ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2023 November 14; 29(42): 5699-5799

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 29 Number 42 November 14, 2023

World Journal of Gastroenterology

Weekly Volume 29 Number 42 November 14, 2023

Contents

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

PUBLICATION DATE

November 14, 2023

PUBLISHING PARTNER

Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS

https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS

https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE

https://www.shca.org.cn
https://www.zs-hospital.sh.cn

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 November 14; 29(42): 5728-5750

DOI: 10.3748/wjg.v29.i42.5728

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Location-based prediction model for Crohn's disease regarding a novel serological marker, anti-chitinase 3-like 1 autoantibodies

Nora Sipeki, Patricia Julianna Kovats, Claudia Deutschmann, Peter Schierack, Dirk Roggenbuck, Maria Papp

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liakina V, Lithuania; Rodrigues AT, Brazil; Sira MM, Egypt

Received: June 28, 2023
Peer-review started: June 28, 2023
First decision: September 1, 2023
Revised: October 3, 2023
Accepted: November 2, 2023
Article in press: November 2, 2023
Published online: November 14, 2023

Nora Sipeki, Patricia Julianna Kovats, Maria Papp, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen H-4032, Hungary

Patricia Julianna Kovats, Kálmán Laki Doctoral School, Faculty of Medicine, University of Debrecen, Debrecen H-4032, Hungary

Claudia Deutschmann, Peter Schierack, Dirk Roggenbuck, Institute of Biotechnology, Faculty Environment and Natural Sciences, Brandenburg University of Technology Cottbus-Senftenberg, Senftenberg 01968, Germany

Peter Schierack, Dirk Roggenbuck, Faculty of Health Sciences Brandenburg, Brandenburg University of Technology Cottbus-Senftenberg, Senftenberg 01968, Germany

Dirk Roggenbuck, Medipan GmbH & GA Generic Assays GmbH, Dahlewitz-Berlin 15827, Germany

Corresponding author: Nora Sipeki, MD, PhD, Assistant Lecturer, Attending Doctor, Doctor, Postdoc, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Nagyerdei blv 98, Debrecen H-4032, Hungary.
sipeki.nora@med.unideb.hu

Abstract

BACKGROUND

Defective neutrophil regulation in inflammatory bowel disease (IBD) is thought to play an important role in the onset or manifestation of IBD, as it could lead to damage of the intestinal mucosal barrier by the infiltration of neutrophils in the inflamed mucosa and the accumulation of pathogens. Like neutrophils in the context of innate immune responses, immunoglobulin A (IgA) as an acquired immune response partakes in the defense of the intestinal epithelium. Under normal conditions, IgA contributes to the elimination of microbes, but in connection with the loss of tolerance to chitinase 3-like 1 (CHI3L1) in IBD, IgA could participate in CHI3L1-mediated improved adhesion and invasion of potentially pathogenic microorganisms. The tolerance brake to CHI3L1 and the occurrence of IgA autoantibodies to this particular target, the exact role and underlying mechanisms of CHI3L1 in the pathogenesis of IBD are still unclear.

AIM

To determine the predictive potential of Ig subtypes of a novel serological marker,

anti-CHI3L1 autoantibodies (aCHI3L1) in determining the disease phenotype, therapeutic strategy and long-term disease course in a prospective referral cohort of adult IBD patients.

METHODS

Sera of 257 Crohn's disease (CD) and 180 ulcerative colitis (UC) patients from a tertiary IBD referral center of Hungary (Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen) were assayed for IgG, IgA, and secretory IgA (sIgA) type aCHI3L1 by enzyme-linked immunosorbent assay using recombinant CHI3L1, along with 86 healthy controls (HCONT).

RESULTS

The IgA type was more prevalent in CD than in UC (29.2% *vs* 11.1%) or HCONT (2.83%; $P < 0.0001$ for both). However, sIgA subtype aCHI3L1 positivity was higher in both CD and UC patients than in HCONT (39.3% and 32.8% *vs* 4.65%, respectively; $P < 0.0001$). The presence of both IgA and sIgA aCHI3L1 antibodies was associated with colonic involvement ($P < 0.0001$ and $P = 0.038$, respectively) in patients with CD. Complicated disease behavior at sample procurement was associated with aCHI3L1 sIgA positivity (57.1% *vs* 36.0%, $P = 0.009$). IgA type aCH3L1 was more prevalent in patients with frequent relapse during the disease course in the CD group (46.9% *vs* 25.7%, $P = 0.005$). In a group of patients with concomitant presence of pure inflammatory luminal disease and colon involvement at the time of diagnosis, positivity for IgA or sIgA type aCH3L1 predicted faster progression towards a complicated disease course in time-dependent models. This association disappeared after merging subgroups of different disease locations.

CONCLUSION

CHI3L1 is a novel neutrophil autoantigenic target in IBD. The consideration of antibody classes along with location-based prediction may transform the future of serology in IBD.

Key Words: Chitinase 3-like 1 autoantibodies; Crohn's disease; Ulcerative colitis; Disease progression; Immunoglobulin subtypes; Enzyme-linked immunosorbent assay

Core Tip: The tolerance brake to chitinase 3-like 1 (CHI3L1), a novel neutrophil autoantigenic target in inflammatory bowel disease (IBD), the presence of immunoglobulin A (IgA) autoantibodies against this specific target, as well as the precise function and underlying processes of CHI3L1 in the development of IBD, continue to be uncertain. In the present prospective observational study, we first reported an enhanced formation of IgA and secretory IgA (sub)type against CHI3L1 in adult patients with Crohn's disease, which was associated with the clinical phenotype and development of a complicated disease course during follow-up in a tertiary referral IBD center in Hungary. By taking into account the classes of antibodies and utilizing location-based predictions, serology in IBD may undergo a significant transformation in the future.

Citation: Sipeki N, Kovats PJ, Deutschmann C, Schierack P, Roggenbuck D, Papp M. Location-based prediction model for Crohn's disease regarding a novel serological marker, anti-chitinase 3-like 1 autoantibodies. *World J Gastroenterol* 2023; 29(42): 5728-5750
URL: https://www.wjgnet.com/1007-9327/full/v29/i42/5728.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i42.5728

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition involving all or parts of the gastrointestinal tract with a potential to present extraintestinal manifestations (EIM). The two main clinical entities are Crohn's disease (CD) and ulcerative colitis (UC), both of which have heterogeneous presentations and disease courses. Their significance lies in their increasing incidence, which mainly affects the young, still active, and working-age population[1].

The exact pathophysiology of the disease has not yet been fully elucidated. Partially unknown environmental factors are thought to trigger an uncontrolled immune-mediated inflammatory process in genetically predisposed individuals, in which altered microbiome, dysfunction of the intestinal mucosal barrier and dysregulation of the mucosal immune response to commensal or pathogenic microbes of the intestinal microbiota are key players[2-5]. This concept is well represented in the new immunological classification of autoimmune and autoinflammatory diseases, where mixed-pattern conditions such as IBD are acknowledged. The latter are considered to belong to the group of immune-mediated inflammatory disorders (IMIDs) in this autoimmune-autoinflammatory spectrum[6-9]. Like other IMIDs (*e.g.*, rheumatoid arthritis), IBD also exhibits features of autoimmunity with a dysregulated adaptive immune response (the breakdown of immune tolerance, the identification of self-antigens, and the activation of T cells and B cells, resulting in the creation of

specific autoantibodies) and autoinflammatory characteristics with the activation of the innate immune system (involvement of neutrophils, macrophages, as well as dendritic-, natural killer-, and mast cells, different granulocyte subsets, and the complement system as major players)[6,10,11].

Crosstalk between the gut microbiota and the host occurs at the intestinal mucosal level[12]. The mucosal immune system maintains the balance between tolerance to commensal bacteria and the immune response against pathogens and is responsible for mucosal homeostasis[13]. Mechanical and/or immunological disruption of the gut barrier can lead to the enhanced uptake of bacteria and bacterial products from the gut lumen [bacterial translocation (BT)], which can trigger and perpetuate chronic inflammation [14,15]. However, whether this phenomenon in IBD is a primary defect or consequence is still under debate[14,16]. Supported by robust scientific data, impaired sensing of intestinal bacteria by cytoplasmic and membrane-bound pattern recognition receptors (NOD-like and Toll-like receptors, respectively) is thought to play a role in IBD development[17]. Currently, evidence is accumulating, that the formation of auto- and antimicrobial antibodies in IBD appears to be the result of enhanced microbial load[18].

Several types of innate immune cells are involved in IBD immunopathogenesis[14]. Dysregulated neutrophil function can lead to damage to the intestinal mucosal barrier due to the infiltration of neutrophils into the inflamed mucosa and the accumulation of harmful pathogens[19,20]. In UC, the infiltration and accumulation of neutrophils were found to be elevated and associated with disease activity, whereas in CD, impaired recruitment of neutrophils, reduced production of cytokines and phagocytosis, and delayed/defective antimicrobial clearance were described[21,22]. Clinical utility of blood-based and fecal neutrophil-related biomarkers has been studied extensively in IBD. In the latter group, fecal calprotectin has been proven to be the most helpful in monitoring disease activity and is recommended by clinical practice guidelines in various clinical settings (initial diagnosis, diagnosis of relapse, and response to treatment)[22,23]. Other fecal neutrophil-derived biomarkers are lactoferrin, lysozyme, polymorphonuclear neutrophil elastase, myeloperoxidase, human neutrophil peptides, neutrophil gelatinase-associated lipocalin, and chitinase 3-like 1 (CHI3L1)[24-26]. Similarly to fecal calprotectin, fecal CHI3L1 appears to correlate well with endoscopic activity in patients with CD[27,28].

Recently, loss of tolerance to a novel neutrophil autoantigenic glycoprotein target, CHI3L1 has been confirmed by our group in IBD patients[21,29,30]. Evaluation of autoantibodies against CHI3L1 (aCHI3L1) was performed in a pediatric IBD cohort[30]. Immunoglobulin A (IgA), a key player in acquired immune responses, contributes to the defense of the intestinal epithelium, similarly to how neutrophils are involved in innate immune responses. Under typical circumstances, IgA plays a crucial role in eliminating microbes through its antibacterial and antiviral activities. However, in the context of diminished tolerance to CHI3L1 in IBD, IgA may participate in the enhanced adhesion and invasion of potentially pathogenic microorganisms, as facilitated by CHI3L1. Given the current state of knowledge, the precise function and mechanism of CHI3L1 in the development of IBD, loss of tolerance to this antigen, formation of IgA autoantibodies against it, and their role in the pathogenesis of IBD remain elusive[21,30].

The main objective of this research was to identify the frequency and predictive value of Ig subtypes of a newly discovered serological marker, aCHI3L1, in relation to the development of disease-specific complications or the need for surgery in a large group of adult IBD patients with a prospective follow-up. Additionally, we aimed to investigate: The long-term stability of aCHI3L1 autoantibodies; the relationship between aCHI3L1 formation and the clinical, serological, and genetic characteristics of CD.

MATERIALS AND METHODS

Patient population

We performed a cohort study among adult CD and UC patients in a tertiary IBD referral center in Hungary (Department of Gastroenterology, Institute of Internal Medicine, University of Debrecen). The baseline clinical data regarding this cohort overlap with those of our previous studies[29,31,32]; however, we present an extended follow-up time with nearly 2.5 years and re-evaluation of the outcomes. We used the same step-by-step thorough statistical evaluations; therefore, the text appeared to reproduce the information reported in detail elsewhere. The clinical characteristics of patients at diagnosis are presented in Table 1 in detail. The original CD cohort consisted of 271 patients, however 5 of them should have been excluded from the statistical analysis after performing total Ig measurements due to decreased or absent serum IgA levels equivalent of international consensus laboratory criteria of severe selective IgA deficiency (serum IgA level less than 7 mg/dL or 0.07 g/L - the lowest detectable limit established by most of the laboratories)[33-35].

