. *anemia*, *thromboembolism*) [79]. EIMs are reported to be present at the time of diagnosis in 6% to 28% of PIBD patients, being more common than in adult-onset IBD, with a possible onset of years before the appearance of gastrointestinal symptoms, particularly among non-VEO-IBD patients [49, 75-77].

The most prominent EICs among IBD patients include inadequate **nutrition and growth**, disturbed **psychosocial well-being**, **fertility** problems**,** and **malignancies**.

Due to chronic blood loss and inflammation, increased energy requirements, intestinal malabsorption, and frequent treatment with corticosteroids, patients with IBD are prone to **malnutrition** [78].

Growth failure is documented in 40% of CD and 10% of UC patients, with 50% of PIBD patients having a 10% lower final height than the general population [78-83].

Patients with IBD, especially those diagnosed with CD are at high risk for **osteoporosis** and **poor bone health**. This primarily stems from the direct effects of pro-inflammatory cytokines released from the intestines on growth plates and bone cells, exacerbated by factors such as loss of muscle strength and corticosteroid usage [34, 84].

Among the PIBD population, 25% to 40% of the patients exhibit signs of **clinical depression**, leading to lower quality of life, elevated rates of anxiety, and adverse effects on their education and medication adherence. This prevalence surpasses not only that of the general population but also of children with other chronic diseases [39, 85-91].

The **birth and fertility rates** among patients with IBD are significantly lower compared to the general population, especially following disease flare-ups and surgical interventions. Among UC patients, this decrease can be as high as 21% [92, 93].

1.1.8. Treatment

The optimal treatment approach for IBD should encompass a **biopsychosocial perspective**, addressing patients' individual *biological* (e.g. medical and physical), *psychological* (e.g. coping, resiliency, and mental health), and *social* (e.g. healthcare system, support, and resources) needs [94]. Currently, the primary goal of treatment is to achieve **deep remission**, **mucosal** and **transmural healing**. The shift from symptomatic treatment and laboratory remission was supported by studies recognising the evolution of pediatric CD to stricturing and fistulising disease phenotypes, as well as the progressing rates of colectomy among UC and IBD-U patients [38].

Surgical management

A surgical intervention is required in 9% of the pediatric CD and 8% of the pediatric UC patients within the first year following the initial diagnosis, reaching 23% and 20% after 5 years of disease duration, respectively [95-97]. As the disease progresses, up to 80% of all CD patients require surgical intervention, with 10% requiring a permanent stoma [6]. Patients with the NOD2/CARD15 genotype, fibrostenosing phenotype, or ASCA positivity have a higher risk of surgery [83]. The most common indications for emergency surgeries among IBD patients are intestinal *perforation*, *exsanguinating hemorrhage*, c*omplete bowel obstruction*, and *peritonitis* [73]. Despite the continuous advances in surgical techniques, IBD patients remain at a higher risk for postoperative infectious and anastomotic complications compared to the general population [98, 99].

Medical and nutritional treatments - Remission induction and maintenance therapy

Exclusive enteral nutrition (EEN) is the first-line recommendation for remission induction in pediatric CD by ESPGHAN and ECCO (*European Crohn's and Colitis Organization*) since 2014. EEN promotes mucosal healing by excluding food additives and preservatives, thus ensuring an anti-inflammatory milieu in the intestines [100-103].

Corticosteroids are effective in inducing remission in both CD and UC, with response rates of 60% to 80% within the first 4 weeks. However, due to their numerous and significant side effects, including *diabetes*, *cataracts*, *osteoporosis*, *hypertrichosis*, *mood swings*, *acne*, and *insomnia*, they are not recommended for maintenance therapy [104]. Furthermore, approximately 50% of PIBD patients on long-term steroid therapy become steroid-dependent and may ultimately require surgery [105].

Immunomodulators used in the treatment of IBD include **thiopurines** (e.g. **azathioprine** and **6-mercaptopurine**) and **methotrexate** [73]. They exert their effects after a build-up period of 3 to 6 months and therefore are primarily used as maintenance therapy. The main safety concerns regarding their long-term usage are *opportunistic infections*, *teratogenic effects*, and *malignancies* (e.g. *lymphomas*, *nonmelanoma skin cancers*). IBD patients treated with thiopurines face a 4-fold increased risk of malignancies, with longer therapy durations associated with higher risks [34, 106, 107].

Dose-dependent side effects include *myelotoxicity*, *hepatotoxicity*, and *allergic reactions*, whereas *pancreatitis* appears in approximately 5% of the patients through an idiosyncratic drug reaction [108, 109].

Aminosalicylates are generally well tolerated and can be used for both remission induction and maintenance therapy in patients with colitis [110]. In a prospective study, 40% of pediatric UC patients receiving aminosalicylate maintenance therapy remained in steroid-free remission during the first year after diagnosis [111].

The **biological treatment** options for PIBD patients currently include **TNF-α inhibitors** (e.g. *adalimumab*, *infliximab)*, **integrin inhibitors** (e.g. *vedolizumab*), **IL-12** and **-23 inhibitors** (e.g. *ustekinumab*). In a follow-up study, Adler et al. found that pediatric CD patients treated with immunomodulators and anti-TNF-α therapy were 59% less likely to develop fistulizing complications compared to those receiving steroids [112]. Additionally, TNF-α agents are associated with improved linear growth in PIBD patients with growth failure [113].

1.1.9. Prognosis, mortality

A 50-year-long Swedish follow-up study, comparing nearly ten thousand PIBD patients with a matched cohort from the general population showed a 3.2-fold increased **risk of death** among the IBD population, specifically with a 4.0-fold risk among the UC, a 2.3-fold risk among CD and a 2.0-fold risk among the IBD-U patients. In the PIBD population, this risk was 4.9-fold increased. Despite ongoing improvements in therapeutic and diagnostic capabilities, the relative risk of death among PIBD patients did not decrease during the study period, spanning from 1964 to 2015 [114]. **Colon cancer** significantly contributes to this increased mortality risk. A population-based study, including more than five thousand patients, demonstrated a 2.75-fold increased risk of colon cancer among UC patients [115]. Among CD patients with colonic involvement, this risk is 1.6-fold increased compared to the general population [116]. The risk of developing colon cancer increases over time and is particularly elevated in patients with an earlier diagnosis, pancolitis, and sclerosing cholangitis [73].

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1.2. TRANSITION AND TRANSFER

Ensuring an uninterrupted, comprehensive, and accessible healthcare throughout adolescence is essential in achieving the best possible disease course and outcome for PIBD patients, underscoring the significance of transition in their care [117]. **Transition** was first defined by Blum et al. in 1993 as a purposeful, planned movement of adolescents or young adults with chronic conditions from the pediatric to the adult healthcare system, including the gradual shift of the healthcare- and disease-related responsibilities from the caregivers and the parents to the patients [118]. In contrast, **transfer** refers solely to the point of handover of care between pediatric and adult healthcare-providing teams, which should be considered as a part of the transitioning process rather than the endpoint (**Figure 3.**) [117, 119, 120]. The *Society for Adolescent Medicine* highlights the complexity and the multiple layers of this changing process, defining transition as "a gradual, multi-dimensional and family-oriented process with a focus on the anticipated developmental stage of an individual and with the ultimate goal of transfer to adult healthcare settings by empowering patients with disease knowledge and self-management skills and by preparing healthcare providers with adequate knowledge" [121].

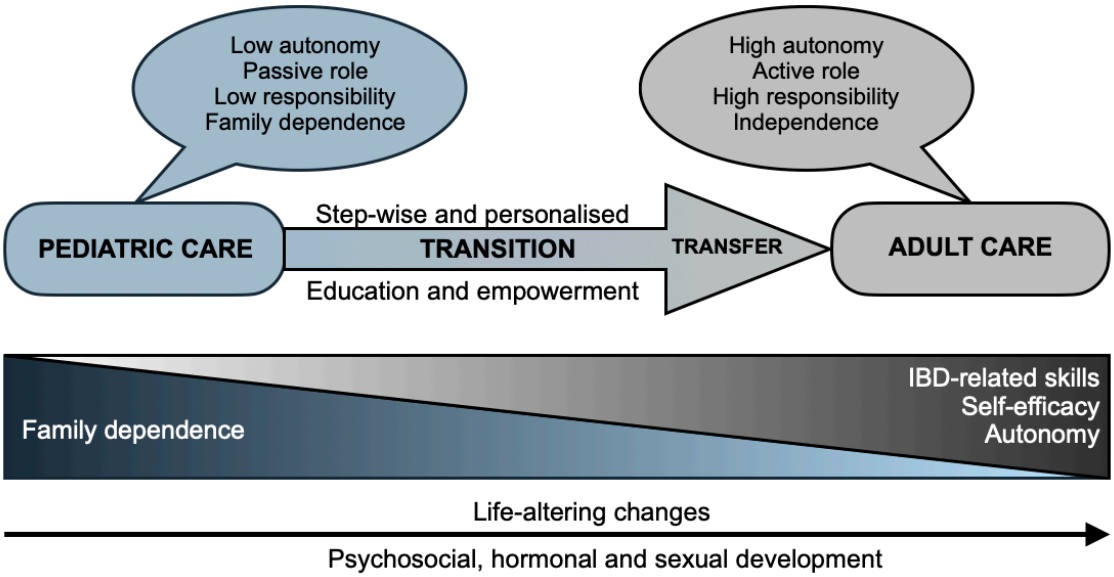

Figure 3. | Transition, transfer and the main characeristics of pediatric and adult care *(own figure) [IBD - inflammatory bowel disease]*

Transitional care has gained increasing attention over the past decade, especially considering the rising incidence of pediatric-onset IBD cases. The focus on transitional care began with the publication of the first position paper by NASPGHAN in 2002. Subsequently, further recommendations were issued, starting in the United States in 2011, followed by national societies such as those of Italy and the United Kingdom in 2015 [118, 122-124]. In 2017, ECCO published a topical review including 14 practice points for healthcare providers, however, similar to previous publications, it is not evidence-based and mostly relies on expert opinions, clinical experience, and literature reviews of other chronic diseases [118-120, 122, 123, 125, 126]. Despite the emerging need, based on the lack of data from primary research to guide the recommendations, there are currently **no official consensus guidelines and standardized transitional practices** regarding IBD patients**.**

Importance of transition

Transition is covering a vulnerable period of life, during which unaddressed medical and healthcare needs can lead to significant long-term consequences [123, 127]. The association between **inadequate transitional care** and adverse health outcomes has been extensively documented across various chronic conditions, including type 1 diabetes mellitus, congenital heart diseases, cystic fibrosis, juvenile rheumatoid arthritis, and hematological disorders [128-131]. **Successful transition** in pediatric-onset diabetes patients, for instance, has been linked to improved objective measures of glycemic control, better outpatient control and engagement with screening programs, higher compliance with adult care providers, and reduced rates of hospitalization and diabetic ketoacidosis [123, 132-135]. In the absence of a structured transitional program, the risk of disengagement with healthcare increases [123]. Following solid organ transplantation, unsuccessful transition is associated with worsening compliance, increased graft loss, and higher mortality [123, 136, 137].

The currently available literature on the effects of transition in IBD is primarily comprised of single-center studies, often lacking randomization or a control group [138]. Inadequate transitional care in IBD is associated with non-adherence to

medications and non-compliance regarding visits, a restricted growth potential, and an increased risk of surgery [123, 138]. Furthermore, in a French study examining 48 PIBD patients, a structured transitional program was associated with improved patient and healthcare provider satisfaction [139].

Practices worldwide and in Hungary

The existing recommendations do not necessarily translate into practice. Reportedly, 40% to 80% of the gastroenterologists do not perform any formalised transition, although 79% of them would consider it highly important, to have transitional guidelines [119, 140]. A survey-based study from the USA revealed, that 60% of pediatric gastroenterologists were unfamiliar with the transitional recommendations of the American Academy of Pediatrics, and only 0.7% of them incorporated all of their suggestions into practice [141]. Moreover, another study involving 141 pediatric gastroenterologists found that 8.5% do not perform either transfer or transition when moving their patients to adult care, whereas an additional 15% exclusively support transfer without a transitioning period [141].

There is currently limited data available on transitional practices for PIBD patients in Hungary. Erős et al. conducted a cross-sectional survey-based study to assess transitional care in both pediatric and adult institutes, achieving a response rate of 31.7%. The yearly number of patients moved to adult care was under 20 in most centers. Transitional care was introduced between the ages of 16 and 18 in 53.8% of the institutions, with 61.5% of centers not adhering to any formalized transitional protocol. Additionally, only 46.15% of centers offered an incorporated educational program, typically initiated after the age of 16 years [142]

Details of a transitional program

The most important domains, that have to be determined regarding a transitional program are: (1) Goals of transition, (2) Model of a transitional program, (3) Transition readiness: education and skills, (4) Way of transfer, (5) Timing of transfer and (6) Special age-related considerations.

1.2.1. Goals of transition

Given the diverse perspectives of patients, parents, and healthcare providers, achieving a successful transitioning process necessitates **collaboration**, **frequent feedback**, and **open communication** from all parties involved [143, 144]. ECCO emphasizes the crucial role of harmonizing divergent attitudes toward transition to ensure its success [126, 145]. Grey et al. conducted an analysis of the perspectives of patients, their parents, and pediatric healthcare providers regarding key factors for a successful transition to adult care. Interestingly, they found the lowest level of agreement between patients and their parents (40%), while a significant agreement was observed between physicians and patients (80%) [144]. Allison et al. examined the most important domains of a successful transition from the viewpoint of the patients, parents, and healthcare providers, identifying 'independence of care' as the sole aspect unanimously recognized by all groups (**Figure 4.**) [146].

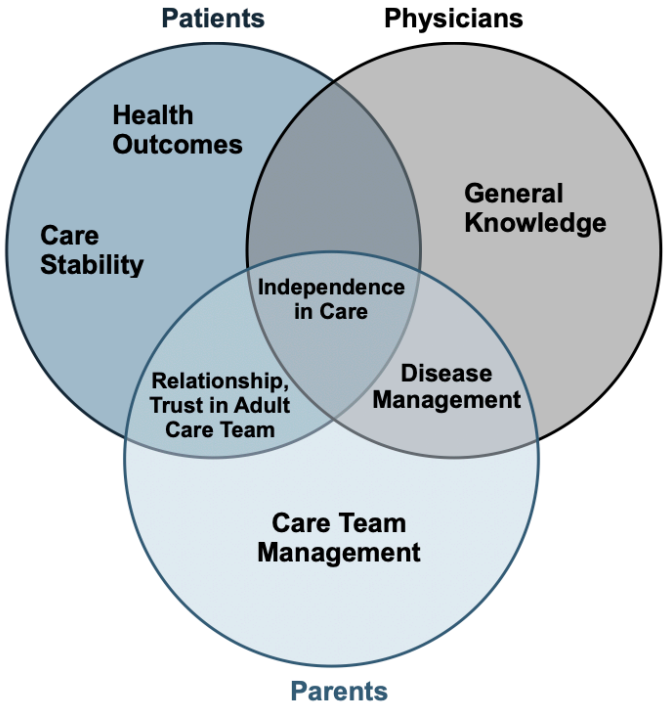

Figure 4. | Factors of a successful transition from the viewpoint of all participants

(own figure, based on: [132])

Defining "*successful transition or transfer*" to adult care is rather challenging. ECCO suggests continuity of care after being moved to adult care as a determining factor for the success, noting several other objective outcome measures, such as endoscopic remission rates, quality of life, or reduced attempts to return to child-centered care as other possible variables to take into consideration [126].