The diagnosis of IBD was based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations equivalent to the recently published European Crohn's and Colitis Organization (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology guidelines[23,36]. Disease phenotype (age at onset, duration, location/extent, and behavior including perianal involvement as a modifier) was determined according to the Montreal Classification[37]. Blood samples and detailed clinical phenotypes were captured at inclusion. Clinical data were determined by a thorough review of the patients' medical records, which were collected in a uniform format. Medical records documenting the disease phenotype, presence of EIM, frequency of flare-ups (frequent flare-up: > 1 clinical relapse/year)[38], medication use (*e.g.*, steroid, immunosuppressive and/or biological use at any time), need for IBD-related surgery (resection and surgical intervention due to perianal disease complications in CD and colectomy in UC), and IBD-related risk factors (the presence of familial IBD, smoking habits and previous appendectomy) were retrospectively analyzed for the period prior to prospective follow-up. At enrolment, clinical disease activity was calculated according to the Harvey-Bradshaw Index (HBI)[39] for CD and the Partial Mayo Score (PMS) for UC[40]. In this study, we followed the ECCO guidelines[41] and defined HBI ≤ 4 as a state of remission and ≥ 5 as a state of active disease. In case of UC, PMS ≤ 3 was defined as a state of remission and PMS > 4 as a state of active disease. Endoscopic

Table 1 Clinical characteristics of inflammatory bowel disease patients, *n* (%)

	CD (*n* = 266)	UC (*n* = 187)
Age at presentation (yr), median (IQR)	25 (19-33)	33 (23-43)
Male/female (*n*)	112/154	86/101
Follow-up (mo) from, median (IQR)		
Diagnosis[1]	143 (99-214)	135 (84-213)
Time of serum collection, median (IQR)	97 (77-118)	78 (51-102)
Location/extent at diagnosis		
L1	58 (21.8%)	E1 30 (16.0%)
L2	86 (32.3%)	E2 104 (55.6%)
L3	121 (45.5%)	E3 53 (28.3%)
L4 only	1 (0.4%)	
Behavior at diagnosis/last follow up		
B1	213 (80.1%)/117 (44.8%)	
B2	32 (12.0%)/54 (20.7%)	
B3	21 (7.9%)/90 (34.5%)	
Perianal disease		
At diagnosis/last follow-up[1]	48 (18.0%)/100 (38.3%)	
Extraintestinal manifestations		
PSC	8 (3.0%)	8 (4.3%)
Arthritis	49 (18.4%)	26 (13.9%)
Skin	35 (13.2%)	16 (8.6%)
Ocular	65 (24.4%)	12 (6.4%)
Smoking habits		
Never	215 (80.8%)	167 (89.3%)
Yes	46 (17.3%)	18 (9.6%)
Previous	5 (1.9%)	2 (1.1%)
Familial IBD	12 (4.4%)	6 (3.2%)
Frequent relapse	52 (20.9%)	
Cumulative exposure of medication and surgeries during follow-up		
Steroid use/refractory	219 (82.3%)/30 (13.7%)	117 (63.9%)/11 (7.6%)
Azathioprine use	198 (74.4%)	70 (38.3%)
Biological use	112 (42.1%)	25 (13.4%)
Resective surgery/multiple in CD	117 (44.8%)/ 33 (12.6%)	
Colectomy in UC		11 (6.0%)
Surgery due to perianal complication/multiple	61 (23.4%)/33 (12.6%)	

[1]261 Crohn's disease and 183 ulcerative colitis patients had follow-up.

Location: L1: Ileal, L2: Colonic, L3: Ileocolonic, L4: Upper gastrointestinal disease. Behavior: B1: Inflammatory (non stricturing/non penetrating), B2: Stenosing (stricturing), B3: Penetrating. Disease extent: E1: Proctitis; E2: Left sided colitis; E3: Extensive colitis. Surgery: Crohn's disease-related abdominal surgery and colectomy in ulcerative colitis. CD: Crohn's disease; IQR: Interquartile range; UC: Ulcerative colitis; PSC: Primary sclerosing cholangitis; IBD: Inflammatory bowel disease.

activity was determined according to the Simple Endoscopic Score for Crohn's Disease (SES-CD) for CD[42] and the endoscopic component of the Mayo score for UC[43]. SES-CD defines endoscopic activity ≥ 3 points and inactive disease ≤ 2 in CD; meanwhile in UC, state of active disease is defined as an invasive PMS ≥ 1.

Phenotypical characterization of IBD patients during prospective follow-up

A total of 261 of 266 patients with CD and 183 of 187 patients with UC were enrolled in a prospective follow-up study. During regular and extraordinary outpatient follow-up visits and inpatient stays, the treating IBD physicians registered laboratory data, endoscopic and imaging results, disease activity, medical treatment regimens, and information on disease-specific complications and surgeries. In Hungary, a follow-up visit is typically scheduled every six months at a specialized gastroenterology center, which can vary between three and six months depending on the center. The medical and surgical treatment algorithms are aligned and conform to the ECCO guidelines[41,44-47]. The decision regarding the need for surgery and its timing involves a multidisciplinary approach, with the collaboration of gastroenterologists, radiologists, and surgeons. The data that was collected was transferred and saved in a database for the purpose of further evaluation. On October 11, 2016, all patient records and databases were revised and updated with the relevant data points. The patient's follow-up was discontinued if there were no additional records. The median duration of follow-up from diagnosis for CD patients was 143 mo [with an interquartile range (IQR) of 99 to 214], while for UC patients, it was 135 mo (with an IQR of 84 to 213). In CD, complicated disease behavior is characterized by the presence of stenosis (stricture) or internal penetration (interintestinal fistula, inflammatory conglomerate, and/or abscess(es) formation). A distinction was made between perianal fistulizing disease and internal penetrating disease, and they were evaluated separately. The need for surgery in CD was defined as CD-related abdominal- (resection) or perianal surgery (oncotomy). Complicated disease behavior in UC was defined as the progression of disease extent or the need for colectomy.

The healthy controls (HCONT) included 86 age- and sex-matched healthy individuals. Of these, 52 were male and 34 were female, with a median age of 28 years at disease onset (range: 24-41). The control group comprised of individuals who were free from gastrointestinal and liver diseases and were obtained from invent Diagnostica GmbH (Hennigsdorf, Germany).

Serological analysis

At enrollment, blood samples were obtained from each participant and were subsequently frozen at a temperature of -80 °C until further testing. All serological assays were conducted in a blinded manner, without prior knowledge of the patient's diagnosis or any other clinical information. To determine the stability of different serologic antibodies, we analyzed samples from the same patient taken at various arbitrary timepoints during the course of their disease. Most patients with CD (n = 165) had at least two serum samples taken and re-tested for all serological antibodies.

Detection of antibodies to CHI3L1 by enzyme-linked immunosorbent assays

Presence of IgG, IgA and secretory (sIgA) (sub)type aCHI3L1 in serum samples of IBD patients (n = 257 in CD and n = 180 in UC) and HCONT (n = 86) were determined by an "in house" enzyme-linked immunosorbent assay technique using recombinant human CHI3L1 as solid-phase antigen. A detailed description of the methodology is available in the authors' previous paper on pediatric IBD[30]. The levels of aCHI3L1 IgG, IgA, or sIgA were read as the ratio of OD_{sample}/OD_{cutoff} (OD_{cutoff}, mean + 3 SD of HCONT) for standardization. Serum samples with a ratio of ≥ 1 were considered positive [30].

Detection of classic auto- and antimicrobial antibodies and NOD2/CARD15 SNP8, 12, 13 mutations

The detection of classic auto- [anti-neutrophil cytoplasmic antibodies (ANCA), anti-pancreatic autoantibodies (PAbs), antiphospholipid antibodies (APLAs)], and antimicrobial [anti-*Saccharomyces cerevisiae* antibodies (ASCA), anti-OMP PlusTM IgA] antibodies has been described in detail by the authors in previous publications[29,31,32]. NOD2/CARD15 SNP8, SNP12, and SNP13 genotyping was performed previously[48] in patients with CD (n = 235). A detailed description of the methodology has been provided in the cited manuscript.

Ethical permission

The study was granted ethical approval by the regional and national committees for research ethics (DE RKEB/IKEB: 4773-2017; DE OEC RKEB/IKEB: 3515-2011; TUKEB: ad.3880/2012-EKU). All patients were informed about the study's details and provided their informed consent.

Statistical analysis

We utilized GraphPad Prism 6 (San Diego,1 CA) and SPSS 22.0 (SPSS Inc., Chicago, IL) for statistical analysis. The study's statistical methods were reviewed by Elek Dinya, from Semmelweis University's Institute of Health Informatics, Development, and Further Training. The normality of variables was evaluated using the Shapiro-Wilk's W test. The continuous variables were presented in the form of means ± SD or medians and IQR based on their consistency. To determine distinctions between the IBD and HCONT groups, as well as among subgroups of patients with IBD, the following statistical methods were employed: Categorical variables were compared using Fisher's exact test or χ^2 test with Yates correction, depending on the situation. To compare continuous variables, we used Student's t-test, one-way analysis of variance (ANOVA), Mann-Whitney's U test, or Kruskal-Wallis H test with post hoc analysis (Dunn's multiple comparison test). The Spearman's nonparametric rank correlation test was used to determine correlations.

The Kaplan-Meier survival curves were used to examine the impact of categorical clinical variables or serologic antibodies on unfavorable disease outcomes during follow-up. To determine the association, the log-rank test or Cox regression analysis was conducted in time-dependent models. Cox regression analysis and a backward elimination method were used to investigate the predictive value of serological antibodies and all clinical variables as cofactors for the development of a complicated disease course in CD patients. The associations were expressed as odds ratio (OR) and hazard ratio (HR) accompanied by 95% confidence interval (CI). A probability value of less than 0.05, indicating a 2-tailed test, was deemed statistically significant.

RESULTS

Frequency of aCHI3L1 antibodies in IBD

The frequencies of different Ig (sub)types of aCHI3L1 antibodies in patients with IBD and controls are summarized in Table 2. The occurrence of IgA-type aCHI3L1 was higher in CD than in UC (29.2% *vs* 11.1%) or HCONT (2.83%; $P <$ 0.0001 for both). The sIgA subtype aCHI3L1 was more prevalent among both CD and UC patients than in the HCONT group (39.3% and 32.8% *vs* 4.65%, respectively; $P < 0.0001$). No differences were found in IgG antibodies in either group. Information on the sensitivity and specificity of aCHI3L1 antibodies as diagnostic tests is available in Supplementary Table 1.

The stability of aCHI3L1 antibodies in CD and its correlation with the overall disease duration

In a subset of CD patients ($n = 165$), more than one serum sample per patient was available at different time points to assess the stability of antibody levels and statuses (positive or negative for the respective antibodies) over time. The median time between sample procurements was 44.4 mo (IQR: 23.3-66.6). Comparing the results of the first and last available serum samples using the Wilcoxon test, no significant differences in aCHI3L1 antibody levels were found for any Ig type. The aCHI3L1 antibody status was equally stable for all Ig types, with an average of < 10% of patients showing a change in antibody status over time. The IgA type antibody status showed a slightly greater change (20.6%). The stability data for different serological antibodies are summarized in Table 3. There were no clinically significant differences in the evaluated study endpoints when considering stability data. Further studies with sequential sampling and serial measurements both before and after the study endpoint events are needed for a more detailed evaluation of aCHI3L1 antibody stability in CD, which is beyond the limits of the current work.

No correlation was found between antibody status and clinical or endoscopic disease activity (as measured by either HBI or SES-CD) or disease duration at the time of sample acquisition (Supplementary Table 2). aCHI3L1 IgG levels were not analyzed further because of the low prevalence of antibody positivity in the CD cohort. IgA and sIgA aCHI3L1 antibody levels did not differ according to clinical activity ($P = 0.385$ and 0.6830, respectively). Nevertheless, the actual CDAI, HBI, and SES-CD indices were also not correlated with IgA and sIgA aCHI3L1 antibody levels, as determined by Spearman correlation analysis (Supplementary Table 3). The levels of aCHI3L1 antibodies were not associated with disease duration (Kruskal-Wallis test).

Association of aCHI3L1 antibody formation with clinical, serological, and genetic characteristics of CD

A summary of the results is presented in Table 4.

Correlation with clinical features: The presence of both IgA and sIgA aCHI3L1 antibodies was associated with colonic involvement (IgA: 35.5% *vs* 7.7%, $P < 0.0001$; sIgA: 43.5% *vs* 26.9%, $P < 0.038$) in CD. The occurrence of aCHI3L1 sIgA was higher in patients with complicated disease behavior at diagnosis compared to those with uncomplicated disease behavior (57.1% *vs* 36.0%, $P = 0.009$). Additionally, a higher prevalence of IgA-type aCH3L1 was observed in patients with frequent relapses during the course of CD than in those without (46.9% *vs* 25.7%, $P = 0.005$).

Association with serological and genetic characteristics: Significant associations were found between the presence of certain IgA antimicrobial (ASCA, anti-OMP), antiphospholipid (anti-PS/PT), and autoantibody [anti-glycoprotein 2 (GP2)] types, and aCHI3L1 IgA and sIgA positivity. The following correlations were found when examining these antibodies. Anti-ASCA, anti-OMP, and anti-PS/PT IgA showed a significantly higher prevalence of anti-CHI3L1 antibody IgA and sIgA in patients positive for the above-mentioned antibodies. For anti-GP2 positive patients, this association was only seen for anti-CHI3L1 sIgA, with no significant difference for anti-CHI3L1 IgA. However, anti-GP2 positive patients had the highest prevalence of anti-CHI3L1 sIgA. In our study, the prevalence of different aCHI3L1 antibodies was not associated with the presence or absence of major NOD2/CARD15 mutations (data not shown).

Significance of aCHI3L1 antibodies in predicting the development of a complicated disease course in CD

In time-dependent univariate models, a trend was observed between the presence of IgA or sIgA aCHI3L1 and the time to development of a complicated disease behavior with borderline significance (Figure 1).

Considering that the prevalence of antibodies against CHI3L1 was significantly higher in patients with colonic involvement (aCHI3L1 IgA positivity: L2/L3 35.5% *vs* L1 7.7%; sIgA: 43.5% *vs* 26.9%), we performed subgroup analysis. Kaplan-Meier analysis was used to analyze a group of patients with CD who had concomitant presence of pure inflammatory luminal disease (B1) and colon involvement at the time of diagnosis. The results showed that positivity for IgA or sIgA type aCH3L1 predicted faster progression towards a complicated disease course in time-dependent models (Figure 2). The association was no longer present after merging the subgroups of different disease locations (as shown in

Table 2 Prevalence of autoantibodies against chitinase 3-like 1 in inflammatory bowel disease patients

Serum aCHI3L1	CD (*n* = 257)		UC (*n* = 180)		HCONT (*n* = 86)	
	n	%	*n*	%	*n*	%
IgG	21	8.2%[b]	3	1.7%[b]	2	2.83%
IgA	75	29.2%[a,c]	20	11.1%[c,d]	2	2.83%[a,d]
sIgA	101	39.3%[a]	59	32.8%[e]	4	4.65%[a,e]

[a]$P \leq 0.0001$. Crohn's disease *vs* controls.
[b]$P = 0.003$. Crohn's disease *vs* ulcerative colitis.
[c]$P \leq 0.0001$. Crohn's disease *vs* ulcerative colitis.
[d]$P = 0.016$. Ulcerative colitis *vs* controls.
[e]$P \leq 0.0001$. Ulcerative colitis *vs* controls.
Using χ^2-test with Yates correction. CD: Crohn's disease; UC: Ulcerative colitis; IgA: Immunoglobulin A; sIgA: Secretory immunoglobulin A; aCHI3L1: Anti-chitinase 3-like 1 autoantibodies; HCONT: Healthy controls.

Table 3 Stability of anti-chitinase 3-like 1 autoantibodies status over time in patients with Crohn's disease during the disease course

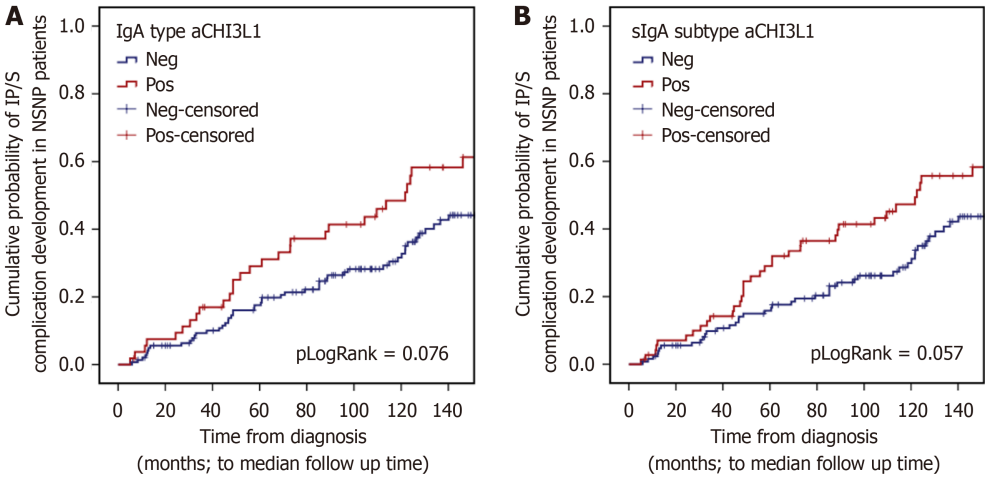
Serologic antibodies	(Sub)type	*n*	Stable negative, *n* (%)	Stable positive, *n* (%)	Negative to positive, *n* (%)	Positive to negative, *n* (%)
aCHI3L1	IgG	165	152 (92.1)	2 (1.2)	2 (1.2)	9 (5.5)
	IgA	165	92 (55.8)	39 (23.6)	17 (10.3)	17 (10.3)
	sIgA	165	83 (50.3)	51 (30.9)	14 (8.5)	17 (1.1)

aCHI3L1: Anti-chitinase 3-like 1 autoantibodies.

Table 4 Association of anti-chitinase 3-like 1 autoantibodies antibody formation with clinical, serological, and genetic characteristics of Crohn's disease at diagnosis and last follow-up

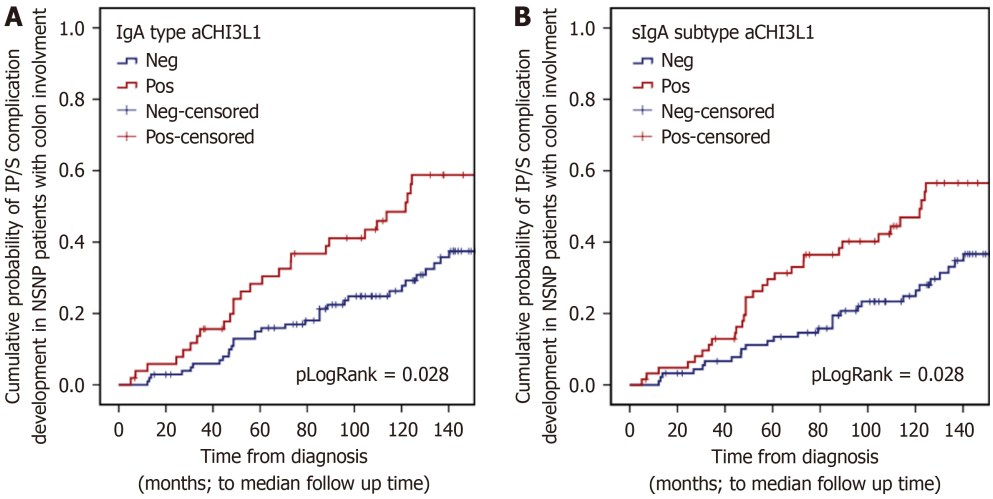
Anti-CHI3L1	IgA		sIgA	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
At diagnosis				
Complicated disease behaviour	1.86 (0.97-3.55)	0.081	2.37 (1.26-4.48)	0.009
Colon involvement	6.61 (2.29-19.07)	< 0.0001	2.09 (1.07-4.10)	0.038
ASCA IgA	4.11 (2.24-7.55)	< 0.0001	4.16 (2.40-7.19)	< 0.0001
OMP IgA	3.16 (1.79-5.57)	< 0.0001	2.64 (1.57-4.44)	< 0.0001
Anti-PS/PT IgA	3.46 (1.49-8.04)	0.005	2.56 (2.15-14.58)	< 0.0001
Anti-GP2 IgA	4.76 (0.87-26.18)	0.108	9.47 (1.12-79.52)	0.018
At last visit				
Frequent relapse	2.56 (1.34-4.91)	0.005	1.89 (1.00-3.56)	0.047

Column corresponding to immunoglobulin G type anti-chitinase 3-like 1 autoantibodies and rows corresponding to age at onset, perianal disease at diagnosis, extraintestinal manifestations, NOD2/CARD15 mutations and therapy were omitted because statistically significant differences for a given parameter were not obtained. Positive associations are indicated in bold and negative associations are in italics (*P* values, odds ratio and 95% confidence interval). IgA: Immunoglobulin A; sIgA: Secretory immunoglobulin A; aCHI3L1: Anti-chitinase 3-like 1 autoantibodies; OR: Odds ratio; CI: Confidence interval; ASCA: Anti-*Saccharomyces cerevisiae* antibody; OMP: Outer membrane protein; Anti-PS/PT: Anti-phosphatidylserine/prothrombin antibody; Anti-GP2: Anti-glycoprotein 2 antibody.



DOI: 10.3748/wjg.v29.i42.5728 **Copyright** ©The Author(s) 2023.

Figure 1 Kaplan-Meier survival analysis for the probability of internal penetrating/stricturing complication development in Crohn's disease patients with non-stricturing and non-penetrating disease at diagnosis. A: Comparing survival curves of immunoglobulin A (IgA)-type anti-CHI3L1 autoantibody (aCHI3L1) positive *vs* negative subgroups; B: Comparing survival curves of secretory IgA-type aCHI3L1 positive *vs* negative subgroups. IP/S: Internal penetrating/stricturing; NSNP: Non-stricturing and non-penetrating; IgA: Immunoglobulin A; sIgA: Secretory immunoglobulin A; aCHI3L1: Anti-CHI3L1 autoantibodies.



DOI: 10.3748/wjg.v29.i42.5728 **Copyright** ©The Author(s) 2023.

Figure 2 Kaplan-Meier survival analysis for the probability of internal penetrating/stricturing complication development in Crohn's disease patients with non-stricturing and non-penetrating disease and colonic involvement at diagnosis. A: Comparing survival curves of immunoglobulin A (IgA)-type anti-CHI3L1 autoantibody (aCHI3L1) positive *vs* negative subgroups; B: Comparing survival curves of secretory IgA-type aCHI3L1 positive *vs* negative subgroups. IP/S: Internal penetrating/stricturing; NSNP: Non-stricturing and non-penetrating; IgA: Immunoglobulin A; sIgA: Secretory immunoglobulin A; CHI3L1: Chitinase 3-like 1.

Figure 1). This relationship is shown in Tables 5-8, which summarizes the time-dependent univariate subgroup analyses for colon involvement.

The results of the Kaplan-Meier and univariate Cox regression analyses regarding associations between clinical factors and the development of complications are summarized in Tables 5-8. The risk of the development of internal penetrating and/or stenotic complications was associated with location, including extensive disease, which remained significant in the subgroup of patients with colonic involvement. In contrast, colon involvement was a protective factor (Table 5). Based on this, the occurrence of perianal penetrating complications in P0 patients was associated with early onset disease, colon involvement, and frequent relapses. Within the subgroup of patients with colonic involvement, this association remained significant in those with frequent relapses (Table 6).

Resective surgery was not associated with any of the clinical factors studied, neither in the B1 patient group nor in patients with colonic involvement (Table 7). Patients with a previous surgery were more likely to undergo a new operation in patients who relapsed frequently, which was also true for the subgroup with colonic involvement (Table 8).