1.2.2. Model of a transitional program

The optimal model and duration of a transitional program are yet to be established [126]. It is recommended to initiate transition planning **early in adolescence**, employing a **personalized**, **step-wise** approach that includes an **educational program** [119, 147]. While existing recommendations predominantly address the pediatric phase of transition, it is important to recognize that patients entering adult care vary significantly in knowledge, skills, and capabilities. Consequently, a well-defined **post-transfer period** may be necessary to address and reconcile these differences [147-150].

In a systematic review of transitional articles, focusing on the continuity of care between pediatric and adult services, four **transitional models** were determined based on the core principles of the different practices [151]. In the *direct model*, the primary focus is on the connection between the healthcare systems and providers, addressing the continuity of information rather than the personal needs of the patient. The *sequential* and *developmental models* offer greater flexibility, acknowledging evolving patient needs (*sequential*) and the necessity for patients to acquire essential skills prior to transition, with an emphasis on personal growth and development (*developmental*). The *professional model* is mostly advised to be used in conditions with short life expectancy, as it focuses on the expertise of the physician side [123].

1.2.3. Transition readiness: education and skills

The crucial domains of transition readiness encompass **transition-related skills**, **disease-specific knowledge**, and **health-related behavior**, such as *autonomy*, *self-efficacy*, *executive functioning*, *communication skills*, and *adherence* [150]. **Disease-specific knowledge** includes an understanding of the diagnosis and previous medical

history, knowledge of current medications, their way of action and possible side effects, an understanding of the value and role of diagnostic procedures, familiarity with the concept of flare-ups, knowledge of how to obtain further IBD-related information, the influence of smoking, drug use, and alcohol consumption, consequences of non-adherence and issues related to sexuality and reproduction [126]. Transitional recommendations advocate for an age-appropriate, adaptable **educational program** to be part of a transitioning process, although a definitive template for its delivery is yet undetermined [123]. The role of patient education in the facilitation of transitional programs has already been described in other chronic conditions, such as *type 1 diabetes mellitus*, where enrollment in an educational program has been associated with improvements in HbA1c levels, self-management skills, disease-specific knowledge, and reduction in complications, however, no quality-of-life improvements were documented [123]. In *juvenile arthritis* patients, an age-appropriate, structured transitional program, and an incorporated disease-specific education were associated with an improvement in disease-specific quality of life and continuous improvements in the knowledge of patients and their parents [152]. Given that acquiring the necessary knowledge is unlikely to occur in a single encounter, a step-wise program is recommended. The focus of the education should align with the emotional and cognitive maturity of the patients. In a study from the USA, both PIBD patients regardless of still being in pediatric or already in adult care, and their healthcare providers chose *independent illness and treatment management* as the most crucial topic for discussion during the transitional program, followed by the *differences between pediatric and adult care* [141].

It has been thoroughly documented, that a high disease-specific knowledge alone is not sufficient for a successful transition, in fact, **self-efficacy** correlates better with self-management and therefore transition readiness [153]. Furthermore, self-efficacy has been positively linked in many chronic diseases to adherence to medical care, advanced coping behaviours, and better self-management skills [154]. These skills include the ability to monitor symptoms and report them to a healthcare professional, to manage medications and maintain adherence to the prescribed regime, to recognise and

effectively handle disease flare-ups, and to be able to work in partnership with healthcare providers [126]. Stollon et al. reported that PIBD patients acquire many healthcare-related skills between the ages of 12 and 14 years, but self-management skills are not mastered until after 18 years of age [155]. Currently, the only validated self-efficacy and -management scores available for IBD patients is the *IBD Self-Efficacy Scale* ('IBD-SES') [126, 156, 157].

The primary objective of transition is to ensure that patients acquire all the necessary IBD-related knowledge and skill-set, that they will require in adult care to be able to properly handle their disease [158]. This process requires a gradual **decrease in the role of the parents** in disease management, as well as an equal increase in self-efficacy and autonomy of the patients [1, 159, 160]. Parents should be encouraged to have confidence in their children's expanding self-management skills and to support interventions aimed at fostering independence, as these should be trusted, supported, and continued at home [126]. PIBD patients take over responsibilities regarding their disease management and treatment later than suggested, as a study reported only 35% of the patients aged 19 to 21 schedule their appointments, and only 30% contact their physician if they are experiencing problems with their disease [153]. Moreover, less than 15% of adolescents are reported to be able to take full responsibility for their IBD care, with 20% being incapable of performing basic disease-related self-management skills [161, 162]. A questionnaire-based study from the USA revelaed that among healthcare providers and PIBD patients, who were already in adult care the *ability of the patients to take care of their treatment independently* was noted as the most important clue for transitional readiness, while among the patients still in pediatric care the *maturity of the patients* stood on the first place [141].

Transition readiness should be **continuously evaluated** using an **interdisciplinary approach** during pediatric care and taken into consideration when planning the transfer to adult care [147]. The most commonly used validated **transitional readiness assessment tools** are the *Transmission Risk Assessment Questionnaire* ('TRAQ') and the NASPGHAN transition checklist [163]. Bensen et al. examined the utilization of validated transition readiness tools among pediatric gastroenterologists and reported a

23% rate [141, 164]. With the application of TRAQ, Gray et al. found, that only 5.6% of the patients on the verge of transfer met the benchmarks for transition readiness [165]. Currently, most patients fail to achieve the necessary knowledge and skills before transferring to adult care, resulting in some centers reporting insufficient knowledge in up to 95% of their patients upon arriving at adult care [147, 165]. Additionally, parents frequently overestimate the self-efficacy of their children, as in a recent study significant differences could be seen between the self-assessment of the patients and the answers of their parents regarding IBD-specific knowledge, self-management, medication use, and transition readiness [166].

Not only the pediatric but also the adult IBD population is shown to have inadequate knowledge about their disease, as in a survey only 21% to 23% knew that IBD has a genetic predisposition, 26% to 46% that not just the intestines can be affected, only 18% to 29% that they have an increased risk for colon cancer and just 68% to 74% that they would still have IBD if they were symptomless after 3 years [150, 167, 168]. Similarly, in a survey-based study, adult gastroenterologists reported inadequate knowledge among PIBD patients upon arriving at adult care, considering their medical history (55%) and medication regimens (69%) [169].

1.2.4. Way of transfer

The **way of transfer** can range from an *overlapping period* of the two health care systems, through *joint or alternating visits* to a simple *handout summary*, without combined visits. An overlapping period did not improve the success rate of the transitioning process in a Canadian study, whereas joint medical visits seemed to enable a successful transition to adult care [135, 147, 170]. Transition models incorporating a joint transitional meeting between the pediatric and adult clinics have been associated with improvements regarding relevant disease- and overall-health-related endpoints among young adults with chronic diseases, but have been sparsely reported in gastroenterology [123]. Survey-based studies reported that patients found joint-transitional visits as the best model for transition, however, only approximately 20% of the PIBD providers reported applying joint visits for transferring care [139-141].

The literature comparing specific transitional models lacks robust evidence, primarily consisting of expert opinions from single-center studies. As a result, a gold-standard transitional model has yet to be established [123]. Consequently, it is recommended that each institution select a transferring method based on its efficiency regarding available resources, geographical location, patient demographics, and existing services within both pediatric and adult care teams [25, 150]. ECCO currently supposes a joint adult-pediatric clinic, as a part of a structured transitional program to be the ideal model for transition [126].

Regardless of whether a joint meeting occurs, it is essential to provide a **handout summary** detailing the patient's disease course, treatment history, and their medical history to the adult healthcare team[126, 171]. Incomplete or missing information transfer between the healthcare providers can lead to suboptimal therapeutic decisions in adult care, consequently worsening the disease outcome and overall health of the patients [122]. In a Quebec survey, 84.7% of adult and 62.5% of pediatric gastroenterologists reported medical summaries as one of the most important transitional tools [172].

It is crucial for PIBD patients to be treated in **IBD centers** both before and after the transition, with a multidisciplinary team that has all the necessary and up-to-date diagnostic and therapeutic possibilities to ensure the best disease outcome and overall health for these patients with a presumably complicated, extensive and severe disease. The adult healthcare providing team should be aware, that the pediatric-onset patients arriving at adult care already have a complex medical and treatment history, with possible former surgeries and IBD-related complications, are prone to be resistant to therapy and their disease course is frequently complicated with growth failure and psychological distress [173, 174].

1.2.5. Timing of transfer

It is essential for the **timing of transfer** to adult care to be **flexible** and take into consideration numerous factors, such as the *chronological age* of the patient, *disease activity*, *adherence to medications*, and *overall compliance* [123]. Anticipating the

timing of the transition has been identified as one of the most crucial factors for a successful process [148, 175]. While the transfer can be targeted at a specific age or after a significant life event, relying solely on chronological age is not recommended [163]. In Europe, based on healthcare regulations, patients are typically transitioned to adult care around the age of 18, whereas in the USA, the transfer is often delayed until around the age of 25 [150]. In a survey-based study from the USA, 52% of gastroenterologists reported waiting with the transfer until their patients start their own family, 55% until they finish high school and 79% felt that the appearance of the first adult comorbidity is the appropriate trigger for transfer [150]. In the United Kingdom 42% of the adult, whereas only 29% of the pediatric gastroenterologists reported that leaving high school is a good time for transfer [119]. Furthermore, a study from Australia found significant differences between the prioritized timing of transfer among pediatric and adult gastroenterologists, with the former favoring the completion of secondary schooling and the latter relying more on caregiver-assessed readiness [176].

The transfer is usually advised to be done during **stable disease remission and psychosocial status**, as the changing process itself may potentially negatively impact disease activity. Hence, flexibility from both pediatric and adult care physicians is crucial. However, individual assessment is recommended to be done before planning the changing process, as among patients on the edge of transfer, who require great changes in their maintenance medications or a surgical intervention to acquire stable disease remission, it can be beneficial to refer them to the adult care team, allowing their future healthcare providers to monitor these changes effectively. Moreover, certain therapeutic options are exclusively available in adult care, so for patients with a complicated disease course the earlier introduction of these medications can delay more radical interventions [147, 150]. Philpott et al. suggested categorising these cases as '**crisis transfer**', regarding patients with an uncontrollable disease or immediate surgical requirements, pregnancy, substance abuse, or in need of medications, that are only available in adult care [163].

1.2.6. Special considerations - Possible barrier factors

Both pediatric and adult care providers play a crucial role in ensuring a successful transition process by regularly assessing potential barriers and providing resources to overcome these challenges [177]. The main contributing factors to an unsuccessful transfer are reported to be the **unpreparedness of the patients**, great **differences between the pediatric and the adult health care systems**, and the **special challenges of adolescence** [122, 138, 150, 160]. An unsuccessful transition to adult care is associated with several adverse outcomes, including increased rates of *emergency interventions*, *hospitalizations*, *higher surgical rates*, more frequent *therapy escalations*, and a *worse overall health disease outcome*. A Canadian study including nearly three thousand PIBD patients reported a 17.5% lost-to-follow-up rate during the changing process to adult care [178]. Similarly, in British Columbia, approximately 15% to 18% of patients discontinued their medical care during the transition process [179]. It is further complicating the process, that even if the transfer is successful, the changing between the healthcare systems itself is associated with the deterioration of patient compliance and higher disease activity, with reportedly 10% of all transitioned patients requiring hospitalization or an emergency intervention during the first 6 months after being moved to adult care [138, 165, 178-181].

Adolescents, the target age group of transition, are unique patients considering several aspects. They are experiencing great *hormonal*, *psychosocial*, and *sexual changes*, additionally facing *life-altering situations* regarding starting their own adult life, including moving out from their parents, enrolling in higher education, or starting to work. These may take priority over their healthcare, resulting in higher levels of anxiety [94, 122, 143, 147, 148, 150, 182]. At the age of 18, many adolescents have not yet completed their psychological transition to adult behavior and vary greatly in their resolution of inner conflicts regarding autonomy and self-esteem [126]. Additionally, they may tend to ignore or deny their disease, defer responsibility, and struggle with processing emotions and managing role changes in their life or medical care [153, 183-185]. The most common coping strategy employed by young adults with chronic conditions is ‘*avoidant coping*’: distracting themselves with social diversions, which

behaviour itself is associated with higher relapse rates. [186, 187]. Other adolescent-specific issues include problems with body image, self-esteem, reproductive health, peer influence and pressure, substance or alcohol usage, and smoking [147]. Surprisingly, up to 50% of PIBD patients do not receive any education on reproductive health or the effects of drugs or alcohol on their disease before transferring to adult care [188]. Several studies reported, that the unwillingness of patients and parents to change their healthcare provider due to their close relationship with their pediatric physician is one of the main transitional barriers [126, 145, 169, 189, 190]. Young adults may feel abandoned following their transfer to adult care, often resulting in regressive behavior considering their disease management [150, 174]. Collectively, these factors contribute that, **compliance and medication adherence are the lowest** among the adolescent IBD population from all age groups, with the non-compliance rate being up to 66% [191, 192].

The **differences between the pediatric and the adult healthcare systems** can also play a great role in the unsuccessful transferring process. In pediatric care, visits are often lengthy, patients have a passive role with low autonomy and high family dependence. On the contrary, in the adult healthcare system, the visits tend to be more business-like, requiring patients to possess a high level of disease-specific knowledge and take an active role with significant responsibility. Pediatric care is characterized by a nurturing environment with possible paternalism and a focus on family-centered care, while the adult system places a greater emphasis on patient autonomy. Upon transitioning to adult care, the medical focus shifts from ensuring adequate growth and development to addressing issues such as family planning, fertility, and cancer surveillance. The unfamiliarity and misinterpretation of these differences can lead to non-compliance and the discontinuation of medical care among IBD patients, consequently resulting in a poorer disease outcome and overall health [143, 148, 173].

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2. Objectives

We aimed our research to examine three main questions:

(1) What are the determinants of a successful transitioning process?

(2) What are the short- and long-term effects of the changing process to adult care, including the comparison between transition and self-transfer on the disease activity, course, and patient compliance?

(3) What are the unique characteristics of PIBD patients that require special attention in adult care?

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3. Methods

Our longitudinal, follow-up, controlled observational study incorporated a retrospective and a prospective data collection period, with the aim to analyse the effects of the changing period to adult care, including the comparison of a structured transitional program with self-transfer on the disease course, activity, and compliance of the patients. Furthermore, we examined the determinants of a successful transfer and the special characteristics of the PIBD patients, that require special attention in adult care. The project was carried out in the *Pediatric Center of Semmelweis University* (Budapest, Hungary), in cooperation with the *Department of Surgery, Transplantation, and Gastroenterology* and the *Department of Internal Medicine and Oncology of Semmelweis University*.

The study was performed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

3.1. Study period and data collection

The study period was 20.5 years, between 01.09.2001 and 01.03.2022. We collected data from the medical systems of the participating Clinics and the *eHealth Infrastructure of Hungary*. The data was reviewed retrospectively until 2018, thenceforth prospectively. Detailed information was collected about the *patients* (date of birth, gender, race, other chronic diseases, family history of IBD), *disease* (subtype, phenotype, extent, activity and disease course, EIMs, complications), *treatments* (medical, nutritional, surgeries, hospitalizations, medication side effects), *anthropometrical data* (height, weight, BMI), *patient compliance* and *medication adherence*. The basic data about the patients were reported at the time of diagnosis, whereas data about the disease, treatments, anthropometrics, compliance, and adherence were noted both at the time of the diagnosis and continuously during the visits during the study period.