In multivariate Cox regression analysis, the subgroup of B1 patients with colonic involvement, IgA-type aCHI3L1 positivity independently predicted a faster progression towards a complicated disease course in time-dependent models

Table 5 Univariate and multivariate Cox regression analyses evaluating the association between clinical and serologic variables and the study end-point events (complicated disease course) in Crohn's disease patients. Subgroup analysis of B1 patients with colonic involvement is shown in the second half of the table

		Development of internal penetrating and/or stenotic complication in B1 patients at diagnosis							Development of internal penetrating and/or stenotic complication in B1 patients at diagnosis with colonic involvement						
		n of subjects	CP of event (%)[1]	pLogRank	HR (95%CI)[2]	*P* value[2]	HR (95%CI)[3]	*P* value[3]	*n* of subjects	CP of event (%)[1]	pLogRank	HR (95%CI)[2]	*P* value[2]	HR (95%CI)[3]	*P* value[3]
Overall population		209	47.5						160	44.4					
Clinical factors															
Age at onset	A1	27	47.7	0.137	1.95 (0.74-5.14)	0.175			26	47.7	0.095	4.12 (0.93-18.28)	0.062	7.26 (0.94-55.89)	0.057
	A2	157	51.0		2.26 (0.98-5.21)	0.055			118	46.7		4.20 (1.02-17.23)	0.046	7.79 (1.07-56.52)	0.042
	A3	25	25.9			0.152			16	19.8			0.137		0.127
Gender	Male	91	47.7	0.494	1.15 (0.77-1.74)	0.495			69	44.8	0.489	1.18 (0.74-1.90)	0.490	1.10 (0.68-1.79)	0.697
	Female	118	47.3						91	43.9					
Location	L1 + L3	129	57.3	0.002	1.98 (1.27-3.08)	0.003			80	55.5	0.013	1.82 (1.13-2.95)	0.014	1.83 (1.12-2.99)	0.016
	L2	80	34.5						80	34.5					
	L2 + L3	160	44.4	0.027	0.59 (0.37-0.95)	0.029									
	L1	49	62.9												
Frequent relapse	No	154	44.8						115	41.7					
	Yes	45	53.3	0.489	1.18 (0.74-1.89)	0.490			38	52.7	0.533	1.19 (0.69-2.04)	0.534		
Antibodies against CHI3L1															
aCHI3L1 IgG	Negative	182	49.7						141	45.5					
	Positive	17	33.9	0.219	0.57 (0.23-1.41)	0.226			14	38.6	0.561	0.76 (0.31-1.90)	0.562		
aCHI3L1 IgA	Negative	145	44.1						103	37.4					
	Positive	54	58.3	0.076	1.49 (0.96-	0.078			52	58.8	0.028	1.71 (1.05-	0.030	1.67 (1.02-	0.041

					2.31)						2.78)		2.71)	
aCHI3L1 sIgA	Negative	127	43.7				92	36.6					
	Positive	72	55.7	0.057	1.50 (0.99-2.29)	0.059	63	56.6	0.028	1.70 (1.05-2.75)	0.031	1.59 (0.98-2.58)	0.061

[1]Cumulative probability of event (%) corresponds to the median follow-up values.
[2]Univariate analysis.
[3]Multivariate analysis.
Rows corresponding to perianal disease according to the Montreal classification at diagnosis, smoking habits, and familial inflammatory bowel diseases were omitted because statistically significant differences for a given parameter were not obtained. HR: Hazard ratio; Age at onset: A1: ≤ 16 years, A2: 17-40 years, A3: > 40 years; Location: L1: Ileal, L2: Colonic, L3: Ileocolonic, L1 + L3: Ileal involvement, L2 + L3: Colonic involvement; Behavior: B1: Inflammatory/non-stricturing and non-penetrating; B2: Stenosing; B3: Internal penetrating; P0: Lack of perianal disease/involvement; P1: Perianal disease/involvement. IBD: Inflammatory bowel diseases; Ig: Immunoglobulin; sIgA: Secretory IgA; aCHI3L1: Anti-chitinase 3-like 1 autoantibodies; CP: Cumulative probability; CI: Confidence interval; HR: Hazard ratio.

(HR = 1.67; 95%CI: 1.02-2.71; P = 0.041). Among the clinical factors, the same was observed for extensive disease (HR = 1.83; 95%CI: 1.12-2.99; P = 0.016). None of the other clinical factors and or serologic antibodies studied were independently associated with the development of unfavorable disease outcomes (Tables 5-8).

DISCUSSION

CHI3L1 (also known as human cartilage glycoprotein-39 or YKL-40 or 40-kDa mammary gland protein) is a 40 kDa heparin-, chitin-, hyaluronan-, and collagen-binding glycoprotein expressed by various cell types such as synovial cells, chondrocytes, endothelial cells, smooth muscle cells, hepatic stellate cells, cancer cells, fibroblast-like cells, macrophages, neutrophils, and colonic epithelial cells (CEC)[21,49]. It belongs to the 18-glycosylhydrolase family and lacks chitinase activity owing to an amino acid change in the catalytic region[21,49-51]. Besides oncogenesis[49] previous studies proposed its role in numerous systemic-[52-57], respiratory-[58-69], digestive-[21,27,28,70-78], cardiovascular-[79-85], endocrine-[80,84,86,87], neurological-[88,89], urinary-[90-94], skeletal-[84,95], autoimmune-[96], and dermatological[97,98] conditions with features of either acute or chronic inflammation.

According to a comprehensive review by Tizaoui *et al*[99], 14 studies were conducted on the role of CHI3L1 in IBD. Our literature search identified only three additional papers from 2019 on the topic in PubMed[100-102]. Elevated serum CHI3L1 levels have been reported in most of those studies; however, there are controversial results regarding their correlation with disease activity[99]. In a study by Vind *et al*[103], serum CHI3L1 levels tended to be elevated in 30% of patients with CD, even when the disease became inactive. In UC, they correlated well with the laboratory and clinical markers of disease activity. These distinctions can be attributed to the different characteristics of inflammation in CD and UC [transmural *vs* (sub)mucosal][104].

Most of the studies were cross-sectional without a detailed prospective follow-up; therefore, it is very difficult to draw any conclusions regarding the usefulness of serum CHI3L1 in monitoring disease activity, even in UC alone. More promising information is available on the use of CHI3L1 as a fecal biomarker in pediatric[27] and adult[28] IBD cohorts as well, since it showed a good correlation with endoscopic activity in both CD and UC, with comparable performance to fecal calprotectin.

Table 6 Univariate and multivariate Cox regression analyses evaluating the association between clinical and serologic variables and the study end-point events (development of perianal complications) in Crohn's disease patients. Subgroup analysis of B1 patients with colonic involvement is shown in the second half of the table

		Development of perianal penetrating complication in P0 patients at diagnosis							Development of perianal penetrating complication in P0 patients at diagnosis with colonic involvement						
		n of subjects	CP of event (%)[1]	pLogRank	HR (95%CI)[2]	*P* value[2]	HR (95%CI)[3]	*P* value[3]	*n* of subjects	CP of event (%)[1]	pLogRank	HR (95%CI)[2]	*P* value[2]	HR (95%CI)[3]	*P* value[3]
Overall population		215	24						157	27.9					
Clinical factors															
Age at onset	A1	25	34.9	0.011	5.05 (1.44-17.7)	0.012			24	34.9	0.109	3.22 (0.92-11.31)	0.068		
	A2	158	23.9		2.46 (0.76-8.01)	0.134			113	28.5		1.94 (0.59-6.33)	0.274		
	A3	30	7			0.016			20	10.5			0.122		
Gender	Male	90	23.1	0.584	0.85 (0.48-1.51)	0.585			68	27.2	0.474	0.81 (0.45-1.45)	0.475		
	Female	123	24						89	28.7					
Location	L1 + L3	147	20.5	0.066	0.60 (0.35-1.04)	0.640			91	27.1	0.634	0.87 (0.49-1.54)	0.635		
	L2	66	28.8						66	28.8					
	L2 + L3	157	27.9	0.002	4.25 (1.53-11.79)	0.001									
	L1	56	8.9												
Frequent relapse	No	160	18						115	22.3					
	Yes	45	40.9	0.000	2.94 (1.68-5.15)	0.000			33	44.2	0.001	2.61 (1.45-4.68)	0.001		
Antibodies against CHI3L1															
aCHI3L1 IgG	Negative	187	22.3						138	25.0					
	Positive	15	33.3	0.988	0.99 (0.36-2.76)	0.988			12	37.5	0.933	0.96 (0.34-2.68)	0.933		
aCHI3L1 IgA	Negative	145	21.7						96	25.2					
	Positive	57	25.8	0.624	1.16 (0.64-	0.624			54	26.7	0.862	0.95 (0.51-	0.862		

					2.11)						1.75)	
aCHI3L1 sIgA	Negative	122	22.0				83	24.9				
	Positive	80	24.7	0.746	0.91 (0.51-1.62)	0.746	67	27.6	0.645	0.87 (0.48-1.58)	0.645	

[1]Cumulative probability of event (%) corresponds to the median follow-up values.
[2]Univariate analysis.
[3]Multivariate analysis.
Rows corresponding to behaviour according to the Montreal classification at diagnosis, smoking habits, and familial inflammatory bowel disease were omitted because statistically significant differences for a given parameter were not obtained. HR: Hazard ratio; Age at onset: A1: ≤ 16 years, A2: 17-40 years, A3: > 40 years; Location: L1: Ileal, L2: Colonic, L3: Ileocolonic, L1 + L3: Ileal involvement, L2 + L3: Colonic involvement; Behavior: B1: Inflammatory/non-stricturing and non-penetrating; B2: Stenosing; B3: Internal penetrating; P0: Lack of perianal disease/involvement; P1: Perianal disease/involvement. IBD: Inflammatory bowel diseases; Ig: Immunoglobulin; sIgA: Secretory IgA; aCHI3L1: Anti-chitinase 3-like 1 autoantibodies; CP: Cumulative probability; CI: Confidence interval; HR: Hazard ratio.

CHI3L1 was first described as an autoantigenic target in rheumatoid arthritis in 1997[105,106] and in IBD in 2019[30]. The latter was confirmed by the authors of this manuscript[30]. To date, autoantibodies against CHI3L1 have only been detected in these two entities[30,107-110]. aCHI3L1 were evaluated in only one cross-sectional study in IBD on a pediatric population (CD: n = 110, UC: n = 95)[30]. To our knowledge, this is the first prospective study on aCHI3L1 as a biomarker with predictive potential in an adult cohort of IBD patients. Similar prevalence rates were reported by Deutschmann *et al* [30] for IgA and sIgA aCHI3L1 in our adult IBD cohort. IgG-type positivity was more prevalent in children. In the pediatric population, ileal-, whilst in adults colonic involvement was associated with higher antibody positivity. The discrepancies between the two studies may be attributed to presumably different immune responses owing to the different maturity of the immune system, age-related changes in the microbiome, and differences in the onset and course of IBD in children[111].

It is suspected that, unlike UC, CD patients are more prone to developing a tolerance break against CHI3L1 due to persistent elevation of CHI3L1 independent of disease activity[30,103,112]. This hypothesis is also supported by our findings regarding the differences in aCHI3L1 autoantibody prevalence among pediatric[30] and adult IBD subgroups. In our study, similar to CHI3L1, no correlation was found between aCHI3L1 positivity and disease activity in CD patients. Regarding autoantibodies against CHI3L1, we did not find any association between aCHI3L1 formation and response to therapy, which is consistent with previous IBD studies. Unlike other disorders, the levels of serum auto- and antimicrobial antibodies in IBD remain largely unchanged regardless of the inflammatory burden or the effects of anti-inflammatory therapy or surgical resection. Unlike other autoimmune diseases such as ANCA-associated vasculitides, classic and newly discovered autoantibodies (*e.g.*, ANCA, PAbs, APLAs, aCHI3L1), and antimicrobial antibodies (ASCA, anti-OMP PlusTM IgA) have no established role in monitoring the efficacy of IBD treatment[18].