3.2. Inclusion and exclusion process

The summary of the inclusion and exclusion process can be seen in **Figure 5**.

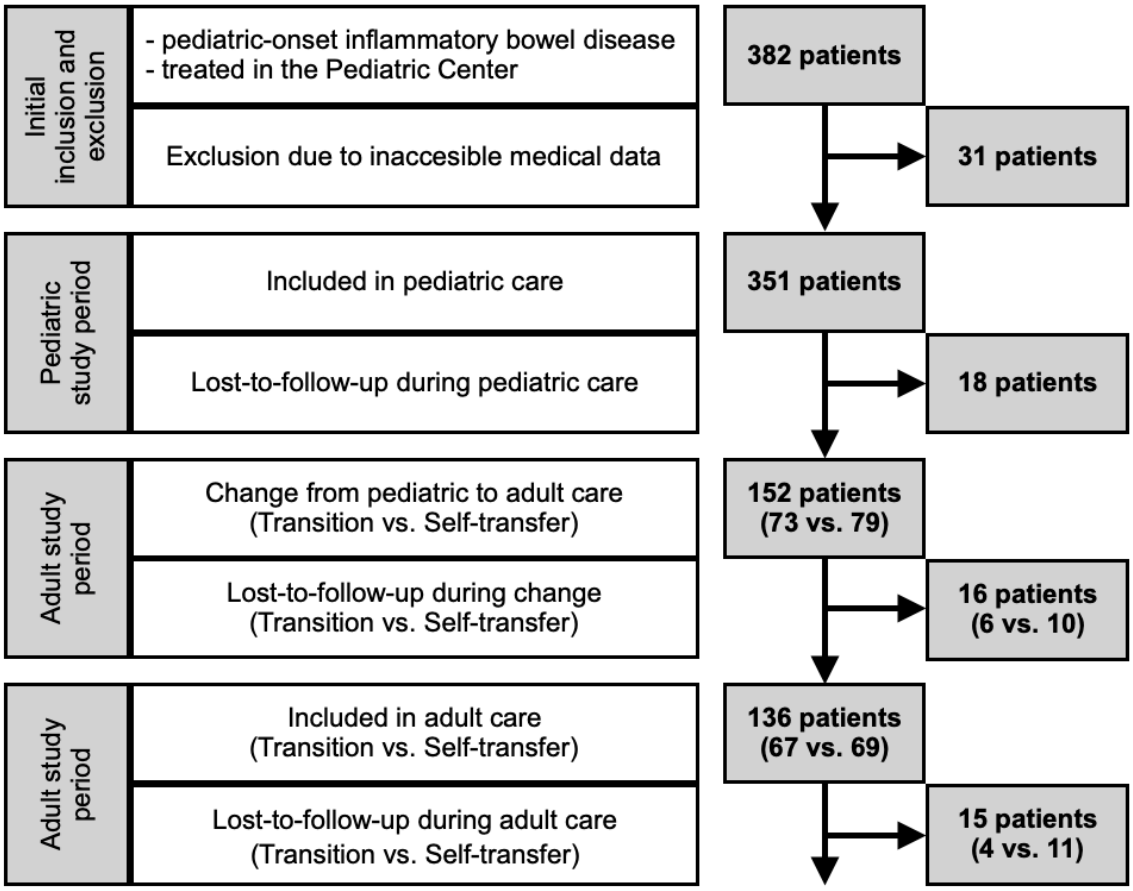

Figure 5. | The inclusion and exclusion process of our study

Inclusion criteria: All 382 PIBD patients (including CD, UC, and IBD-U) treated partially or entirely in our Pediatric Center during the examination period were available for the initial inclusion process in the study.

Exclusion criteria: Due to inaccessible medical data from the study period 31 patients were excluded, resulting in 351 patients being enrolled in our research.

Transition and self-transfer: Of the included 351 patients, 152 were moved to adult care during the examination period, of whom 73 were enrolled in our transitional program, whereas 79 adolescents self-transferred to adult care and served as our control group. Every patient had the opportunity to enroll in the transitional program, but the inclusion

was not mandatory. The patients who decided against the transitional program then self-transferred, with reasons behind their decision as declining to enroll in a structured transition, a completely different timing of their transfer as suggested, or transfer to a hospital not included in our transitional program. There was no significant difference between the two groups considering either of the examined patient-, disease-, or treatment-related variables noted in the data collection section. Both self-transfer and transition were initiated in 2015. Until 2018 the transitional meetings were held irregularly, thereafter monthly.

Addressing the lost-to-follow-up patients: 18 patients discontinued their medical care during pediatric care, 16 during the changing period between the two healthcare systems, and 15 patients after being moved to adult care. As patient compliance and the determinants of a successful transferring process to adult care were among the aims of our study, the lost-to-follow-up patients were examined separately.

3.3. Study design

Our transitional program consisted of an integrated *educational (mentor) program* and a *joint transitional meeting* with a written *handout summary*.

Mentor program: From the age of twelve, patients had the opportunity to be enrolled in our age-appropriate, personalized educational program. The teaching occasions took place before their scheduled visits, to make it accessible for all patients. They could learn in a step-wise manner during these one-by-one meetings from our transitional coordinator about their disease characteristics, the most important diagnostic methods, their medications, possible complications of their disease and non-compliance, family planning, and the effects of alcohol and smoking on their disease course. Our educational program was initiated in 2018.

Last year before moving to adult care: A year before the planned transfer to adult care, we actively started to prepare all of our patients, regardless of their participation in the mentor program. We encouraged them to take more responsibility in handling their disease, we required them to take a more active role during their visits and initiated talks about the differences between the two healthcare systems and the changing process.

During this last year, the scheduled endoscopic procedures were preferably performed with the attendance of both the pediatric and the future adult care providers.

Timing of the transfer: We aimed the transfer after finishing high school, around 18 to 19 years of age, with a disease in stable remission. Special requests from the patients considering the timing of their transfer were also taken into consideration.

Joint transitional meeting, adult healthcare providers: The joint transitional meetings were held in our Pediatric Center, with the attendance of the former pediatric and the future adult care provider, the transitional coordinator, and the patient. In most cases, parents were also present, depending on the request of the patient.

A detailed *handout summary* was prepared for the meeting, which summarised the most important information about the medical history of the patient, as well as the former disease course, treatments, hospitalizations, surgeries, and diagnostic results regarding their inflammatory bowel disease.

At the end of the meeting, the date of the first adult-care visit was planned, as well as the bridging medical therapy during the changing period.

During the examination period of our study, we worked together with three adult gastroenterologist specialists, from two adult IBD Centers in Budapest, Hungary. There were both male and female adult physicians in our transition team, so we could recommend a physician with the same gender to each of the patients if requested.

3.4. Statistical analysis

The statistical tests were performed and figures were created using GraphPad Prism version 10.0.2 for macOS, GraphPad Software, Boston, Massachusetts USA. $P < 0.05$ was considered significant.

We employed Fisher's exact test to assess the association between categorical variables. The resulting odds ratio (OR) with a 95% confidence interval (CI) was reported. To examine the differences between continuous variables, Welch's test was used, and in the case of non-normal distributions, the Mann-Whitney test was employed. The specific test names can be found in the figure descriptions. The Cox proportional hazard model was applied to evaluate the impact of various variables on the occurrence of the

outcome variable. The results of the Cox proportional hazard model were reported as OR with a 95% CI. Both univariate and multivariate modeling were conducted using the enter method. Dichotomous variables were encoded as 0/1 during model development. In the construction of Kaplan-Meier curves, cumulative events were plotted, and the curves were compared using the log-rank test. The resulting hazard ratios (HR) with 95% CI were reported.

3.5. Applied definitions and scores

Disease activity: To exclude intraobserver differences between the participating physicians, for documenting disease activity age- and disease-subtype-specific, validated scores were applied. In pediatric care, these were PCDAI [67] and PUCAI [193], while in adult care CDAI [66] and Mayo score [194], for CD and UC patients, respectively. For IBD-U patients the applied scoring system was determined based on the decision of the healthcare provider. The cut-off values for the different activities were defined based on the official recommendation of the scoring systems.

Relapse: Relapse was defined as a significant worsening of the disease activity and/or a reported moderate or severe disease activity. Both the terms significant change and disease activity were defined based on the above-mentioned disease activity scores.

Disease extent and phenotype: The Paris classification was used [61].

Hospitalizations and surgeries: Only the IBD-related interventions were analysed.

Medical and nutritional therapy: Examined medical treatments included steroids, biologics, aminosalicylates, antibiotics, and immunomodulators (e.g. azathioprine, methotrexate) taken either as maintenance therapy or for remission induction for IBD. EEN, Crohn’s disease exclusion diet (CDED), and tube feeding were considered and noted as nutritional treatments. Only the IBD-related treatments were analysed.

Successful transfer to adult care: A successful transfer to adult care was defined based on the ECCO proposal as continuity of care, determined as the patient attending at least one planned adult care visit during the examination period. Emergency room visits without further follow-up were not considered a successful transfer.

Lost-to-follow-up patients: During pediatric care, if at least a year elapsed since their last attended visit and the patients did not recontinue their medical care during the follow-up period they were considered lost-to-follow-up.

Those patients, who during their last pediatric visit took part in a transitional meeting or expressed their will to self-transfer to adult care, but during the examination period neither attended any adult care visit nor requested prescriptions for their medications and at least a year elapsed since their last pediatric visit were considered lost-to-follow-up during the changing period.

Of those patients, who attended at least one planned visit in adult care, but then discontinued their medical care for more than a year, neither requested medications nor attended any more visits until the end of the study period were considered lost-to-follow-up during adult care. Exception: some adult healthcare providers requested visits with an active disease, without any regular planned visits, these patients were not considered lost-to-follow-up, if a year elapsed since their last visit.

Non-compliance: The regular visits during pediatric care took place every 3 to 4 months for CD and 4 to 6 months for UC patients, therefor after 190 days of non-appearance to visits patients were reported non-compliance. Furthermore, non-compliance was documented when the patients showed non-adherence to their medications or discontinued them.

3.6. Ethical considerations

Our study was approved by the Semmelweis University Clinical Research Ethics Committee. The de-identification of data ensured the anonymity of the patients.

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4. Results

4.1. Main characteristics

351 PIBD patients were eligible to be enrolled in our study, whose characteristics can be seen in **Table 2**. The number of patients diagnosed with the different IBD subtypes yearly during the examination period can be seen in **Figure 6**.

Table 2. | Main characteristics of the patients enrolled in our study

Category	Patient data
Gender (female), n (%)	181 (51.5%)
Race (caucasian), n (%)	351 (100%)
Age at diagnosis, mean ± SD (years)	11.99 ± 4.19
Disease subtype **- Crohn's disease**, n (%) **- Ulcerative colitis**, n (%) **- Inflammatory bowel disease unclassified (IBD-U)**, n (%)	 187 (53.28%) 117 (33.33%) 47 (13.39%)
Very early onset inflammatory bowel disease (VEO-IBD), n (%)	41 (11.68%)
Disease duration at the end of the study period, mean ± SD (years)	6.51 ± 4.14
Family history positivity to inflammatory bowel disease, n (%)	79 (22.51%)

SD - standard deviation

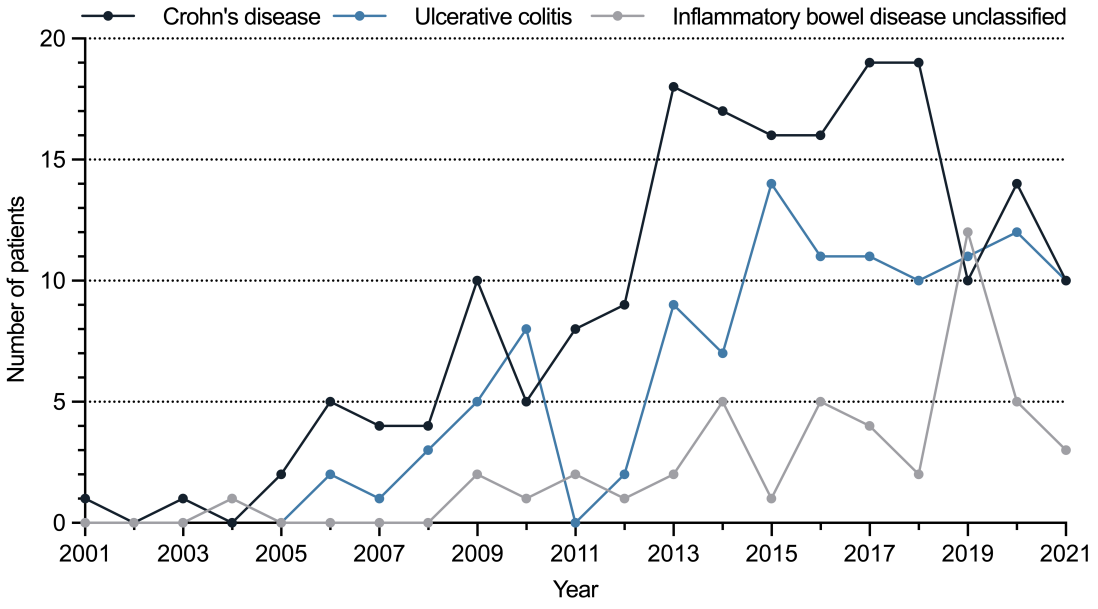

Figure 6. | The yearly number of patients newly diagnosed with the different inflammatory bowel disease subtypes enrolled in our study

The initially determined **subtype was changed** in 13.11% of the patients (n = 46), with a mean disease duration of 4.05 ± 3.72 years. After being moved to adult care 5.15% of the patients (n = 7) had a diagnosis change, after a mean of 1.39 ± 0.99 years spent in adult care. The primary UC diagnosis changed in 24.79% of the patients, which was significantly higher than the proportion of either the CD (4.81%) or the IBD-U (17%) patients ($p < 0.0001$ and $p = 0.0086$) (**Figure 7.**).

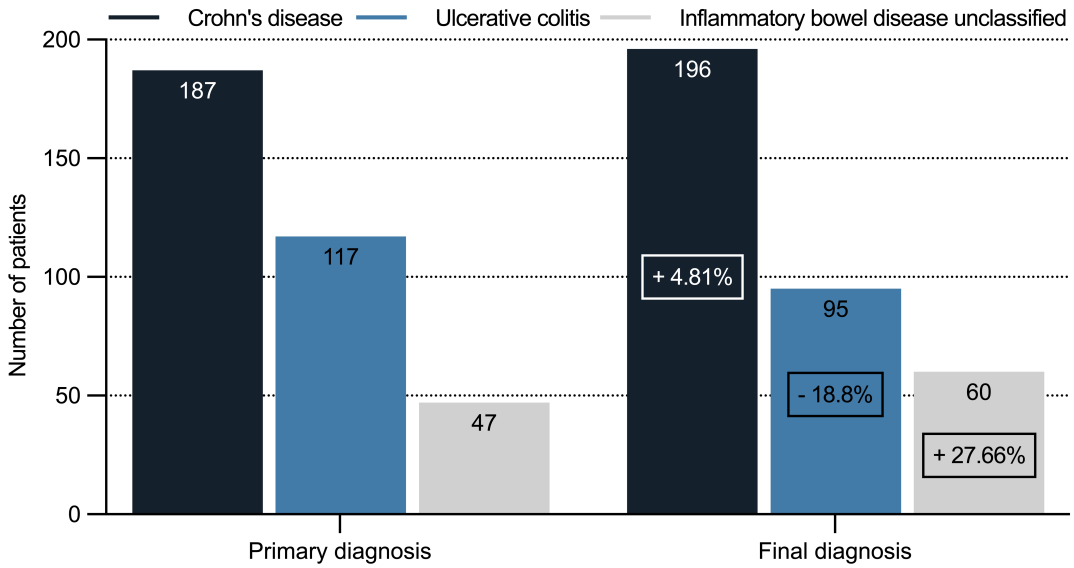

Figure 7. | Diagnosis changes regarding the inflammatory bowel disease subtype

The **Paris classification** regarding the disease extent and behaviour was documented in 295 patients (84.05%).

The most commonly affected localisations in CD were *ileocolonic* (57.81%) and *upper gastrointestinal* (57.29%) with a 31,77% of the patients having either *stricturing or fistulising* phenotype and with 15.63% having a *perianal manifestation*.

The most common extent of UC was *pancolitis* (55%), followed by *left-sided colitis* (21.36%), with 66.02% of the UC patients having a *non-severe* disease behaviour.

The disease extent was documented in more than one endoscopic examination for 110 CD and 23 UC patients, of whom the disease became more extensive during the study period in 34.55% (n = 38) and in 30.44% (n = 7), respectively.

4.2. Mentor program

During the study period, 43 patients enrolled in the educational program (14.93%), of whom 11 patients (25.58%) already joined at the time of their diagnosis. The main characteristics of these can be seen in **Table 3**.

Table 3. | Main characteristics of the patients enrolled in our mentor program

Category	**Patient data**
Enrolled patients	
- from all patients (n = 351), n (%)	43 (12.25%)
- from the patients eligible for enrollment (n = 288), n (%)	43 (14.93%)
Gender (female), n (%)	24 (55.81%)
Age at enrollment, mean ± SD (years)	15.41 ± 0.85
Disease duration at enrollment, mean ± SD (years)	2.71 ± 3.32
Disease subtype	
- Crohn's disease, n (%)	21 (48.84%)
- Ulcerative colitis, n (%)	9 (20.93%)
- Inflammatory bowel disease unclassified, n (%)	13 (30.23%)
Transition / Self-transfer characteristics	
- Moved to adult care, n (%)	17 (39.54%)
- Transition, n (%)	10 (58.82%)
- Self-transfer, n (%)	7 (41.18%)

SD - standard deviation

4.3. Transition and self-transfer to adult care

During the examination period, **43.3% (n = 152) of all patients got moved to adult care, of whom 73 (48%) enrolled in our transitional program and 79 (52%) self-transferred to adult care**. Their main characteristics can be seen in **Table 4.**, and the yearly number of patients moved to adult care in **Figure 8**. With multivariable logistic regression, none of the examined variables showed to be a significant determinant for patients to be more likely to be enrolled in the transition or to self-transfer, including patient variables (gender, chronic diseases, age, disease duration, compliance), disease variables (subtype, extent, phenotype, activity, EIMs, complications), and treatment variables (medications, hospitalizations, surgeries, side effects).

A significantly **higher proportion of the transitioned patients had their disease in remission at the time of transfer** to adult care than the self-transferred patients (91.04% vs. 68.16%, $p = 0.0012$; OR 0.2101 [95% CI: 0.08115 - 0.5472]). At the first

adult visit, the proportion of patients with their disease in remission was 83.58% among the transitioned and 69.57% among the self-transferred patients (*p = 0.0691*). **The mean time elapsed between the last pediatric and the first adult care visit was significantly higher in the self-transferred group than in the transitional group** (361.95 ± 476.01 days vs. 141.44 ± 158.43 days, *p = 0.0002)*.

After being moved to adult care, the mean **follow-up time** was 3.04 ± 1.67 years, accounting for 3.73 ± 1.72 years in the self-transferred and 2.13 ± 1.27 years in the transitioned group ($p < 0.0001$).

Table 4. | Main characteristics of the patients moved to adult care

	Moved to adult care (n = 152)	**Self-transfer** (n = 79)	**Transition** (n = 73)	**P-value**
Gender (female), n (%)	78 (51.32%)	44 (55.7%)	34 (46.58%)	*0.3299*
Disease subtype				*0.5950*
- **Crohn's disease**, n (%)	99 (65.13%)	52 (65.82%)	47 (64.38%)	
- **Ulcerative colitis**, n (%)	38 (25%)	21 (26.58%)	17 (23.29%)	
- **IBD-U**, n (%)	15 (9.86%)	6 (7.6%)	9 (12.33%)	
Transfer characteristics				
- **Disease duration**, mean ± SD (years)	5.78 ± 3.62	5.49 ± 3.43	6.16 ± 3.75	*0.2461*
- **Age**, mean ± SD (years)	19.03 ± 1.08	18.75 ± 1.02	19.32 ± 1.07	*0.3693*

IBD-U - inflammatory bowel disease unclassified, SD - standard deviation

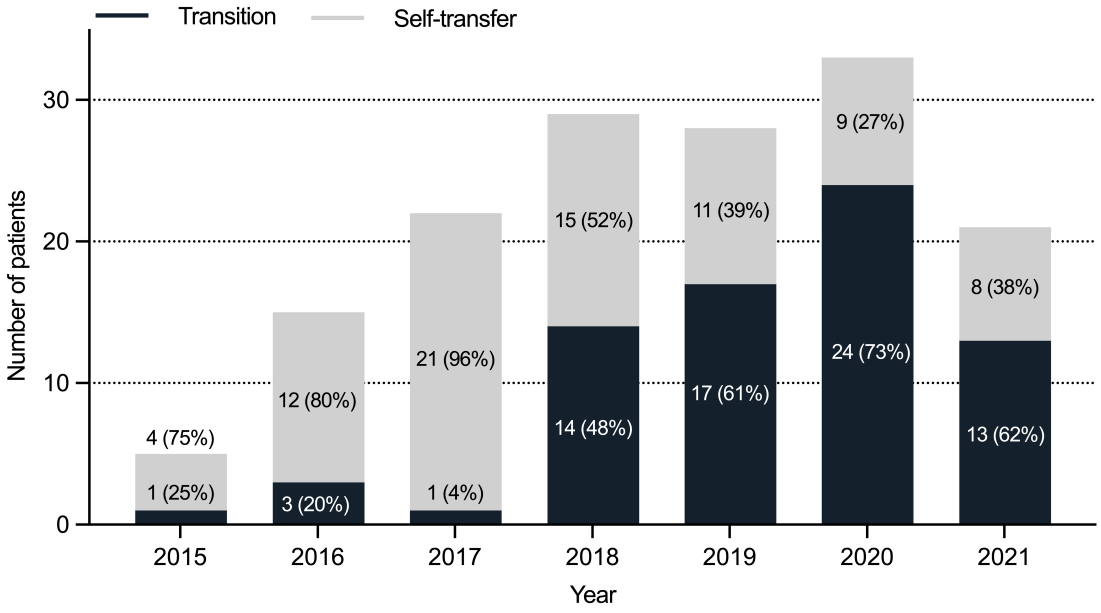

Figure 8. | The yearly number of patients moved to adult care

4.4. Lost-to-follow-up patients, discontinuing medical care

During the study period, 49 patients discontinued their medical care, accounting for 13.96% of all patients. The 5.13% **lost-to-follow-up rate reported in pediatric care significantly increased after being transferred to adult care**, affecting every fifth patient (20.4%, *p ‹ 0.0001*, OR 5.331 [95% CI: 2.900 to 9.798]). **The rate of discontinuation of care was the highest during the changing period from the pediatric to the adult health care system**, reaching 12.66% of all patients, accounting for 8.22% of the transitioned and 10.53% of the self-transferred patients (*p = 0.4540*; OR 0.6179 [95% CI: 0.2109 - 1.6650]). The characteristics of the lost-to-follow-up patients can be seen in **Table 5**.

Table 5.| Main characteristics of lost-to-follow-up patients during the different periods of care

	Pediatric care	***P-value***	**Transferring period**	***P-value***	**Adult care**	***P-value***
Number of patients, n (%)	18 (5.13%)	-	16 (12.66%)	-	15 (11.03%)	-
Gender: female, n (%)	7 (38.89%)	*0.4055*	14 (87.5%)	*0.0027*	6 (40.0%)	*0.4985*
Disease subtype		*0.3423*		*0.8022*		*0.0527*
- Crohn's disease, n (%)	12 (66.67%)		11 (68.75%)		9 (60,0%)	
- Ulcerative colitis, n (%)	4 (22.22%)		3 (18.75%)		5 (33.33%)	
- IBD-U, n (%)	2 (11.11%)		2 (12.5%)		1 (6.67%)	
Transitioned, n (%)	-		6 (37.5%)	*0.4352*	4 (26.67%)	*0.0635*
Disease duration, mean ± SD (years)	2.99 ± 3.09	-	4.70 ± 4.09	-	7.67 ± 3.21	-
Age, mean ± SD (years)	15.8 ± 3.33	-	18.62 ± 0.93	-	21.28 ± 1.31	-

IBD-U - inflammatory bowel disease unclassified, SD - standard deviation

Transition showed to be a significant protective factor for continuing care, as after the initiation of the healthcare provider changes 13.7% (n = 10) of the transitioned and 26.58% (n = 21) of the self-transferred patients discontinued their medical care (*p = 0.0367*; OR 0.4384 [95% CI: 0.193 - 1.018]. With Kaplan-Meier analysis, compared to the transitioned group the **self-transferred patients were shown to be at a 1.59-fold higher risk of discontinuing their medical care after leaving pediatric care**, including both the changing and the adult healthcare period (*p = 0.0489*) (**Figure 9.**).

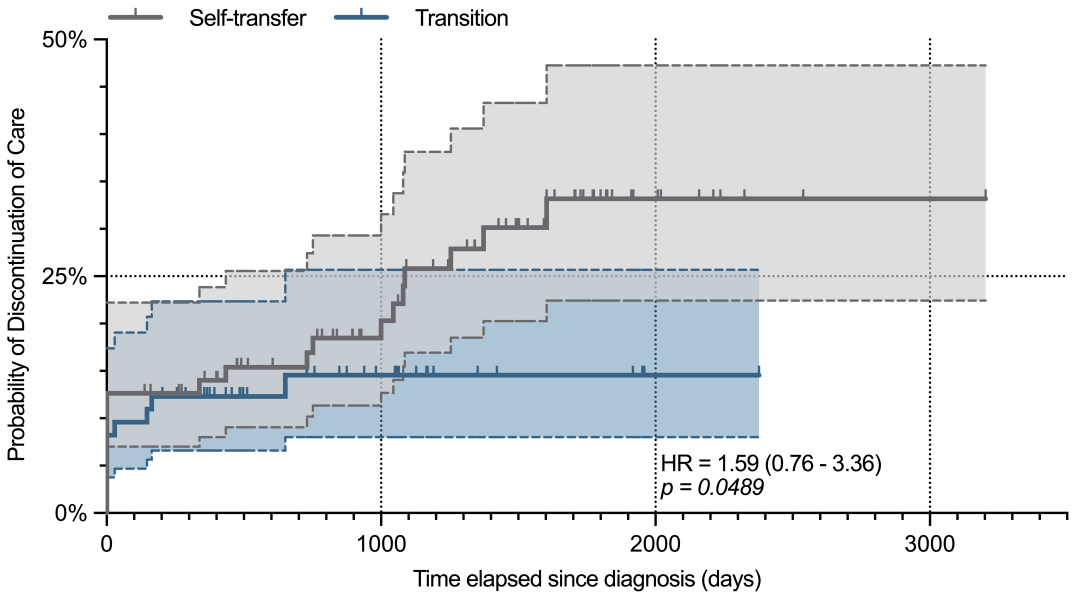

Figure 9. | Kaplan-Meier curve analysis of the self-transferred and transitioned patients regarding the probability of discontinuation medical care *(HR - hazard ratio)*
The shaded area represents the 95% confidence interval around the Kaplan-Meier survival estimates.

The mean time elapsed since loss of care (last attended visit) was significantly higher among the self-transferred patients compared to the ones enrolled in our transitional program (2.71 ± 1.48 years vs. 1.65 ± 0.90 years, *p = 0.0490*).

After performing multiple univariate and multivariate logistic regressions examining the risk factor for discontinuation of medical care (**Table 6.**), the **higher number of days being hospitalized yearly showed to be a risk factor during pediatric care** (17.85 ± 23.1 days vs. 9.27 ± 10.2 days, *p = 0.014*; OR 1.036 [95% CI: 0.010 - 0.062]). **Female gender was a risk factor during the changing period between the two healthcare systems**, with 87.5% (n = 14) of the lost patients being female (*p = 0.010*). This accounts for 17.95% of all female patients being moved to adult care compared to 2.7% of the male patients being lost (*p = 0.0027*; OR 7.875 [95% CI: 1.946 - 35.61]). **The only significant protective factor for continuing care in the adult system was the enrollment in our transitional program** (*p = 0.0007*), with a lost-to-follow-up-rate of 5.97% (n = 4) vs. 15.94% (n = 11) among the transitioned and self-transferred patients.

Treatment with biologics was a protective factor for continuing care both during pediatric care and the changing period (*p = 0.028* and *p = 0.038*), but after multivariate analysis, it failed to reach the level of significance.