The prevalence of IgA-type aCHI3L1 antibodies was significantly higher in CD patients than in UC patients and HCONT. A similarly elevated prevalence was also observed for the sIgA subtype, with the difference that this was independent of IBD subtype. In our previous studies, significant differences in favor of IgA and sIgA (sub)types were also detected in the evaluated classic auto- (PAB, ACA, aPS/PT) and antimicrobial antibodies (ASCA, anti-OMP) in IBD[29,31,113,114]. In parallel, in the aforementioned studies, we found associations between complications in CD for IgA and not IgG types[29,31,113,114]. The mucosal immune system in the gut plays a central role in IgA antibody production. In previous studies, the increased IgA_2 subtype ratio and concomitant presence of the secretory component (SC) were considered as evidence for a mucosal origin of IgA secretion[115,116]. Our research group previously reported the

Table 7 Univariate and multivariate Cox regression analyses evaluating the association between clinical and serologic variables and the study end-point events (need for resective surgery) in Crohn's disease patients. Subgroup analysis of B1 patients with colonic involvement is shown in the second half of the table

		Need for resective surgery in B1 patients at diagnosis							Need for resective surgery in B1 patients at diagnosis with colonic involvement						
		n of subjects	CP of event (%)[1]	pLogRank	HR (95%CI)[2]	*P* value[2]	HR (95%CI)[3]	*P* value[3]	*n* of subjects	CP of event (%)[1]	pLogRank	HR (95%CI)[2]	*P* value[2]	HR (95%CI)[3]	*P* value[3]
Overall population		209	38						160	36					
Clinical factors															
Age at onset	A1	27	29.1	0.937	0.94 (0.38-2.35)	0.896			26	29.1	0.989	0.96 (0.33-2.80)	0.945		
	A2	157	39.8		1.06 (0.50-2.22)	0.887			118	37		1.01 (0.40-2.58)	0.980		
	A3	25	40.4			0.937			16	43			0.989		
Gender	Male	91	34.2	0.958	0.99 (0.62-1.57)	0.958			69	33.7	0.977	0.99 (0.59-1.66)	0.977		
	Female	118	40.8						91	37.7					
Location	L1 + L3	129	31.1	0.109	1.48 (0.91-2.40)	0.112			80	41.5	0.174	1.45 (0.85-2.43)	0.176		
	L2	80	43.7						80	31.1					
	L2 + L3	160	50.2	0.382	0.78 (0.44-1.38)	0.384									
	L1	49	36.0												
Frequent relapse	No	154	36.9	0.950					115	35.8					
	Yes	45	38.7		0.98 (0.58-1.68)	0.950			38	32.4	0.602	0.85 (0.47-1.56)	0.852		
Antibodies against CHI3L1															
aCHI3L1 IgG	Negative	182	38.9						141	36.4					
	Positive	17	34.7	0.997	1.00 (0.43-2.32)	0.997			14	39.9	0.623	1.24 (0.53-2.89)	0.624		
aCHI3L1 IgA	Negative	145	34.1						103	30.3					
	Positive	54	48.5	0.246	1.34 (0.82-2.18)	0.248			52	47.6	0.255	1.36 (0.80-2.29)	0.257		

aCHI3L1 sIgA	Negative	127	33.8				92	29.8			
	Positive	72	46.3	0.159	1.40 (0.88-2.24)	0.161	63	46.4	0.227	1.37 (0.82-2.31)	0.230

[1]Cumulative probability of event (%) corresponds to the median follow-up values.

[2]Univariate analysis.

[3]Multivariate analysis.

Rows corresponding to perianal disease according to the Montreal classification at diagnosis, smoking habits, and familial inflammatory bowel diseases were omitted because statistically significant differences for a given parameter were not obtained. HR: Hazard ratio; Age at onset: A1: ≤ 16 years, A2: 17-40 years, A3: > 40 years; Location: L1: Ileal, L2: Colonic, L3: Ileocolonic, L1 + L3: Ileal involvement, L2 + L3: Colonic involvement; Behavior: B1: Inflammatory/non-stricturing and non-penetrating; B2: Stenosing; B3: Internal penetrating; P0: Lack of perianal disease/involvement; P1: Perianal disease/involvement. IBD: Inflammatory bowel diseases; Ig: Immunoglobulin; sIgA: Secretory IgA; aCHI3L1: Anti-chitinase 3-like 1 autoantibodies; CP: Cumulative probability; CI: Confidence interval; HR: Hazard ratio.

mucosal origin of ANCA IgA in a group of patients with liver cirrhosis indirectly by demonstrating the presence of SC [117]. Similarly, we were able to demonstrate the mucosal origin of ASCA IgA in CD using flow cytometry (unpublished results, first presented at the 12th Congress of the ECCO)[114]. In the present study, we also demonstrated the presence of aCHI3L1 antibodies of mucosal origin in IBD. The higher prevalence of aCHI3L1 IgA in CD than in UC may be due to the different nature of mucosal inflammation (degree of intestinal wall involvement more pronounced in CD - transmural *vs* mucosal)[104], as well as its localisation. In CD, serum total sIgA levels were also significantly higher (median: 51 *vs* 29 μg/mL; $P < 0.001$), which was more pronounced in the presence of certain antimicrobial antibody IgA types[114]. This phenomenon, namely the tendency for IgA-dominant antibody formation in IBD, is thus not specific for antibodies produced against CHI3L1 and may reflect an immune response to an enhanced microbial load. This hypothesis is also supported by the significant associations between the presence of certain IgA antimicrobial (ASCA, anti-OMP), antiphospholipid (anti-PS/PT), and autoantibody (anti-GP2) types and aCHI3L1 IgA and sIgA positivity found in our study. Meanwhile, IgA-type autoantibodies are viewed as an indication of an immune response to enteric antigens, which in other ailments has been linked to a rise in BT[29]. BT refers to the increased uptake of bacteria or bacterial products from the intestinal lumen into systemic circulation[118,119]. In IBD, the combination of structural and functional intestinal barrier damage due to chronic intestinal inflammation, reduced intestinal mucosal defenses, altered microbiome, and dysregulated immune response to specific bacterial components is thought to lead to chronic BT. The uncontrolled uptake of various luminal bacteria and/or bacterial products exacerbates the local and systemic proinflammatory processes already underway, thereby contributing to disease exacerbation and complications[104,120-125]. However, it remains unclear whether these alterations can directly contribute to the development of IBD or whether they are just an epiphenomenon.

Roggenbuck *et al*[126] first hypothesized the pathophysiological role of anti-pancreatic antibodies in CD in inducing and maintaining increased BT[127]. Following loss of tolerance to GP2, plasma cells synthesize anti-GP2 IgA, which is transported by intestinal epithelial cells into the intestinal lumen. Secreted anti-GP2 IgA can form a bridge between GP2-derived pancreatic GP2-opsonized FimH-positive bacteria and membrane-bound GP2 on the surface of M cells. These processes lead to microbial overload of the mucosa due to increased transcytosis in CD, which amplifies the inflammatory processes in the gut[29]. In the case of CHI3L1 and antibodies against it, very similar mechanisms can enhance BT if an increased tendency to form antibodies against this glycoprotein develops as a consequence of loss of CHI3L1 tolerance.

Under normal conditions, CHI3L1 levels are extremely low, but under inflammatory conditions, they are also expressed at elevated levels in CEC and macrophages[51,128]. Mizoguchi[129] demonstrated an upregulated expression of CHI3L1 in the lamina propria and CECs of IBD patients and animal models. This upregulation, along with the loss of

Table 8 Univariate and multivariate Cox regression analyses evaluating the association between clinical and serologic variables and the study end-point events (reoperation after resection) in Crohn's disease patients. Subgroup analysis of B1 patients with colonic involvement is shown in the second half of the table

		Need for resective surgery in B1 patients with previous CD-related abdominal surgery							Need for resective surgery in B1 patients with previous CD-related abdominal surgery and colonic involvement						
		n of subjects	CP of event (%)[1]	pLogRank	HR (95%CI)[2]	*P* value[2]	HR (95%CI)[3]	*P* value[3]	*n* of subjects	CP of event (%)[1]	pLogRank	HR (95%CI)[2]	*P* value[2]	HR (95%CI)[3]	*P* value[3]
Overall population		73	28.2						58	26.6					
Clinical factors															
Age at onset	A1	11	60.2	0.186	4.47 (0.52-38.57)	0.173			11	60.2	0.122	3.16 (0.36-27.59)	0.298		
	A2	54	23.8		1.94 (0.25-15.25)	0.530			42	17.9		0.97 (0.12-8.13)	0.976		
	A3	8	12.5			0.214			5	20.0			0.150		
Gender	Male	32	29.5		1.03 (0.38-2.77)	0.956			26	19.8	0.368	0.58 (0.17-1.93)	0.374		
	Female	41	28.4	0.956					32	33.2					
Location	L1 + L3	45	31.0	0.339	1.67 (0.58-4.82)	0.345			30	29.5	0.454	1.55 (0.49-4.92)	0.457		
	L2	28	23.2						28	23.2					
	L2 + L3	58	26.6	0.430	0.64 (0.20-1.98)	0.434									
	L1	15	35.8												
Familial IBD	No	68	25.5						55	23.8					
	Yes	5	60.0	0.010	4.59 (1.29-16.36)	0.019			3	66.7	0.002	8.19 (1.64-40.86)	0.010		
Frequent relapse	No	51	14.9						40	9.0					
	Yes	19	61.0	0.006	3.79 (1.36-10.55)	0.011			15	73.3	0.000	7.94 (2.03-31.00)	0.003		
Antibodies against CHI3L1															
aCHI3L1 IgG	Negative	64	27.3						51	23.7					
	Positive	4	40.0	0.595	1.50 (0.34-	0.597			6	40.0	0.485	1.72 (0.37-	0.490		

					6.69)						8.04)	
aCHI3L1 IgA	Negative	46	21.5				34	16.3				
	Positive	24	42.1	0.238	1.83 (0.66-5.04)	0.245	23	39.3	0.220	2.07 (0.63-6.80)	0.230
aCHI3L1 sIgA	Negative	40	17.2				31	13.9				
	Positive	30	46.2	0.052	2.68 (0.95-7.58)	0.062	26	41.0	0.086	2.82 (0.82-9.68)	0.100

[1]Cumulative probability of event (%) corresponds to the median follow-up values.
[2]Univariate analysis.
[3]Multivariate analysis.
Rows corresponding to perianal disease according to the Montreal classification at diagnosis, smoking habits were omitted because statistically significant differences for a given parameter were not obtained. HR: Hazard ratio; Age at onset: A1: ≤ 16 years, A2: 17-40 years, A3: > 40 years; Location: L1: Ileal, L2: Colonic, L3: Ileocolonic, L1 + L3: Ileal involvement, L2 + L3: Colonic involvement; Behavior: B1: Inflammatory/non-stricturing and non-penetrating; B2: Stenosing; B3: Internal penetrating; P0: Lack of perianal disease/involvement; P1: Perianal disease/involvement. IBD: Inflammatory bowel diseases; Ig: Immunoglobulin; sIgA: Secretory IgA; aCHI3L1: Anti-chitinase 3-like 1 autoantibodies; CP: Cumulative probability; CI: Confidence interval; HR: Hazard ratio.

tolerance to CHI3L1, enhances the adhesion and invasion of certain commensal and/or pathogenic bacteria *via* carbohydrate binding [chitin binding protein (CBP) 21] or homologous motifs (for example, ChiA)[21,30]. Significantly higher prevalence of IgA and sIgA (sub)type antibodies against CHI3L1 in patients with colonic involvement (aCHI3L1 IgA positivity: L2/L3 35.5% *vs* L1 7.7%; sIgA: 43.5% *vs* 26.9%) along with a positive predictive value for complicated disease course in only this subgroup of CD patients could be considered as an indirect confirmation of colonic origin of these antibodies. Further studies to assess the presence of aCHI3L1 antibodies in different parts of the gut mucosa of IBD patients are needed to confirm this hypothesis.