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Table 6. | Multivariate logistic regression for discontinuation of care

Multivariate models	**Pediatric care**		**Transferring / transitioning period**		**Adult care**	
Variables	**OR [95% CI]**	***P-value***	**OR [95% CI]**	***P-value***	**OR [95% CI]**	***P-value***
Gender (female)	0.918 [-1.293 - 1.122]	*0.890*	10.410 [0.553 - 4.132]	***0.010***	0.554 [-2.019 - 0.838]	*0.418*
Compliance problems	1.322 [-1.623 - 2.182]	*0.774*	1.926 [-1.079 - 2.389]	*0.459*	$7.9240x10^{+7}$ [-6544.17 - 6580.55]	*0.996*
Coexisting chronic disease	0.424 [-2.288 - 0.573]	*0.424*	0.322 [-3.142 - 0.874]	*0.268*	0.381 [-2.716 - 0.787]	*0.281*
Family history positivity to IBD	1.774 [-0.774 - 1.920]	*0.404*	2.508 [-0.796 - 2.634]	*0.293*	1.005 [-1.883 - 1.893]	*0.996*
Disease activity (% of active disease)	0.615 [-3.771 - 2.800]	*0.772*	8.130 [-2.129 - 6.320]	*0.331*	0.230 [-5.828 - 2.884]	*0.508*
IBD-related complications	$6.168x10^{7}$ [-2669.66 - 2705.54]	*0.990*	0.529 [-3.083 - 1.809]	*0.610*	2.341 [-1.483 - 3.184]	*0.475*
Disease subtype (IBD-U)	0.404 [-3.069 - 1.254]	*0.411*	4.560 [-0.754 - 3.789]	*0.190*	0.673 [-3.364 - 2.571]	*0.793*
Disease subtype (UC)	0.307 [-2.898 - 0.534]	*0.177*	0.849 [-2.073 - 1.746]	*0.867*	1.549 [-1.431 - 2.306]	*0.646*
Extraintestinal manifestations	0.506 [-1.974 - 0.610]	*0.301*	0.780 [-2.059 - 1.562]	*0.788*	1.423 [-1.381 - 2.087]	*0.690*
Age at the time of diagnosis	0.893 [-0.314 - 0.087]	*0.267*	$4.269x10^{-50}$ [-317.107 - 89.751]	*0.273*	$1.690x10^{-45}$ [-276.675 - 70.491]	*0.244*
Biologics	0.287 [-3.147 - 0.647]	*0.197*	0.200 [-3.679 - 0.456]	*0.127*	1.251 [-1.782 - 2.231]	*0.827*
Aminosalicylates	1.182 [-1.358 - 1.693]	*0.830*	0.732 [-3.803 - 3.180]	*0.861*	$2.187x10^{+8}$ [-9452.31 - 9490.72]	*0.997*
Immunomodulators (AZA, MTX)	0.505 [-2.191 - 0.825]	*0.375*	15.624 [-0.195 - 5.692]	*0.067*	0.389 [-2.921 - 1.033]	*0.349*
Steroids	0.505 [-2.051 - 0.685]	*0.328*	0.259 [-3.306 - 0.602]	*0.175*	0.372 [-2.822 - 0.844]	*0.290*
Side effects of IBD medications	0.812 [-1.763 - 1.345]	*0.792*	0.335 [-2.959 - 0.773]	*0.251*	0.461 [-2.468 - 0.919]	*0.370*
Surgeries	0.248 [-4.513 - 1.725]	*0.381*	0.561 [-3.574 - 2.418]	*0.705*	0.284 [-3.680 - 1.163]	*0.308*
Hospitalizations (days / year)	1.056 [0.011 - 0.097]	***0.014***	1.021 [-0.086 - 0.128]	*0.697*	1.116 [-0.050 - 0.270]	*0.179*
Mentor program	0.439 [-3.054 - 1.407]	*0.469*	1.663 [-1.481 - 2.499]	*0.616*	$9.395x10^{-9}$ [-7118.96 - 7118.96]	*0.996*
Age at transfer	-	-	$1.571x10^{49}$ [-89.918 - 316.48]	*0.275*	$1.020x10^{+45}$ [-70.004 - 277.28]	*0.242*
Disease activity at transfer	-	-	0.935 [-0.210 - 0.076]	*0.357*	0.926 [-0.221 - 0.068]	*0.300*
Disease duration at transfer	-	-	$3.997x10^{-50}$ [-317.169 - 89.68]	*0.273*	$1.542x10^{-45}$ [-276.82 - 70.45]	*0.244*
Transition vs. Self-transfer	-	-	0.479 [-2.302 - 0.828]	*0.356*	0.091 [-4.145 - -0.641]	***0.007***

OR - odds ratio, CI - confidence interval, IBD - inflammatory bowel disease, IBD-U - inflammatory bowel disease unclassified, UC - ulcerative colitis, AZA - azathioprine, MTX - methotrexate

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4.5. Disease activity

The mean and median time patients spent with each disease activity, as well as with a disease in remission in both adult and pediatric care can be seen in **Figure 10**.

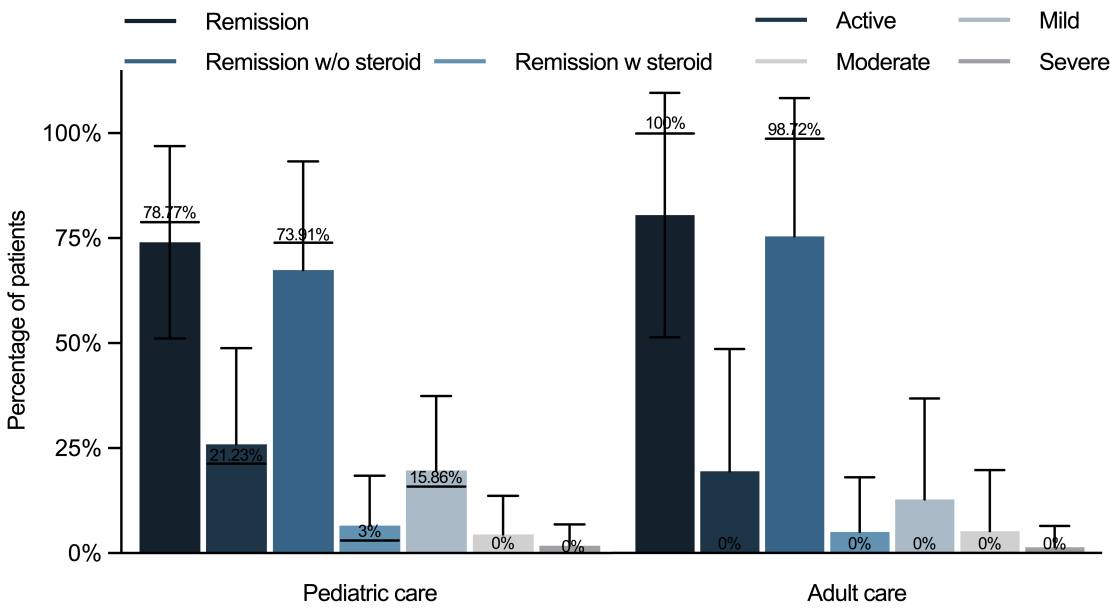

Figure 10. | Disease activity of the patients in pediatric and adult care

(mean with SD and median) (w/o - without, w - with)

After being moved to adult care, **48.53% (n = 66) of the patients experienced a relapse during the follow-up period**, accounting for **significantly more patients of the self-transferred group than of the transitioned patients** (59.42% vs. 37.31%, *p = 0.0108*; OR 2.460 [1.258 - 4.993]). With Kaplan-Meier curve analysis (**Figure 11.**) this difference was also shown to be significant, resulting in a **1.88-fold increased risk of relapse among the self-transferred patients** compared to the transitioned group during the same timeframe in adult care (95% CI 1.13 - 3.09, *p = 0.013*). The mean time elapsed until the first relapse since the last pediatric visit was 358.68 ± 343.68 days, without a significant difference between the self-transferred and the transitioned group (*p = 0.6116*).

The mean follow-up time among the patients who did not experience a relapse was 2.36 ± 1.36 years.

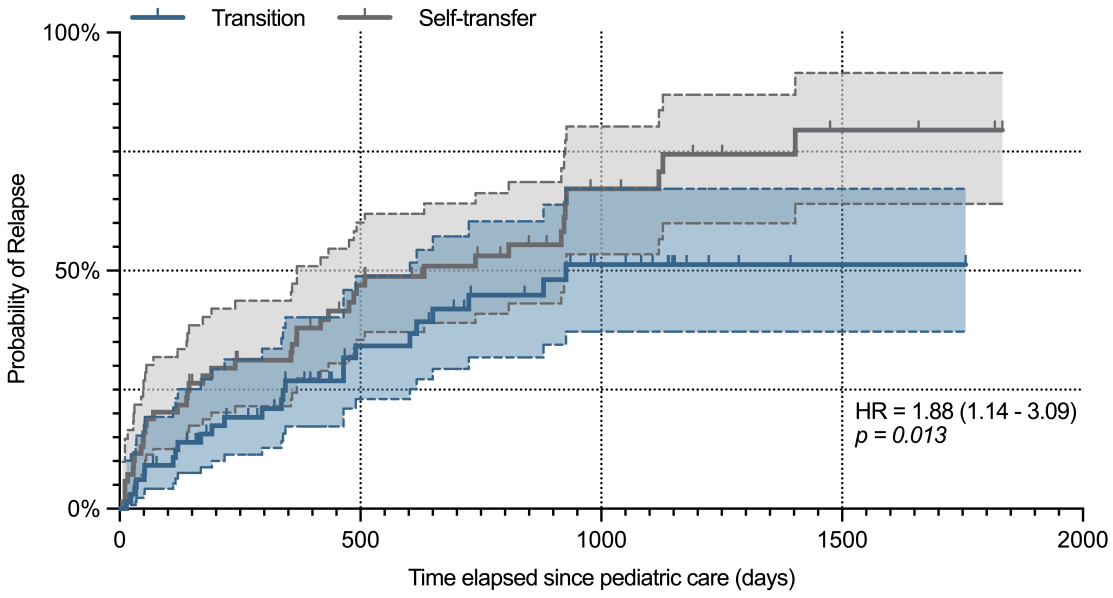

Figure 11. | Kaplan-Meier curve analysis of the self-transferred and transitioned patients regarding the probability of relapse *(HR - hazard ratio)*

The shaded area represents the 95% confidence interval around the Kaplan-Meier survival estimates.

The transitioned patients spent a significantly higher proportion of time with a disease in remission in adult care compared to the self-transferred patients (83.63% ± 28.5% vs. 77.47% ± 29.65%, *p = 0.0339*; OR 0.7703 [0.7448 - 0.7967]). Additionally, **the time while the disease of the self-transferred patients had severe disease activity was significantly higher** compared to the transitioned patients (1.66% ± 4.88% vs. 1.15% ± 5.27%, *p = 0.0204*). To exclude that the baseline disease activity was already higher among the self-transferred patients, we also compared the disease activity of the 2 groups during pediatric care. There was no significant difference either between the proportion of time spent in remission (*p = 0.1337*) or with severe disease activity (*p = 0.5390*) in pediatric care, therefore in our study **transition was shown to be a protective factor against serious disease activity, as well as a significant determinant of disease remission in adult care** (**Figure 12./ A. and B.**).

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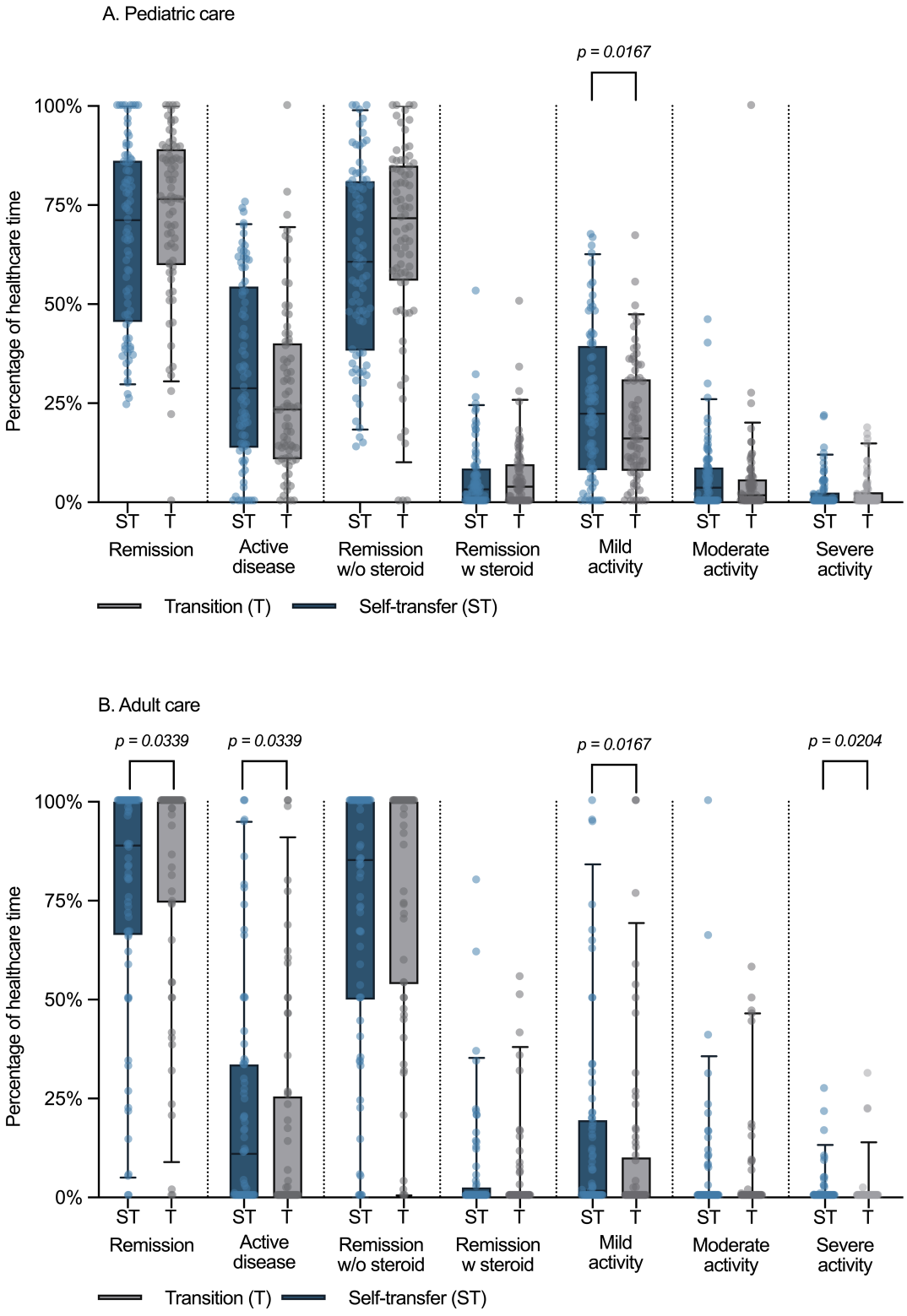

Figure 12./ A. and B. | Disease activity of the self-transferred and transitioned patients in pediatric and in adult care *(w - with, w/o - without)*

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4.6. Patient compliance

Compliance problems were reported in 69.52% (n = 244) of all patients, with a mean of 3.03 ± 2.57 occasions per person. **The non-compliance rate was increasing with both age and disease duration**, exceeding 50% non-compliance rate by the time of transferring to adult care (**Figure 13./ A. and B.**).

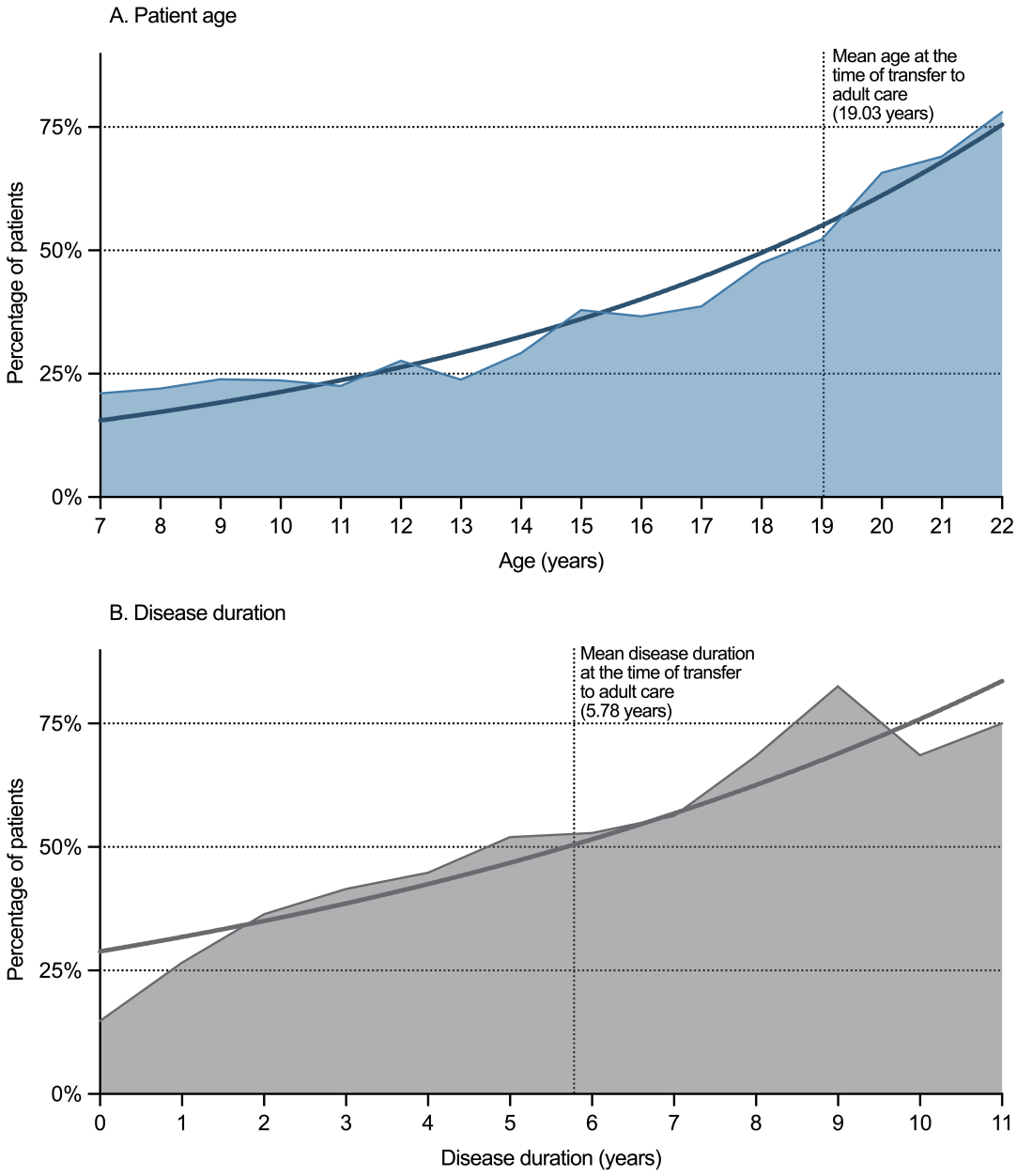

Figure 13./ A. and B. | Non-compliance rate of all patients regarding age and disease duration with logarithmic trend line

After being moved to adult care the compliance of all patients significantly decreased (38.46% vs. 28.95%, *p = 0.0002*; OR 0.4148 [0.2591 - 0.6666]). The non-compliance rate was 77.5% among the self-transferred and 63.01% among the transitioned patients (*p = 0.0534*), resulting in a **significantly higher adherence to medications among the transitioned group compared to the self-transferred patients** (31.88% vs. 16.42% non-adherence rate, *p = 0.0455*; OR 2.383 [CI 95%: 1.042 - 5.156]).

Non-frequent clinical attendance accounted for the majority of the non-compliance in both pediatric and adult care (68.08% and 78.8%), followed by non-adherence to medications (26.49% and 20.74%). Regarding medication non-adherence, 55% of the patients discontinued all of their medications, with the highest discontinuation rate for *azathioprine* (16.88%) and the lowest for *biologics* (3.75%). Interestingly, the most common therapeutic method that patients refused was also *biologics* (31.25%), followed by *EEN* (15.63%). **During the changing period to adult care, 8.89% of all patients discontinued their medications**, accounting for 10.94% of the self-transferred and 7.04% of the transitioned patients (*p = 0.2900*), with the majority discontinuing *aminosalicylates* (50%) or *azathioprine* (33.33%).

4.7. Healthcare providers and visits

The mean time elapsed between visits was significantly longer in adult care than in pediatric care (165.53 ± 202.1 days vs. 92.28 ± 84.35 days, *p ‹ 0.0001*), without a significant difference between the transitioned and self-transferred patients (*p = 0.2510*). **The transitioned patients continued their medical care during the majority (96.06%) of the follow-up period in IBD Centers**, classified as healthcare providers specialized in the treatment of IBD patients, which rate was significantly lower among the self-transferred patients (36.7%, *p ‹ 0.0001*; OR 0.0238 [0.0218 - 0.0261]). The proportion of the patients, who **changed their adult care physician** at least once during the follow-up period was 21.74% of the self-transferred and 8.96% of the transitioned patients (*p = 0.0564*).

4.8. Hospitalizations and surgical interventions

Hospitalizations

As the initial diagnostic examinations were performed as in-patient tests, the hospitalization rate was 100% during pediatric care, and decreased to 20.59% in adult care, accounting for 16.42% of the transitioned and 24.64% of the self-transferred patients (*p = 0.2908*, OR 1.396 [95% CI: 0.6258 - 3.102]). The mean time spent in the hospital because of IBD-related reasons years was 6.51 ± 7.20 days in pediatric and 4.35 ± 4.71 days in adult care yearly. The reasons for hospitalizations and the proportion of affected patients in both pediatric and adult care can be seen in **Table 7**.

During pediatric care, 3.7% of all patients (n = 13) required intensive care treatment, for IBD-related complications (60%), surgeries (15%), and IBD relapses (15%). During the follow-up period in adult care only one patient was admitted to the intensive care unit, she was a female with CD, self-transferred to adult care, and needed intensive care treatment after an emergency bowel resection surgery.

Table 7. | Reasons of hospitalisations and the proportion of affected patients in pediatric and adult care

	Pediatric care (n = 351)*		**Adult care** (n = 136)	
	Hospitalizations, n (%)	**Affected patients**, n (%)	**Hospitalizations**, n (%)	**Affected patients**, n (%)
Relapse	421 (29.5%)	154 (43.88%)	19 (31.67%)	15 (11.03%)
Surgery	48 (3.36%)	31 (8.83%)	20 (33.33%)	14 (10.29%)
Endoscopic procedures	369 (25.86%)	177 (50.43%)	3 (5%)	3 (2.21%)
Biological therapy	157 (11%)	74 (21.08%)	1 (1.167%)	1 (0.74%)
IBD-related other diseases	47 (3.29%)	16 (4.56%)	9 (15%)	1 (0.74%)
IBD-related compliactions	75 (5.26%)	34 (9.69%)	8 (13.33%)	4 (2.94%)
Medication side effects	19 (1.33%)	18 (5.13%)	0 (0%)	0 (0%)

**excluding the initial diagnostic hospitalizations, IBD - inflammatory bowel disease*

Surgical interventions

During pediatric care, **15.01% of our patients required surgery** (n = 53), a mean of 1.89 times per person, with 25.74% of these procedures being emergency interventions.

Six patients (1.71%) required surgery already at the time of diagnosis. The mean age of patients at the time of the first surgical intervention was 14.56 ± 3.76 years, with a mean disease duration of 2.79 ± 2.94 years. The surgical rate was significantly higher among the CD patients than either among the IBD-U or the UC patients (23.98% vs. 6.67% vs. 2.11%, $p = 0.0028$ and $p < 0.0001$).

During the follow-up period in adult care, 12.5% of the patients required surgical intervention, accounting for 13.04% of the self-transferred and 11.94% of the transitioned patients ($p = 1.0$), resulting in a mean of 1.82 surgery per person. 22.58% of these procedures were emergency interventions. The mean time elapsed from the last pediatric visit until the first surgical intervention in adult care was 1.86 ± 1.5 years, without a significant difference between the self-transferred and the transitioned group ($p = 0.8245$). The most common surgical interventions both in pediatric and adult care can be seen in **Figure 14**.

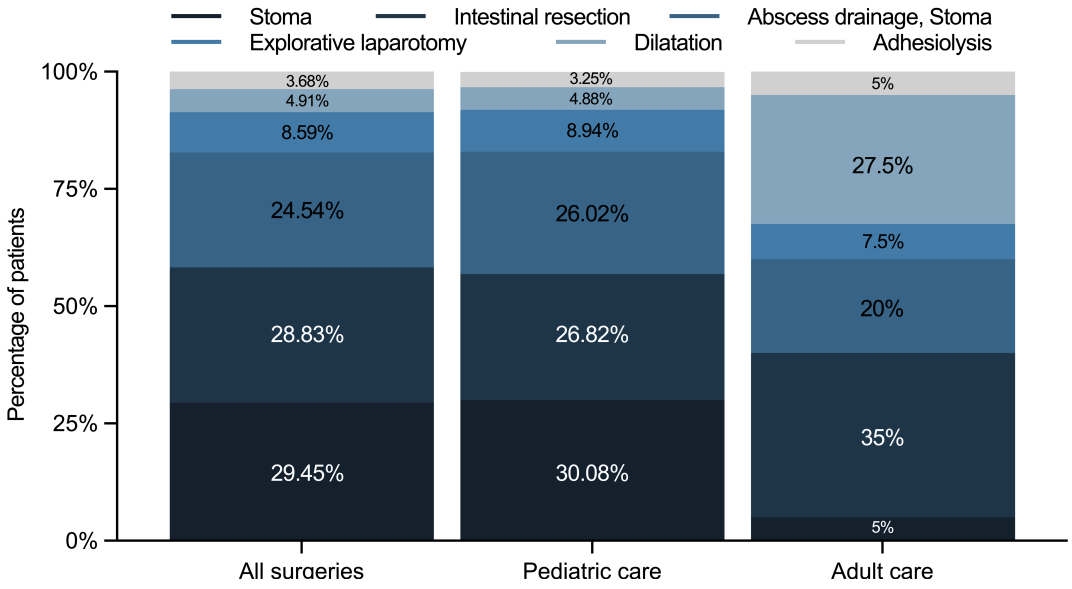

Figure 14. | Surgical interventions in adult and pediatric care

The most common **resection surgeries** were *ileocaecal resection* (43.86%), followed by *total colectomy* (19.3%) and *right hemicolectomy* (19.3%). The reasons behind an **explorative laparotomy** were *intraabdominal abscesses* (40%), *peritonitis of unknown origin* (33.33%), *intestinal perforation* (20%), and *gastrointestinal bleeding* (6.67%).

4.9. Extraintestinal manifestations

EIMs were reported in 70.66% (n = 248) of all patients, with 10.92% (n = 37) having them already at the time of their IBD diagnosis. The proportion of affected patients was the highest among the ones with CD (75.51%), followed by the IBD-U (70%) and the UC (61.05%) patients. Of the 22 different EIMS reported during the examination period, *musculoskeletal* (46.97%) and *"general"* (33.88%) complaints were the most common, with the symptoms being *arthralgia* (45.34%) and *fever* (33.88%).

4.10. IBD-related complications

IBD-related complications were reported in 23.36% of all patients (n = 218), with a mean of 3.02 ± 3.59 complications per person. The mean age at the time of the appearance of complications was 15.64 ± 4.5 years, with a mean disease duration of 4.83 ± 4.13 years. The lowest complication rate was seen among the UC patients (11.58%), with a significant difference compared to both the CD (28.06%) and the IBD-U patients (26.67%) ($p = 0.0016$ and $p = 0.0282$).

A severe disease course resulted in complications in 77.49% of the cases, followed by 10.49% due to treatment, and in 11.69% both played a role. **Hospitalization was necessary in 51.24% of the cases, with a significantly higher surgical rate in adult care compared to pediatric care** (30% vs. 12%; $p = 0.0255$; OR 0.3475 [0.151 - 0.8323]). The most common complications were *severe anemia* (43.55%), *osteoporosis* (9.27%), and *intraabdominal abscess* (9.27%). Altogether 16 different complications were categorized as severe, being reported 64 times, accounting for 25.8% of all cases.

Bone densitometry was performed in 77.49% of our patients (n = 272). **Bone density was decreasing with both age and longer disease duration, with most patients being at high risk for low bone density at the time of transfer** (**Figure 15./ A. and B.**). The mean age of patients with osteopenia was 15.52 ± 3.32 years with a mean disease duration of 3.69 ± 2.98 years and 16.44 ± 2.27 years of age and 6.10 ± 4.37 years disease duration for **osteoporosis**. Pathologic fractures were reported in 5 patients, on 6 occasions.

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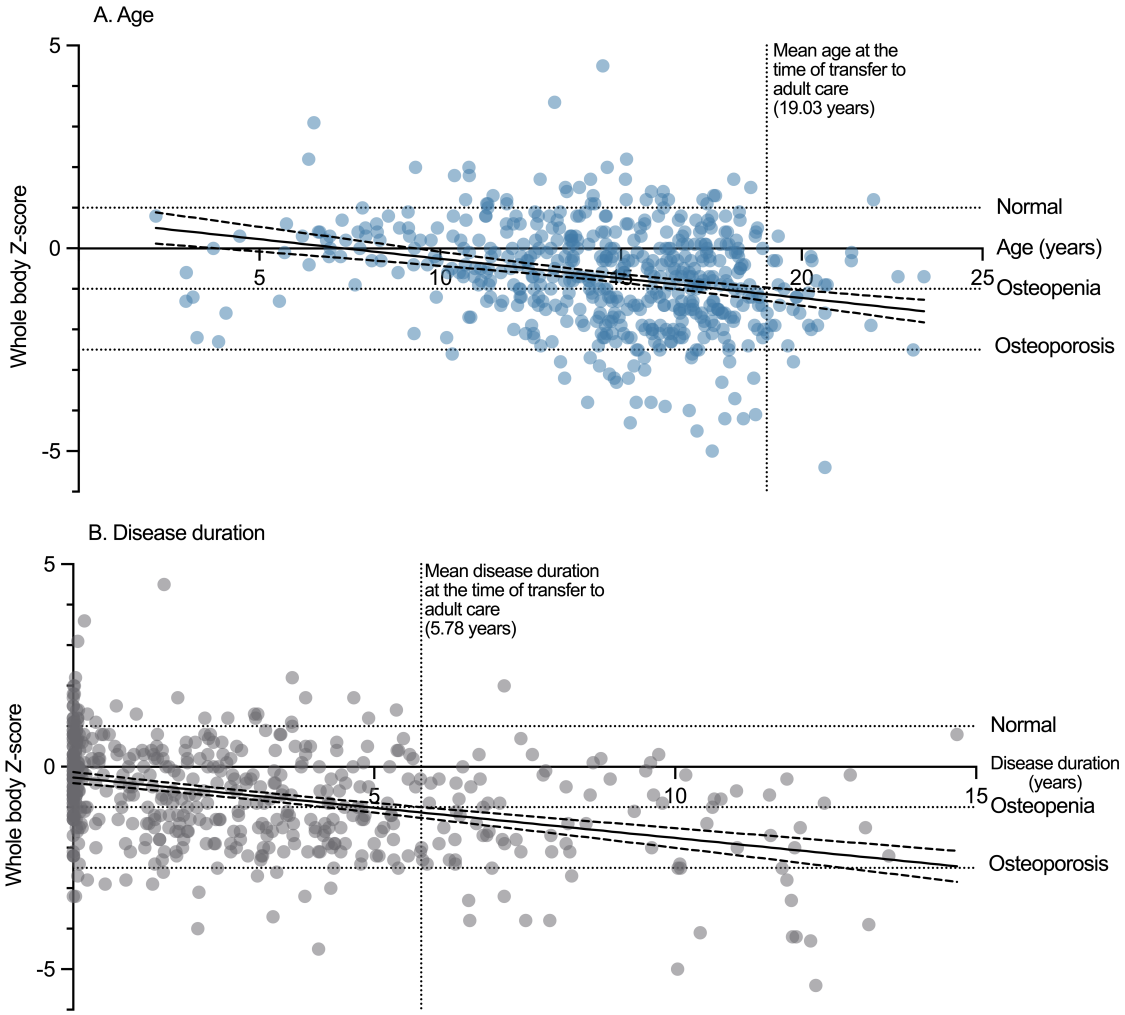

Figure 15./ A. and B. | Bone densitometry results of the patients regarding age and disease duration with linear trend model and 95% CI

Malignancies

Malignancies were reported in 2 patients, both of them are male and have CD.