CHI3L1 is recognized as a biomarker of fibrosis due to its contribution to tissue remodeling and fibrosis by hindering the degradation of type I collagen and hyaluronic acid, and by regulating the enzymatic activity of matrix metalloproteinases, ultimately affecting cell adhesion and migration[39,40,101]. Previously it has been shown by Erzin *et al*[130] that increased serum CHI3L1 was associated with intestinal stricture formation in CD patients. Here, we present confirmatory results that autoantibodies against CHI3L1 may be involved in stricture and fistula formation in CD patients. In pediatric IBD patients with complicated disease behavior, a trend toward higher prevalence of IgA and sIgA (subtype) aCHI3L1 was observed (38.5% *vs* 22.0% and 53.8% *vs* 35.6%, respectively)[30]. The lack of statistical significance in this case can be explained by the relatively low number of patients in these subgroups of patients (aCHI3L1 IgA- and sIgA-positive patients with complicated disease behavior: n = 5 and 7, respectively). In adults aCHI3L1 sIgA positivity was associated with complicated disease behavior at diagnosis (OR = 2.37, 95%CI: 1.26-4.48). The results of cross-sectional single-time point studies should be interpreted with caution[18]. After more than sixty years longitudinal follow-up studies are still considered rare in the field of IBD serology[18]. This study offers, for the first time, longitudinal and prospective data regarding the predictive capabilities of aCHI3L1 antibodies in identifying disease-specific complications and surgical requirements. The presence of IgA or sIgA aCH3L1 antibodies in patients with both inflammatory luminal disease and colon involvement at the time of diagnosis indicates a faster progression towards a complicated disease course in time-dependent models. This association remained significant in multivariate models as well in case of IgA type. This observation, together with our previous results, highlights the need to consider location in addition to antibody class when predicting disease progression. Based on both pathogenic and clinical heterogeneity of IBD, instead of "the one size

fits all" model, an increasing amount of data as this point towards the need for the development and application of prognostic matrix models[131]. As no data are available on the prognostic potential of aCHI3L1 antibodies in IBD, a literature search was performed in this regard in rheumatoid arthritis (RA), the only other entity where the presence of aCHI3L1 was described. Based on these findings, CHI3L1 was not considered a long-term prognostic biomarker for RA [99]. As for autoantibodies against this particular target, no data are available on the predictive potential of RA[107-110].

Similar to other diseases, where CHI3L1 is involved in pathogenesis, CHI3L1 could also serve as a potential therapeutic target in IBD. Kawada *et al*[132] found that by inhibiting CHI3L1 with anti-CHI3L1 antibodies or CHI3L1-specific small interfering RNA, the adhesion of *E. coli* cells overexpressing CBP to CECs was reduced. Ongoing clinical trials are evaluating the use of antibodies against the active region of CHI3L1, and recombinant nasal CHI3L1 (Org39141) to reach tolerance in RA[49].

In conclusion, the integration of IgA and sIgA against CHI3L1 with newly applied CD-specific antibodies (*e.g.*, anti-GP2) in laboratory screening of patients suspected of having CD may improve the sensitivity and specificity of the screening process. Further research is required to determine whether antibodies against CHI3L1 have a diagnostic potential and whether elevated aCHI3L1 levels are only a concomitant feature of CD or contribute to the development and presentation of IBD[30].

A drawback of our study was that the prevalence of antibodies against CHI3L1 was not high. Moreover, these antibodies do not play an exclusive role in prognostics. Although the number of cohorts was significant, we could detect significant differences only in a subgroup of patients, so it would be important to investigate these parameters in a larger group of patients. It would be necessary to establish a validation cohort, also of adults, with a large number of cases, followed prospectively, whose results could confirm or refute our findings.

CONCLUSION

In conclusion, we observed increased IgA autoantibody production in CD patients in an adult IBD cohort by testing autoantibodies against a novel neutrophil autoantigen target, CHI3L1. Antibodies against CHI3L1 showed long-term stability over the course of the disease. It was associated with the clinical phenotype of the disease and identified patients with colonic involvement, complicated disease course, or ASCA IgA and/or anti-OMP positivity. It was correlated with a more rapid onset of a complicated disease (B2 and/or B3) during disease progression in the subgroup of CD patients with no complications at diagnosis (B1) and with colonic involvement. In conclusion, the combined consideration of antibody classes and location in predicting disease progression may revolutionize IBD serology. IgA-type anti-CHI3L1 antibodies may interfere with innate immunity against intestinal bacteria or may reflect an immune response against microbial overload in the intestinal barrier.

ARTICLE HIGHLIGHTS

Research background

Chitinase 3-like 1 (CHI3L1) is a 40 kDa heparin-, chitin-, hyaluronan-, and collagen-binding glycoprotein expressed by various cell types, including fibroblast-like cells, macrophages, neutrophils, and colonic epithelial cells (CEC). Under normal conditions, CHI3L1 levels are extremely low; however, under inflammatory conditions, they are also expressed at elevated levels in CEC and macrophages. Upregulated expression of CHI3L1 in the lamina propria and CECs has been described in patients with inflammatory bowel disease (IBD). This upregulation, along with the loss of tolerance to CHI3L1, can enhance the adhesion and invasion of certain commensal and/or pathogenic bacteria *via* carbohydrate binding (chitin binding protein 21) or homologous motifs (for example, ChiA). Microbial overload, along with mechanical and/or functional derangement of the gut barrier, can lead to the uncontrolled uptake of various luminal bacteria and/or bacterial products. As a result, enhanced bacterial translocation exacerbates local and systemic proinflammatory processes already underway, thereby contributing to disease exacerbation and complications.

Research motivation

Given the current state of knowledge, the precise function and mechanism of CHI3L1 in the development of IBD, loss of tolerance to this antigen, formation of immunoglobulin A (IgA) autoantibodies against it, and their role in the pathogenesis of IBD remain elusive. Concomitantly, there is an unmet need to identify new biomarkers to identify patients with IBD with a complicated disease course.

Research objectives

To evaluate the predictive value of different immunoglobulin subtypes of the novel serological marker, anti-CHI3L autoantibodies (aCHI3L1), in terms of their ability to define the disease phenotype, therapeutic strategy, and long-term disease course in a group of adult IBD patients with prospective follow-up.

Research methods

A total of 257 patients with Crohn's disease (CD) and 180 patients with ulcerative colitis (UC) from a tertiary IBD referral center in Hungary (Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of

Debrecen) were tested for IgG, IgA, and secretory IgA (sIgA) type aCHI3L1 using enzyme-linked immunosorbent assay with recombinant CHI3L1, along with 86 healthy controls.

Research results

Enhanced formation of IgA and sIgA (sub)-type against CHI3L1 was first detected in adult patients with CD, which was associated with the clinical phenotype in a tertiary referral IBD center in Hungary. This observational study presents, for the first time, longitudinal and prospective results on the predictive ability of aCHI3L1 antibodies to identify disease-specific complications and surgical requirements, which are critical for patient care. The presence of IgA or sIgA aCH3L1 antibodies in CD patients with both inflammatory luminal disease and colon involvement at the time of diagnosis indicates a faster progression towards a complicated disease course in time-dependent models.

Research conclusions

CHI3L1 is a newly discovered neutrophil autoantigenic target in IBD. By taking into account the classes of antibodies and utilizing location-based predictions, serology in IBD may undergo a significant transformation in the future.

Research perspectives

Based on both the pathogenic and clinical heterogeneity of IBD, instead of the "the one size fits all" model, an increasing amount of data points towards the need for the development and application of prognostic matrix models. Therefore, identifying new biomarkers for this purpose is of utmost importance. A significantly higher prevalence of IgA and sIgA (sub)type antibodies against CHI3L1 in patients with colonic involvement, along with a positive predictive value for complicated disease course in only this subgroup of CD patients, could be considered as an indirect confirmation of colonic origin of these antibodies. Further studies to assess the presence of aCHI3L1 antibodies in different parts of the gut mucosa of IBD patients are needed to confirm this hypothesis. Unravelling the role of CHI3L1 and aCHI3L1 autoantibodies in IBD pathogenesis can help identify new potential therapeutic targets for IBD.

FOOTNOTES

Author contributions: Sipeki N, Roggenbuck D, and Papp M made the concept and designed the present study; Sipeki N and Kovats PJ were responsible for clinical data acquisition; Deutschmann C, Schierack P, and Roggenbuck D made the experimental work and were responsible for laboratory data acquisition; Sipeki N, Kovats PJ, and Papp M made the analysis and interpretation of the data, and wrote paper; Deutschmann C, Schierack P, and Roggenbuck D supervised the work, provided expert insights and made critical revisions related to important intellectual content of the manuscript; all authors have read and approved the final manuscript.

Supported by the German Federal Ministry of Education and Research (BMBF- Wachstumskern- PRAEMED.BIO), 03WKDB2C. Papp M was supported by the Janos Bolyai Research Scholarship of the Hungarian Academy of Sciences, BO/00232/17/5; Research Grants of National Research Development and Innovation Office, K115818/2015/1; and New National Excellence Program of the Ministry of Human Capacities, ÚNKP-18-4 Bolyai Plus. These funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Hungarian National Review Board and the Institutional Review Board of the University of Debrecen (DE RKEB/IKEB: 4773-2017; DE OEC RKEB/IKEB: 3515-2011; TUKEB: ad.3880/2012-EKU).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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

Country/Territory of origin: Hungary

ORCID number: Nora Sipeki 0000-0002-6806-2991; Patricia Julianna Kovats 0000-0003-0975-7168; Claudia Deutschmann 0000-0002-3350-8332; Peter Schierack 0000-0002-6445-3506; Dirk Roggenbuck 0000-0002-6861-6827; Maria Papp 0000-0003-3662-4010.

S-Editor: Wang JJ
L-Editor: A

P-Editor: Xu ZH

REFERENCES

1 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]

2 **Wehkamp J**, Götz M, Herrlinger K, Steurer W, Stange EF. Inflammatory Bowel Disease. *Dtsch Arztebl Int* 2016; **113**: 72-82 [PMID: 26900160 DOI: 10.3238/arztebl.2016.0072]

3 **Malik TA**. Inflammatory Bowel Disease: Historical Perspective, Epidemiology, and Risk Factors. *Surg Clin North Am* 2015; **95**: 1105-1122, v [PMID: 26596917 DOI: 10.1016/j.suc.2015.07.006]

4 **Xavier RJ**, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; **448**: 427-434 [PMID: 17653185 DOI: 10.1038/nature06005]

5 **Knights D**, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. *Gut* 2013; **62**: 1505-1510 [PMID: 24037875 DOI: 10.1136/gutjnl-2012-303954]

6 **Szekanecz Z**, McInnes IB, Schett G, Szamosi S, Benkő S, Szűcs G. Autoinflammation and autoimmunity across rheumatic and musculoskeletal diseases. *Nat Rev Rheumatol* 2021; **17**: 585-595 [PMID: 34341562 DOI: 10.1038/s41584-021-00652-9]

7 **Hedrich CM**. Shaping the spectrum - From autoinflammation to autoimmunity. *Clin Immunol* 2016; **165**: 21-28 [PMID: 26948930 DOI: 10.1016/j.clim.2016.03.002]

8 **Hedrich CM**, Tsokos GC. Bridging the gap between autoinflammation and autoimmunity. *Clin Immunol* 2013; **147**: 151-154 [PMID: 23587745 DOI: 10.1016/j.clim.2013.03.006]

9 **McGonagle D**, McDermott MF. A proposed classification of the immunological diseases. *PLoS Med* 2006; **3**: e297 [PMID: 16942393 DOI: 10.1371/journal.pmed.0030297]

10 **Arakelyan A**, Nersisyan L, Poghosyan D, Khondkaryan L, Hakobyan A, Löffler-Wirth H, Melanitou E, Binder H. Autoimmunity and autoinflammation: A systems view on signaling pathway dysregulation profiles. *PLoS One* 2017; **12**: e0187572 [PMID: 29099860 DOI: 10.1371/journal.pone.0187572]

11 **McInnes IB**, Gravallese EM. Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat Rev Immunol* 2021; **21**: 680-686 [PMID: 34518662 DOI: 10.1038/s41577-021-00603-1]

12 **Somineni HK**, Kugathasan S. The Microbiome in Patients With Inflammatory Diseases. *Clin Gastroenterol Hepatol* 2019; **17**: 243-255 [PMID: 30196163 DOI: 10.1016/j.cgh.2018.08.078]

13 **Vindigni SM**, Zisman TL, Suskind DL, Damman CJ. The intestinal microbiome, barrier function, and immune system in inflammatory bowel disease: a tripartite pathophysiological circuit with implications for new therapeutic directions. *Therap Adv Gastroenterol* 2016; **9**: 606-625 [PMID: 27366227 DOI: 10.1177/1756283X16644242]