The gastrointestinal neuroendocrine tumor was an accidental finding during the histological examination of a bowel segment resected during emergency surgery after an ileus. The patient was 16.25 years old at the time, with a disease duration of 0.25 years.

The lymphoma was reported to be potentially caused by the infliximab treatment. The patient was 19.69 years old, with a disease duration of 7.77 years. He underwent a total of 1023 days of infliximab treatment with the last 382 days being intensified.

4.11. Anthropometry

Weight

CD patients were prone to malnutrition during the examination period, with 11.94% of their weight measurements being at the severely low range, and a significantly lower proportion of their measurements being in the normal range (69.14%), compared to either the IBD-U or the UC patients (81.57% and 78.27%, $p < 0.0001$). The proportion of patients with severely high weight percentile was significantly higher after 5 years of disease duration (1.15% vs. 4.65%, $p = 0.0158$; OR 0.1530 [95% CI: 0.03117 - 0.6379]) (**Figure 16./ A. and B.**).

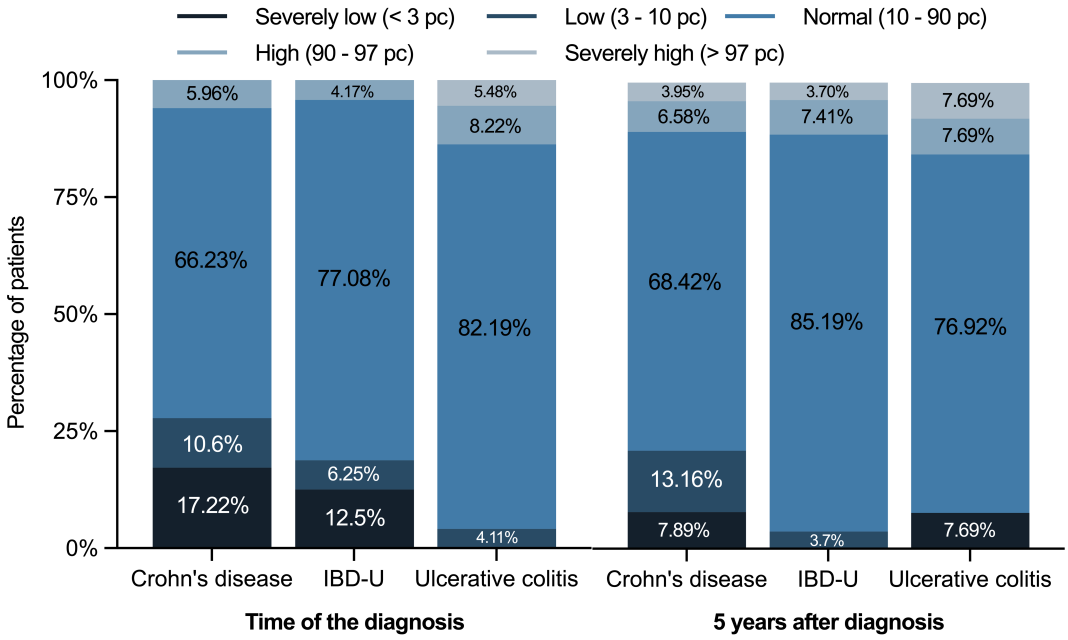

Figure 16./ A. and B. | Weight percentile ranges at the time and 5 years after diagnosis *(IBD-U - inflammatory bowel disease unclassified, pc - percentile)*

Height

IBD-U patients were shown to be at high risk of inadequate growth, as 9.23% of all their height measurements were at the severely low range (< 3 pc), compared to the 4.62% reported among the CD and 0.26% of the UC patients ($p = 0.0089$ and $p < 0.0001$; OR 0.4767 [0.2884 - 0.8179]. The proportion of measurements of the UC patients (98.21%) in the normal range was significantly higher compared to either the

IBD-U (86.54%) or the CD patients (89.03%) ($p < 0.0001$). There was no significant difference in either IBD subgroup regarding the proportion of patients in each height percentile at the time of the diagnosis and after 5 years of disease onset.

BMI

At the time of the diagnosis, all patients had their BMI percentile in the normal range (5 - 85 pc). **The proportion of the patients being in the normal BMI percentile range significantly decreased for all disease subtypes after 5 years of disease duration**, resulting in a high risk for non-adequate nutrition and/or growth by the time of transfer to adult care ($p < 0.0001$ for CD and UC and all patients, $p = 0.0116$ for IBD-U; OR 149.1 [9.012 - 2468]) (**Figure 17.**). **CD patients had a low BMI percentile in 13.55% of the measurements**, which was significantly higher than the proportion of either the IBD-U or the UC patients ($p = 0.0054$ and $p = 0.0093$).

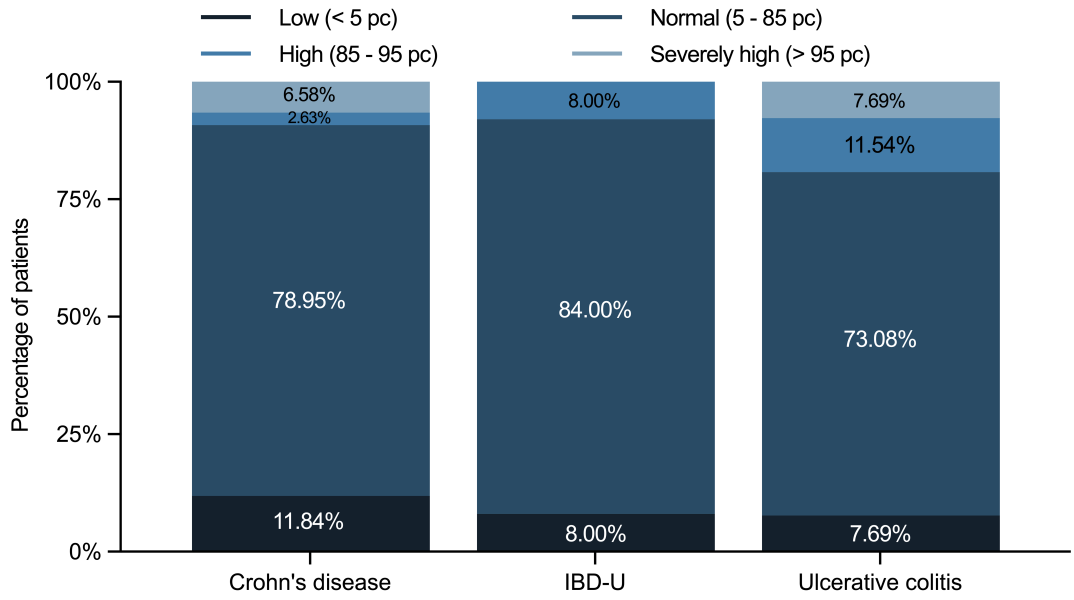

Figure 17. | BMI percentile ranges 5 years after diagnosis *(IBD-U - inflammatory bowel disease unclassified, pc - percentile)*

4.12. Medical and nutritional treatments

The proportion of patients receiving each medication group, also regarding their disease subtype can be seen in **Figure 18.**

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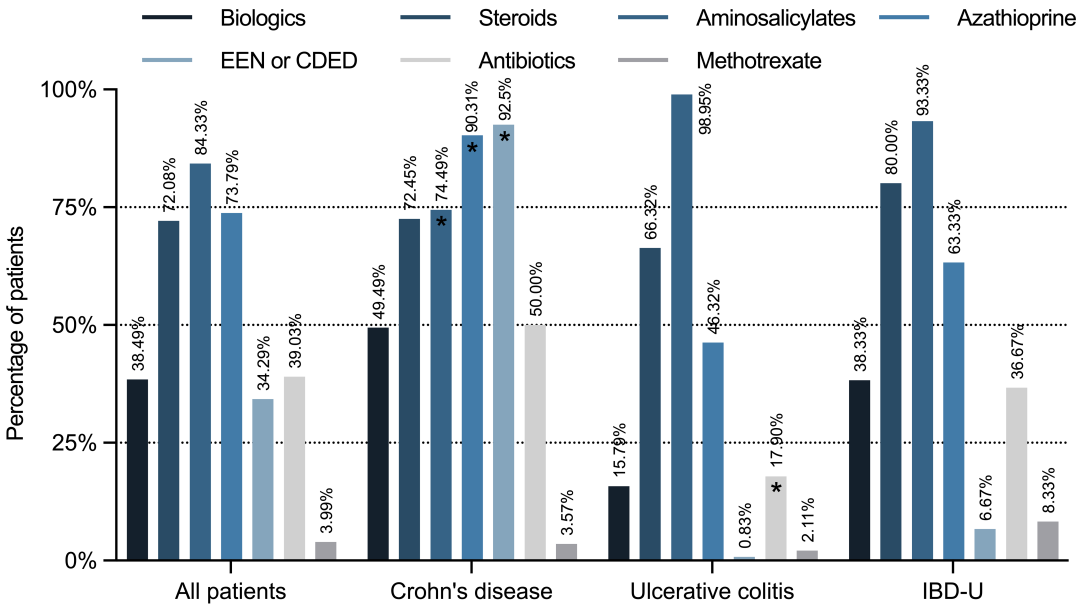

Figure 18. | The proportion of patients recieving each therapeutical subgroup

(significant difference to both other disease subtypes) (IBD-U - undetermined inflammatory bowel disease, EEN - exclusive enteral nutrition, CDED - Crohn's disease exclusion diet)*

In adult care, 63.97% (n = 87) of all patients required a therapy change, without a significant difference between the self-transferred (62.32%, n = 43) and the transitioned (65.67%, n = 44) group (*p = 0.7233*). The mean time elapsed until the first therapy change was 230.82 ± 320.86 days among the transitioned and 154.47 ± 236.46 days among the self-transferred patients (*p = 0.2107*). **Therapy escalations accounted for 62.5% of all these treatment modifications, of which 5% were the reinduction of the self-discontinued medications**. Every third therapy escalation was steroid application (33.33%), whereas biological therapy induction or intensification accounted for 14.67% of these changes.

The proportion of patients receiving **biologics** was 38% in both pediatric and adult care, with 7.35% of the patients having their therapy induced after being transferred.

Steroid treatment was applied in 72.08% of the patients in pediatric and 63.24% in adult care, accounting for 66.67% of the self-transferred and 59.7% of the transitioned group (*p = 0.4775*). The mean time of steroid treatment was 30.92 ± 78.98 days per year for topical and 73.63 ± 113.76 days per year for systemic steroid therapy. The mean

follow-up time of the patients who remained steroid-free since their diagnosis (n = 98) was 4.59 ± 3.29 years, accounting for 33.68% of the UC, 27.55% of the CD and 20% of the IBD-U patients ($p = 0.0095$).

Every third patient (34.19%, n = 120) received **EEN** during the study period, accounting for 92.5% of the CD, 6.67% of the IBD-U, and 0.83% of the UC patients. The mean length of EEN was 45.69 ± 25.79 days. In adult care, there was only one patient, a male with CD who received EEN, for 82 days. **CDED** therapy was used in 11.4% of all patients, of whom 90% had CD and 10% had IBD-U. The mean length was 350.48 ± 277.37 days. Five patients (1.43%) needed **tube feeding**, for a mean time of 32.67 ± 34.29 days. 3 patients had CD, and 1-1 had UC and IBD-U.

Side effects

Side effects of IBD medications were reported in 34.76% of all patients, accounting for 39.8% of CD, 33.3% of the IBD-U, and 25.26% of UC patients. Evaluating the frequency of appearance of side effects, there was an event reported every 1069.63 days during methotrexate treatment, every 1252.05 days during steroid, every 1300.23 days during infliximab, every 4969 days during adalimumab and every 5043.76 days during azathioprine therapy. Based on the evaluation of the health care providing physicians 57.78% of the reported side effects were categorized as mild, 31.56% as moderate, and 10.67% as severe. The most common side effects were *steroid signs* (20%), *allergic reaction* (13.35%), *gastritis* (6.67%), *abdominal pain* (6.67%), and *pancreatitis* (5.78%). The 10 different side effects categorized as severe by the healthcare providers were caused by either azathioprine, infliximab, aminosalicylates, or steroids.

4.13. Mortality

One patient (0.285%) died during the examination period at the age of 16.6 years, 9.44 years after being diagnosed with CD. The cause of his death was multi-organ failure and myocarditis.

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5. Discussion

This study aimed to define the clinical determinants of a successful transition and examine the objective and measurable effects of the changing process from pediatric to adult care on the disease course, activity, and patient compliance, including the comparison of a structured transitional program with self-transfer. Furthermore, we wanted to determine the unique characteristics of PIBD patients, that require special attention in adult care.

Despite transition being inevitable for PIBD patients and in the past decades it has been increasingly recognised as an essential, yet challenging element in ensuring the best possible disease outcome and overall health for patients, there are currently no consensus transitional guidelines and practices [195]. To date, most of the transitional recommendations are based on single-center studies, expert opinions, or surveys, and did not detect the long-term outcomes of structured transitional interventions [196]. However, extrapolating from the research data from a broader pediatric spectrum, young adults are expected to face similar difficulties during and after the healthcare-changing period, resulting in disruptions in their medical care, more frequent relapses, complications, and increased morbidity [141].

What are the determinants of a successful transitioning process?

As there is no clear definition of the term "*successful transition*", it is rather challenging to compare studies evaluating the success rate of different transitioning practices or a structured program with self-transfer [196]. The most commonly used outcome to measure the success of a transitional program, as suggested by ECCO, is the continuity of care**,** but other objective measures are also in use, such as hospitalization or surgical rates, quality of life, or corticosteroid usage [197]. Continuity of care is a multi-dimensional, patient-oriented construct, composed of health-service-related domains, including care coordination, care integration, and patient-provider communication [198]. The importance of continuity of care has been documented and objectively measured in numerous pediatric-onset chronic diseases [198]. Even with a successful

transition, it is challenging to keep up the continuity between the last pediatric and the first adult care visit, as this is the most vulnerable period of the changing process, without a definitive connection to either of the healthcare systems. This changing period was reported to be longer, than 6 months among *type 1 diabetes mellitus* patients, whereas Yearushalmy-Fehler et al. found it to be less, than 3 months for their IBD patients [199, 200]. Among our patients who were successfully moved to adult care, this time spent without definitive care between the healthcare systems was significantly longer among the self-transferred group, with a mean of nearly one year elapsed until the first attended adult care visit.

Disease-specific knowledge, self-efficacy, and autonomy are thoroughly studied and recognised as critical parts of transition readiness. The reluctance of patients and their parents, due to the close relationship with their pediatric healthcare providers is generally considered one of the main limitations to a successful transfer [126, 145, 169, 189, 190]. Furthermore, worries about working with a new healthcare provider, preconceptions of receiving poorer care in the adult healthcare system and parental involvement are frequently reported as barrier factors [201]. There are fewer studies examining the effects of clinical variables on the success of the transitioning process, and their reported results show great variability. Keefer et al. found, that patient demographics, disease, or socioeconomics did not impact transition readiness, once self-efficacy and resilience were taken into account [177, 202, 203]. In a study examining patients between 16 and 25 years, higher age and female gender were associated with better transition readiness [165]. McManus et al. in their survey-based study found that male patients, and those with developmental, physical, or psychological impairments were less likely to successfully transition to adult care [204]. Brink et al. examined 50 PIBD patients who enrolled in a structured transition and evaluated their clinical data after a 2- to 6-year-long follow-up period. Female patients and the ones with active disease before the transferring process were more likely to have an unsuccessful transfer, although these results did not reach the level of significance [205]. In correspondence with the results of Brink et al., we found female gender to be a significant barrier factor for a successful transfer, with 87.5% of the patients who

discontinued their medical care during the transferring period being female, regardless of their involvement in the transitioning process.