14 **Ahluwalia B**, Moraes L, Magnusson MK, Öhman L. Immunopathogenesis of inflammatory bowel disease and mechanisms of biological therapies. *Scand J Gastroenterol* 2018; **53**: 379-389 [PMID: 29523023 DOI: 10.1080/00365521.2018.1447597]

15 **Yu S**, Sun Y, Shao X, Zhou Y, Yu Y, Kuai X, Zhou C. Leaky Gut in IBD: Intestinal Barrier-Gut Microbiota Interaction. *J Microbiol Biotechnol* 2022; **32**: 825-834 [PMID: 35791076 DOI: 10.4014/jmb.2203.03022]

16 **Michielan A**, D'Incà R. Intestinal Permeability in Inflammatory Bowel Disease: Pathogenesis, Clinical Evaluation, and Therapy of Leaky Gut. *Mediators Inflamm* 2015; **2015**: 628157 [PMID: 26582965 DOI: 10.1155/2015/628157]

17 **Cananzi M**, Wohler E, Marzollo A, Colavito D, You J, Jing H, Bresolin S, Gaio P, Martin R, Mescoli C, Bade S, Posey JE, Dalle Carbonare M, Tung W, Jhangiani SN, Bosa L, Zhang Y, Filho JS, Gabelli M, Kellermayer R, Kader HA, Oliva-Hemker M, Perilongo G, Lupski JR, Biffi A, Valle D, Leon A, de Macena Sobreira NL, Su HC, Guerrerio AL. IFIH1 loss-of-function variants contribute to very early-onset inflammatory bowel disease. *Hum Genet* 2021; **140**: 1299-1312 [PMID: 34185153 DOI: 10.1007/s00439-021-02300-4]

18 **Papp M**, Lakatos PL. Serological studies in inflammatory bowel disease: how important are they? *Curr Opin Gastroenterol* 2014; **30**: 359-364 [PMID: 24811052 DOI: 10.1097/MOG.0000000000000076]

19 **Wéra O**, Lancellotti P, Oury C. The Dual Role of Neutrophils in Inflammatory Bowel Diseases. *J Clin Med* 2016; **5** [PMID: 27999328 DOI: 10.3390/jcm5120118]

20 **Zhou GX**, Liu ZJ. Potential roles of neutrophils in regulating intestinal mucosal inflammation of inflammatory bowel disease. *J Dig Dis* 2017; **18**: 495-503 [PMID: 28857501 DOI: 10.1111/1751-2980.12540]

21 **Deutschmann C**, Roggenbuck D, Schierack P. The loss of tolerance to CHI3L1 - A putative role in inflammatory bowel disease? *Clin Immunol* 2019; **199**: 12-17 [PMID: 30543919 DOI: 10.1016/j.clim.2018.12.005]

22 **Magalhaes D**, Peyrin-Biroulet L, Estevinho MM, Danese S, Magro F. Pursuing neutrophils: systematic scoping review on blood-based biomarkers as predictors of treatment outcomes in inflammatory bowel disease. *Therap Adv Gastroenterol* 2023; **16**: 17562848231155987 [PMID: 36923488 DOI: 10.1177/17562848231155987]

23 **Maaser C**, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, Calabrese E, Baumgart DC, Bettenworth D, Borralho Nunes P, Burisch J, Castiglione F, Eliakim R, Ellul P, González-Lama Y, Gordon H, Halligan S, Katsanos K, Kopylov U, Kotze PG, Krustinš E, Laghi A, Limdi JK, Rieder F, Rimola J, Taylor SA, Tolan D, van Rheenen P, Verstockt B, Stoker J; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019; **13**: 144-164 [PMID: 30137275 DOI: 10.1093/ecco-jcc/jjy113]

24 **Vermeire S**, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? *Gut* 2006; **55**: 426-431 [PMID: 16474109 DOI: 10.1136/gut.2005.069476]

25 **Di Ruscio M**, Vernia F, Ciccone A, Frieri G, Latella G. Surrogate Fecal Biomarkers in Inflammatory Bowel Disease: Rivals or Complementary Tools of Fecal Calprotectin? *Inflamm Bowel Dis* 2017; **24**: 78-92 [PMID: 29272479 DOI: 10.1093/ibd/izx011]

26 **Vernia F**, Viscido A, Di Ruscio M, Stefanelli G, Valvano M, Latella G. Fecal Lactoferrin and Other Putative Fecal Biomarkers in Crohn's Disease: Do They Still Have a Potential Clinical Role? *Digestion* 2021; **102**: 833-844 [PMID: 34518458 DOI: 10.1159/000518419]

27 **Aomatsu T**, Imaeda H, Matsumoto K, Kimura E, Yoden A, Tamai H, Fujiyama Y, Mizoguchi E, Andoh A. Faecal chitinase 3-like-1: a novel biomarker of disease activity in paediatric inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **34**: 941-948 [PMID: 21848856 DOI: 10.1111/j.1365-2036.2011.04805.x]

28 **Buisson A**, Vazeille E, Minet-Quinard R, Goutte M, Bouvier D, Goutorbe F, Pereira B, Barnich N, Bommelaer G. Faecal chitinase 3-like 1 is a reliable marker as accurate as faecal calprotectin in detecting endoscopic activity in adult patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* 2016; **43**: 1069-1079 [PMID: 26953251 DOI: 10.1111/apt.13585]

29 **Papp M**, Sipeki N, Tornai T, Altorjay I, Norman GL, Shums Z, Roggenbuck D, Fechner K, Stöcker W, Antal-Szalmas P, Veres G, Lakatos PL. Rediscovery of the Anti-Pancreatic Antibodies and Evaluation of their Prognostic Value in a Prospective Clinical Cohort of Crohn's Patients: The Importance of Specific Target Antigens [GP2 and CUZD1]. *J Crohns Colitis* 2015; **9**: 659-668 [PMID: 25968583 DOI: 10.1093/ecco-jcc/jjv087]

30 **Deutschmann C**, Sowa M, Murugaiyan J, Roesler U, Röber N, Conrad K, Laass MW, Bogdanos D, Sipeki N, Papp M, Rödiger S, Roggenbuck D, Schierack P. Identification of Chitinase-3-Like Protein 1 as a Novel Neutrophil Antigenic Target in Crohn's Disease. *J Crohns Colitis* 2019; **13**: 894-904 [PMID: 30753386 DOI: 10.1093/ecco-jcc/jjz012]

31 **Sipeki N**, Davida L, Palyu E, Altorjay I, Harsfalvi J, Szalmas PA, Szabo Z, Veres G, Shums Z, Norman GL, Lakatos PL, Papp M. Prevalence, significance and predictive value of antiphospholipid antibodies in Crohn's disease. *World J Gastroenterol* 2015; **21**: 6952-6964 [PMID: 26078573 DOI: 10.3748/wjg.v21.i22.6952]

32 **Kovacs G**, Sipeki N, Suga B, Tornai T, Fechner K, Norman GL, Shums Z, Antal-Szalmas P, Papp M. Significance of serological markers in the disease course of ulcerative colitis in a prospective clinical cohort of patients. *PLoS One* 2018; **13**: e0194166 [PMID: 29590158 DOI: 10.1371/journal.pone.0194166]

33 **Cunningham-Rundles C**. Physiology of IgA and IgA deficiency. *J Clin Immunol* 2001; **21**: 303-309 [PMID: 11720003 DOI: 10.1023/A:1012241117984]

34 **Yel L**. Selective IgA deficiency. *J Clin Immunol* 2010; **30**: 10-16 [PMID: 20101521 DOI: 10.1007/s10875-009-9357-x]

35 **Singh K**, Chang C, Gershwin ME. IgA deficiency and autoimmunity. *Autoimmun Rev* 2014; **13**: 163-177 [PMID: 24157629 DOI: 10.1016/j.autrev.2013.10.005]

36 **Lennard-Jones JE**. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989; **170**: 2-6; discussion 16 [PMID: 2617184 DOI: 10.3109/00365528909091339]

37 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV Jr, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5A-36A [PMID: 16151544 DOI: 10.1155/2005/269076]

38 **Stange EF**, Travis SP, Vermeire S, Beglinger C, Kupcinkas L, Geboes K, Barakauskiene A, Villanacci V, Von Herbay A, Warren BF, Gasche C, Tilg H, Schreiber SW, Schölmerich J, Reinisch W; European Crohn's and Colitis Organisation. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut* 2006; **55** Suppl 1: i1-15 [PMID: 16481628 DOI: 10.1136/gut.2005.081950a]

39 **Vermeire S**, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol* 2010; **8**: 357-363 [PMID: 20096379 DOI: 10.1016/j.cgh.2010.01.001]

40 **Lewis JD**, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008; **14**: 1660-1666 [PMID: 18623174 DOI: 10.1002/ibd.20520]

41 **Van Assche G**, Dignass A, Panes J, Beaugerie L, Karagiannis J, Allez M, Ochsenkühn T, Orchard T, Rogler G, Louis E, Kupcinskas L, Mantzaris G, Travis S, Stange E; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 2010; **4**: 7-27 [PMID: 21122488 DOI: 10.1016/j.crohns.2009.12.003]

42 **Daperno M**, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, Rutgeerts P. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; **60**: 505-512 [PMID: 15472670 DOI: 10.1016/S0016-5107(04)01878-4]

43 **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317**: 1625-1629 [PMID: 3317057 DOI: 10.1056/nejm198712243172603]

44 **Caprilli R**, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, Hommes DW, Lochs H, Angelucci E, Cocco A, Vucelic B, Hildebrand H, Kolacek S, Riis L, Lukas M, de Franchis R, Hamilton M, Jantschek G, Michetti P, O'Morain C, Anwar MM, Freitas JL, Mouzas IA, Baert F, Mitchell R, Hawkey CJ; European Crohn's and Colitis Organisation. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* 2006; **55** Suppl 1: i36-i58 [PMID: 16481630 DOI: 10.1136/gut.2005.081950c]

45 **Dignass A**, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4**: 28-62 [PMID: 21122489 DOI: 10.1016/j.crohns.2009.12.002]

46 **Esser D**, Cornillie F, Diamond RH, Spiegel RJ. On the updated ECCO consensus guidelines for medical management of Crohn's disease. *J Crohns Colitis* 2011; **5**: 165-166 [PMID: 21453888 DOI: 10.1016/j.crohns.2010.02.002]

47 **Travis SP**, Stange EF, Lémann M, Oresland T, Chowers Y, Forbes A, D'Haens G, Kitis G, Cortot A, Prantera C, Marteau P, Colombel JF, Gionchetti P, Bouhnik Y, Tiret E, Kroesen J, Starlinger M, Mortensen NJ; European Crohn's and Colitis Organisation. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006; **55** Suppl 1: i16-i35 [PMID: 16481629 DOI: 10.1136/gut.2005.081950b]

48 **Papp M**, Lakatos PL, Harsfalvi J, Farkas G, Palatka K, Udvardy M, Molnar T, Farkas K, Nagy F, Veres G, Lakatos L, Kovacs A, Dinya T, Kocsis AK, Papp J; Hungarian IBD Study Group, Altorjay I. Mannose-binding lectin level and deficiency is not associated with inflammatory bowel diseases, disease phenotype, serology profile, and NOD2/CARD15 genotype in a large Hungarian cohort. *Hum Immunol* 2010; **71**: 407-413 [PMID: 20079790 DOI: 10.1016/j.humimm.2010.01.012]

49 **Zhao T**, Su Z, Li Y, Zhang X, You Q. Chitinase-3 like-protein-1 function and its role in diseases. *Signal Transduct Target Ther* 2020; **5**: 201 [PMID: 32929074 DOI: 10.1038/s41392-020-00303-7]

50 **Patel S**, Goyal A. Chitin and chitinase: Role in pathogenicity, allergenicity and health. *Int J Biol Macromol* 2017; **97**: 331-338 [PMID: 28093332 DOI: 10.1016/j.ijbiomac.2017.01.042]

51 **Ziatabar S**, Zepf J, Rich S, Danielson BT, Bollyky PI, Stern R. Chitin, chitinases, and chitin lectins: Emerging roles in human pathophysiology. *Pathophysiology* 2018; **25**: 253-262 [PMID: 30266339 DOI: 10.1016/j.pathophys.2018.02.005]