The currently reported overall success rate of the changing process between the pediatric and adult healthcare systems is similar across the globe. In a Canadian study examining nearly three thousand PIBD patients a 17.5% lost-to-follow-up rate was documented, whereas in British Columbia it was reported as 15% to 18% [178, 179]. Correspondingly, we found a 13% lost-to-follow-up rate among our patients during transfer, which was higher than the one found in either pediatric or adult care. An unsuccessful transition to adult care is shown to be associated with an increased number of *emergency interventions*, *hospitalizations*, *higher surgical rate*, more frequent *therapy escalation*, and a *worse overall disease outcome and health* [178].

What are the short- and long-term effects of the changing process to adult care, including the comparison between transition and self-transfer on the disease activity, course, and patient compliance?

The changing process to adult care is very complex and dependent on numerous patient-, healthcare provider-, and family-related factors. Inadequate transitional care is associated with *non-adherence to medications* and *non-compliance regarding visits*, *restricted growth potential*, *higher disease activity*, and an *increased risk of surgery* [123]. Without a structured transitional program, adolescents and young adults with chronic medical conditions face many risks, with possible lifelong consequences, including *delays in appropriate medical care* and *loss-to-follow-up* [117, 133, 134, 206]. The risk of adverse health outcomes after transferring to adult care due to a poor or lack of a transitional process is firmly established [129, 173, 197, 207-211]. Improved health-related outcomes have been documented among patients with numerous different chronic conditions after being enrolled in transition as opposed to transfer, however, there is a lack of data comparing these two for IBD patients [165]. The transfer is advised to be done during stable disease and psychosocial remission, as the changing process itself is thought to have a negative effect on the disease activity [147, 150]. A study from the Netherlands comparing direct transfer with structured transitional care

among IBD patients reported a significantly higher disease activity at the time of the changing process among the transferred patients, with every third patient having an active disease, compared to less, than 10% among the transitioned patients [212]. We found the same difference among our patients, as a significantly higher proportion of the self-transferred patients had an active disease during transfer, affecting every third patient, therefore the timing of the transfer was better among the patients enrolled in our transitional program.

Continuity of care is a core issue during the changing process from pediatric to adult healthcare systems [213]. A study reported a decreased lost-to-follow-up rate in adult care after being enrolled in a structured transition among *type 1 diabetes mellitus* patients [133]. Cole et al. in the United Kingdom compared the patients enrolled in a transitional program with a historical group without any formalised transitioning process and reported significantly higher medication adherence rates and lower nonattendance, hospitalization, and surgical rates, although the treatment characteristics were not the same between the two groups [138]. The lost-to-follow-up rate among our patients after the initiation of transfer to adult care was significantly higher than it was during pediatric care, with every fifth patient discontinuing their medical care. After being moved to adult care, transition was shown to be the only significant protective factor in continuing care, resulting in a 1.59-fold increased risk among the self-transferred patients to discontinue their medical care.

The compliance of adolescent IBD patients is reported to be the lowest among all age groups and even tends to deteriorate after being moved to adult care [191]. We found the same tendency, with a significant worsening in the compliance of the patients after being moved to adult care, exceeding a 70% non-compliance rate. This accounted for 77% of the self-transferred and 63% of the transitioned patients and although it did not reach the level of significance, but showed a trend. The medication-nonadherence rate of adolescent IBD patients in the current publications ranges from 50% to 88% [214-216]. Consequently, among nonadherent patients, a 5.5-fold greater risk of relapse had been reported, raising the annual healthcare costs by 12.5% compared to the adherent patients [217, 218]. A retrospective study from Canada, reviewing the cases of

95 pediatric-onset IBD patients who were moved to adult care without a structured transitional program reported significantly fewer outpatient visits and higher non-compliance rates in adult care, without differences in the hospitalization, surgical, or emergency visit rates [219]. During the changing process to adult care, nearly 10% of our patients discontinued their medications. After being successfully moved to adult care, the medication adherence of the transitioned patients was significantly higher, with a non-adherence rate being twice as high among the self-transferred patients. Brooks et al. found the same result in their study, as medication adherence was higher among the patients being enrolled in a transitional program [123].

A structured transitional program is potentially associated with a positive impact on patient compliance, disease course, and activity and promotes a better healthcare resource utilisation [126]. Accordingly, significantly more of the self-transferred patients enrolled in our study experienced relapses during the follow-up period in our study, resulting in a 1.88-fold increased risk of relapse after being moved to adult care compared to the transitioned patients. Furthermore, the self-transferred patients had severe disease activity in a significantly higher and remission significantly lower proportion of the follow-up time in adult care compared to the transitioned patients. We found no difference between the two groups regarding hospitalization or surgery rates, as reported by Cole et al [138].

What are the unique characteristics of PIBD patients that require special attention in adult care?

PIBD is more extensive compared to the adult-onset form, with more than 40% of pediatric-onset CD patients having simultaneous ileocolonic and upper gastrointestinal involvement compared to 3% among adult patients [48]. Significantly more pediatric UC patients have pancolitis than adult-onset patients, with a 60% to 80% rate compared to a 20% to 30% rate, with up to 40% of the pediatric patients requiring colectomy after a 10-year-long disease duration [48, 220, 221]. Accordingly, simultaneous ileocolonic involvement was documented in 57% of our CD patients, with 55% of our UC patients

having pancolitis. Additionally, the disease of every third patient became more extensive during the follow-up period.

PIBD is usually characterised by a rapid disease progression, with every tenth patient requiring surgery in the first year following the diagnosis and every third to fifth after 5 years of disease duration [95-97]. The colectomy rate among pediatric UC patients is reaching 40%, compared to half as much reported among adults [48, 49]. Of all CD patients, up to 80% require surgical intervention, with every tenth needing a permanent stoma [6]. Among our patients, the surgical rate during pediatric care was 15%, after a mean of less, than three years of disease duration at the time of surgery and every fourth intervention being an emergency procedure.

By the time they arrive at adult care, PIBD patients are frequently affected by the complications of their disease, making their treatment especially complicated. The most commonly reported EICs of PIBD are *inadequate nutrition and growth*, *poor bone health*, *fertility problems***,** and *malignancies* [78-82]. Every third pediatric CD patient is reported to experience linear growth retardation prior to the gastrointestinal manifestations, secondary to malnutrition and chronic inflammation, which consequently can lead to delayed puberty and further related complications [222, 223]. Approximately in half of the adult patients with PIBD the final height is 10% lower than in the general population [83]. Among our patients, IBD-U patients were reported to be at high risk for growth retardation, with nearly 10% of their measurements being in the severely low range. During our study period, the CD patients were at high risk for malnutrition, with more, than 10% of their measurements being in the severely low range. Additionally, considering all of our patients, the range of patients being in the normal BMI percentile significantly decreased after 5 years of disease duration, affecting every disease subgroup.

Chronic blood loss and inflammation, increased energy requirements, intestinal malabsorption, and frequent treatment with corticosteroids contribute to poor bone health among IBD patients [78]. The measured bone density of our patients was decreasing with both higher age and longer disease duration, with patients being at high risk for osteoporosis and consequential pathologic fractures at the time of transfer to

adult care. Every fifth patient experienced an IBD-related complication already during their pediatric care, further complicating their disease by the time of transfer.

Despite adolescents with IBD tend to have a medically more complex disease compared to adult patients, they have lower compliance to their care or adherence to their medications [173, 219]. During our study, 14% of all patients discontinued their medical care before being moved to adult care, in which the higher number of days spent in hospital yearly was a risk factor. A systematic review of studies published since 2005 found a 93% oral medication non-adherence rate among adolescents. They pointed out that this high non-adherence rate can lead to mistakenly perceived treatment failure, prompting ill-founded therapy escalations [224]. Other researchers are reporting a slightly lower medication non-adherence rate, it being between 50% to 66% [192]. Non-compliance was reported in two-thirds of our patients, with the most common problem being non-adherence to clinical attendance, followed by every third of patients having medication non-adherence. Of our patients, every third experienced a medication side-effect during the examination period, which can also contribute to medication non-adherence. The non-compliance rate was increasing with both higher age and longer disease duration among our patients, reaching more than 50% at the mean age and disease duration of transfer.

The differences between the pediatric- and adult-onset IBD and two healthcare systems, the high complication rate and rapid progression of the PIBD, the inadequate knowledge and self-efficacy of young adults on the verge of being transferred to adult care emphasise the need for a structured, organised, and planned transitional process [200]. Furthermore, it is essential for PIBD patients to be treated in IBD Centers both before and after transition, where the healthcare-providing multidisciplinary team has access to all those diagnostic and therapeutic interventions that are necessary to ensure the best possible disease outcome for this unique patient group [173, 174]. During the follow-up period in adult care, the transitioned patients continued their medical care in IBD Centers 96% of the time, compared to 37% found among the self-transferred patients. This can result in suboptimal disease control and impaired treatment possibilities, with a higher complication rate and a worse overall disease outcome among the self-

transferred patient group. Adult healthcare providers should be aware, that the patients being transferred to them greatly differ from the same-aged, but adult onset-IBD patients, with a medically already complex disease course with former surgeries, often complicated with growth impairment and malnutrition, emotional distress, and non-compliance. Addressing the differences in the clinical characteristics and the course of pediatric- and adult-onset IBD, as well as the differences among the two healthcare systems is a critical step in understanding how to manage and perform a successful transition [196].

Strength and limitations

To our knowledge, our study has the highest number of patients enrolled in a structured transitional program with a comparable control group, that examined objective and measurable clinical outcomes with a long follow-up period.

We acknowledge that our research has limitations. The enrollment in the transitional and the self-transfer groups was not randomised, although there was no difference in any patient-, disease-, or treatment-specific variable between the two groups. The transition readiness was not objectively measured, but rather based on the assessment of the pediatric care physician, and the opinion of the patients and their parents. Finally, from the pediatric time period the study included a single center, as patients just partially were treated in other clinics.

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6. Conclusions

We found a positive association between a structured transitional program and lower disease activity, fewer relapses, and better adherence to medications as opposed to self-transfer. Furthermore, enrollment in transition was shown to be the only significant protective factor for continuing medical care after transfer. The changing process to adult care was linked to a deterioration in medication adherence and in overall compliance of the patients, with a high lost-to-follow-up rate between the healthcare systems regardless of enrollment in a structured transition, in which female gender was a risk factor. The PIBD patients had an extensive and medically complex disease upon arriving at adult care, with a history of former surgeries and IBD-related complications, high rates of malnutrition, growth impairment, and poor bone health, and with their compliance worsening with both higher age and longer disease duration.

Based on our results and the corresponding reports of the current literature, the conduction of numerous, multi-centric transitional studies is advised in the future, as structured transitional programs seem to have a key role in ensuring the best possible disease outcome for PIBD patients. These studies could guide future recommendations, and help the establishment of a gold-stand transitional and educational method.

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7. Summary

Despite 10% of every IBD having a pediatric onset, there are no established transitional guidelines and the existing recommendations are mostly based on expert opinions, single-center studies, and being extrapolated from other disciplines.

Our longitudinal, follow-up, controlled clinical study incorporated a retrospective and prospective data collection period of 20 years, including 351 PIBD patients, of whom 73 were enrolled in our transitional program, whereas 79 self-transferred to adult care and served as our control group. We aimed our study to examine the clinical determinants of a successful transition and define the objective and measurable effects of the changing process from pediatric to adult care on the disease course, activity, and patient compliance, including the comparison of a structured transitional program with self-transfer. Furthermore, we wanted to determine the unique characteristics of PIBD patients, that require special attention in adult care.

Transition was positively associated with lower disease activity, fewer relapses, better medication adherence, and a lower lost-to-follow-up rate as opposed to self-transfer. Enrollment in our structured transitional program was shown to be the only significant protective factor in adherence to medical care after the initiation of transfer to adult care. The changing process to adult care caused a deterioration in both medical adherence and overall compliance of the patients, with a high lost-to-follow-up rate, in which the female gender was a risk factor. PIBD patients had an extensive and medically complex disease upon arriving at adult care, with a history of former surgeries and IBD-related complications, high rates of malnutrition, growth impairment, and poor bone health, and with their compliance worsening with both higher age and longer disease duration.

To our knowledge, our study has the highest number of patients enrolled in a structured transitional program with a comparable control group, that examined the objective and measurable clinical outcomes with a long follow-up period. The results of our study correspond to the current state of literature and emphasize the critical role of a structured transition in providing the best possible disease outcome for PIBD patients.

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DOI:10.14753/SE.2025.3153

9. Bibliography of the candidate's publications

9.1. Publications related to the thesis

A gyermekkori kezdetű gyulladásos bélbetegség sajátosságai 20 éves vizsgálatunk alapján

Tóbi Luca, Cseh Áron

Orvosi Hetilap

Doi: 10.1556/650.2025.33249

Impact factor: 0.8

Date: accepted for publication: 26.01.2025

Transition is associated with lower disease activity, fewer relapses, better medication adherence, and lower lost-to-follow-up rate as opposed to self-transfer in pediatric-onset inflammatory bowel disease patients: results of a longitudinal, follow-up, controlled observational study

Tóbi Luca, Prehoda Bence, Balogh Anna M, et al.

Therapeutic Advances in Gastroenterology

Impact factor: 3.9

Date: 31.04.24

A gyulladásos bélbetegség korszerű kezelése gyermekkorban: fókuszban a diéta és a biológiai terápia

Cseh Áron, Prehoda Bence, **Tóbi Luca**, et al.

Orvosi Hetilap, CLXIV., 25./2023, 963-970.

Doi: 10.1556/650.2023.32819.

Impact factor: 0.8

Date: 06.2023

A gasztroenterológiai betegek tranzíciója a felnőttgondozásba

Tóbi Luca, Cseh Áron

Orvostovábbképző szemle, XXIX. 8/2022.

Date: 09.2022

A COVID-19 fertőzés gastrointestinalis hatásai gyermekkorban és a gyulladásos bélbeteg gyermekekben

Tóbi Luca, Prehoda Bence, Balogh Anna, Dezsőfi-Gottl Antal, Cseh Áron

Orvosi Hetilap, CLXIII., 6./2022; 214-221.

Doi: 10.1556/650.2022.32443.

Impact factor: 0.8

Date: 02.2022

Újabb ismeretek a gyulladásos bélbetegségről

Cseh Áron, **Tóbi Luca**, Arató András

Gyermekorvos Továbbképzés, IX., 1./2021, 2-5.

Date: 02.2021

9.2. Publications not related to the thesis

A comparative in vivo study of hyperthermic intraperitoneal chemotherapy with cisplatin versus doxorubicin versus cisplatin plus doxorubicin for the treatment of intra-abdominally disseminated alveolar rhabdomyosarcoma in mice

Martynov Illya, Gesche Jens, Dhaka Lajwanti, **Tobi Luca**, Hoyer Paul, Seitz Guido

Pediatric blood & cancer, 71(12), e31366.

Doi: 10.1002/pbc.31366

Impact factor: 3.8

Date: 12.2024

Féregfertőzések gyermekkorban - A leggyakrabban felmerülő kérdések és tévhitek

Tóbi Luca

Gyermekorvos Továbbképzés, XX., 3./2021; 80-85.

Date: 07.2021

DOI:10.14753/SE.2025.3153

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