52 **Kjaergaard AD**, Helby J, Johansen JS, Nordestgaard BG, Bojesen SE. Elevated plasma YKL-40 and risk of infectious disease: a prospective study of 94665 individuals from the general population. *Clin Microbiol Infect* 2020; **26**: 1411.e1-1411.e9 [PMID: 31972315 DOI: 10.1016/j.cmi.2020.01.010]

53 **Kornblit B**, Hellemann D, Munthe-Fog L, Bonde J, Strøm JJ, Madsen HO, Johansen JS, Garred P. Plasma YKL-40 and CHI3L1 in systemic inflammation and sepsis-experience from two prospective cohorts. *Immunobiology* 2013; **218**: 1227-1234 [PMID: 23706599 DOI: 10.1016/j.imbio.2013.04.010]

54 **Hattori N**, Oda S, Sadahiro T, Nakamura M, Abe R, Shinozaki K, Nomura F, Tomonaga T, Matsushita K, Kodera Y, Sogawa K, Satoh M, Hirasawa H. YKL-40 identified by proteomic analysis as a biomarker of sepsis. *Shock* 2009; **32**: 393-400 [PMID: 19197227 DOI: 10.1097/SHK.0b013e31819e2c0c]

55 **Johansen JS**, Krabbe KS, Møller K, Pedersen BK. Circulating YKL-40 levels during human endotoxaemia. *Clin Exp Immunol* 2005; **140**: 343-348 [PMID: 15807860 DOI: 10.1111/j.1365-2249.2005.02763.x]

56 **Kucur M**, Tuten A, Oncul M, Acikgoz AS, Yuksel MA, Imamoglu M, Balci Ekmekci O, Yilmaz N, Madazli R. Maternal serum apelin and YKL-40 levels in early and late-onset pre-eclampsia. *Hypertens Pregnancy* 2014; **33**: 467-475 [PMID: 25068525 DOI: 10.3109/10641955.2014.944709]

57 **Seol HJ**, Lee ES, Jung SE, Jeong NH, Lim JE, Park SH, Hong SC, Oh MJ, Kim HJ. Serum levels of YKL-40 and interleukin-18 and their relationship to disease severity in patients with preeclampsia. *J Reprod Immunol* 2009; **79**: 183-187 [PMID: 19200605 DOI: 10.1016/j.jri.2008.10.003]

58 **Jin Y**, Song J, Xu F, Zhang D, He J, Zheng J, Zhang Y, Li J, Guo Y, Xu M, Yu X, Liu Y, Liu Q, Yan J. Association between YKL-40 and asthma: a systematic meta-analysis. *Sleep Breath* 2022; **26**: 1011-1022 [PMID: 34657273 DOI: 10.1007/s11325-021-02495-w]

59 **Kimura H**, Shimizu K, Tanabe N, Makita H, Taniguchi N, Kimura H, Suzuki M, Abe Y, Matsumoto-Sasaki M, Oguma A, Takimoto-Sato M, Takei N, Matsumoto M, Goudarzi H, Sato S, Ono J, Izuhara K, Hirai T, Nishimura M, Konno S. Further evidence for association of YKL-40 with severe asthma airway remodeling. *Ann Allergy Asthma Immunol* 2022; **128**: 682-688.e5 [PMID: 35342020 DOI: 10.1016/j.anai.2022.03.016]

60 **Pan R**, Li Q, Zhu X, Zhou Y, Ding L, Cui Y. Diagnostic value of YKL-40 for patients with asthma: A meta-analysis. *Allergy Asthma Proc* 2021; **42**: e167-e173 [PMID: 34871165 DOI: 10.2500/aap.2021.42.210078]

61 **Shao J**, Yang X, Ren D, Luo Y, Lai W. A genetic variation in CHI3L1 is associated with bronchial asthma. *Arch Physiol Biochem* 2021; **127**: 279-284 [PMID: 31295039 DOI: 10.1080/13813455.2019.1634737]

62 **Konrad ER**, Soo J, Conroy AL, Namasopo S, Opoka RO, Hawkes MT. Circulating markers of neutrophil activation and lung injury in pediatric pneumonia in low-resource settings. *Pathog Glob Health* 2023; **117**: 708-716 [PMID: 36562081 DOI: 10.1080/20477724.2022.2160885]

63 **Sohn MH**, Kang MJ, Matsuura H, Bhandari V, Chen NY, Lee CG, Elias JA. The chitinase-like proteins breast regression protein-39 and YKL-40 regulate hyperoxia-induced acute lung injury. *Am J Respir Crit Care Med* 2010; **182**: 918-928 [PMID: 20558631 DOI: 10.1164/rccm.200912-1793OC]

64 **Lee CM**, He CH, Nour AM, Zhou Y, Ma B, Park JW, Kim KH, Dela Cruz C, Sharma L, Nasr ML, Modis Y, Lee CG, Elias JA. IL-13Rα2 uses TMEM219 in chitinase 3-like-1-induced signalling and effector responses. *Nat Commun* 2016; **7**: 12752 [PMID: 27629921 DOI: 10.1038/ncomms12752]

65 **Permain J**, Appleton L, Ho SSC, Coffey M, Ooi CY, Keenan JI, Day AS. Children With Cystic Fibrosis Have Elevated Levels of Fecal Chitinase-3-like-1. *J Pediatr Gastroenterol Nutr* 2022; **75**: 48-51 [PMID: 35622011 DOI: 10.1097/MPG.0000000000003477]

66 **Lee SY**, Lee CM, Ma B, Kamle S, Elias JA, Zhou Y, Lee CG. Targeting Chitinase 1 and Chitinase 3-Like 1 as Novel Therapeutic Strategy of Pulmonary Fibrosis. *Front Pharmacol* 2022; **13**: 826471 [PMID: 35370755 DOI: 10.3389/fphar.2022.826471]

67 **Majewski S**, Szewczyk K, Jerczyńska H, Miłkowska-Dymanowska J, Białas AJ, Gwadera Ł, Piotrowski WJ. Longitudinal and Comparative Measures of Serum Chitotriosidase and YKL-40 in Patients With Idiopathic Pulmonary Fibrosis. *Front Immunol* 2022; **13**: 760776 [PMID: 35222369 DOI: 10.3389/fimmu.2022.760776]

68 **Majewski S**, Tworek D, Szewczyk K, Kiszałkiewicz J, Kurmanowska Z, Brzeziańska-Lasota E, Jerczyńska H, Antczak A, Piotrowski WJ, Górski P. Overexpression of chitotriosidase and YKL-40 in peripheral blood and sputum of healthy smokers and patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2019; **14**: 1611-1631 [PMID: 31413557 DOI: 10.2147/COPD.S184097]

69 **Sun X**, Nakajima E, Norbrun C, Sorkhdini P, Yang AX, Yang D, Ventetuolo CE, Braza J, Vang A, Aliotta J, Banerjee D, Pereira M, Baird G, Lu Q, Harrington EO, Rounds S, Lee CG, Yao H, Choudhary G, Klinger JR, Zhou Y. Chitinase 3 like 1 contributes to the development of pulmonary vascular remodeling in pulmonary hypertension. *JCI Insight* 2022; **7** [PMID: 35951428 DOI: 10.1172/jci.insight.159578]

70 **Kim M**, Chang JY, Lee DW, Kim YR, Son DJ, Yun J, Jung YS, Lee DH, Han S, Hong JT. Chitinase 3 like 1 deficiency ameliorates lipopolysaccharide-induced acute liver injury by inhibition of M2 macrophage polarization. *Mol Immunol* 2023; **156**: 98-110 [PMID: 36921490 DOI: 10.1016/j.molimm.2023.02.012]

71 **Shan Z**, Li L, Atkins CL, Wang M, Wen Y, Jeong J, Moreno NF, Feng D, Gui X, Zhang N, Lee CG, Elias JA, Lee WM, Gao B, Lam FW, An Z, Ju C. Chitinase 3-like-1 contributes to acetaminophen-induced liver injury by promoting hepatic platelet recruitment. *Elife* 2021; **10** [PMID: 34110284 DOI: 10.7554/eLife.68571]

72 **Pizano-Martínez O**, Yañez-Sánchez I, Alatorre-Carranza P, Miranda-Díaz A, Ortiz-Lazareno PC, García-Iglesias T, Daneri-Navarro A, Vázquez-Del Mercado M, Fafutis-Morris M, Delgado-Rizo V. YKL-40 expression in CD14$^+$ liver cells in acute and chronic injury. *World J Gastroenterol* 2011; **17**: 3830-3835 [PMID: 21987626 DOI: 10.3748/wjg.v17.i33.3830]

73 **Lee DH**, Han JH, Lee YS, Jung YS, Roh YS, Yun JS, Han SB, Hong JT. Chitinase-3-like-1 deficiency attenuates ethanol-induced liver injury by inhibition of sterol regulatory element binding protein 1-dependent triglyceride synthesis. *Metabolism* 2019; **95**: 46-56 [PMID: 30935969 DOI: 10.1016/j.metabol.2019.03.010]

74 **Qiu H**, Zhang X. The Value of Serum CHI3L1 for the Diagnosis of Chronic Liver Diseases. *Int J Gen Med* 2022; **15**: 5835-5841 [PMID: 35789773 DOI: 10.2147/IJGM.S364602]

75 **Li Y**, Li C, Zhang L, Hu W, Luo H, Li J, Qiu S, Zhu S. Serum CHI3L1 as a diagnostic marker and risk factor for liver fibrosis in HBeAg-negative chronic hepatitis B. *Am J Transl Res* 2022; **14**: 4090-4096 [PMID: 35836859]

76 **Huang X**, Zhuang J, Yang Y, Jian J, Ai W, Liu C, Tang W, Jiang C, He Y, Huang L, Peng S. Diagnostic Value of Serum Chitinase-3-Like Protein 1 for Liver Fibrosis: A Meta-analysis. *Biomed Res Int* 2022; **2022**: 3227957 [PMID: 35360517 DOI: 10.1155/2022/3227957]

77 **Bao J**, Ouyang Y, Qiao L, He J, Liu F, Wang Y, Miao L, Fu A, Lou Z, Zang Q, Huang W, Huang J, Li Z. Serum CHI3L1 as a Biomarker for Non-invasive Diagnosis of Liver Fibrosis. *Discov Med* 2022; **33**: 41-49 [PMID: 36274212]

78 **Huang Q**, Wu J, Huang C, Wang X, Xu Z. A noninvasive diagnostic model for significant liver fibrosis in patients with chronic hepatitis B based on CHI3L1 and routine clinical indicators. *Ann Palliat Med* 2021; **10**: 5509-5519 [PMID: 34107703 DOI: 10.21037/apm-21-957]

79 **Dong R**, Li J, Jiang G, Han N, Zhang Y, Shi X. Novel immune cell infiltration-related biomarkers in atherosclerosis diagnosis. *PeerJ* 2023; **11**: e15341 [PMID: 37151293 DOI: 10.7717/peerj.15341]

80 **Rathcke CN**, Vestergaard H. YKL-40--an emerging biomarker in cardiovascular disease and diabetes. *Cardiovasc Diabetol* 2009; **8**: 61 [PMID: 19930630 DOI: 10.1186/1475-2840-8-61]

81 **Schroder J**, Jakobsen JC, Winkel P, Hilden J, Jensen GB, Sajadieh A, Larsson A, Ärnlöv J, Harutyunyan M, Johansen JS, Kjøller E, Gluud C, Kastrup J. Prognosis and Reclassification by YKL-40 in Stable Coronary Artery Disease. *J Am Heart Assoc* 2020; **9**: e014634 [PMID: 32114892 DOI: 10.1161/JAHA.119.014634]

82 **Kjaergaard AD**, Johansen JS, Bojesen SE, Nordestgaard BG. Role of inflammatory marker YKL-40 in the diagnosis, prognosis and cause of cardiovascular and liver diseases. *Crit Rev Clin Lab Sci* 2016; **53**: 396-408 [PMID: 27187575 DOI: 10.1080/10408363.2016.1190683]

83 **Xu T**, Zhong C, Wang A, Guo Z, Bu X, Zhou Y, Tian Y, HuangFu X, Zhu Z, Zhang Y. YKL-40 Level and Hypertension Incidence: A Population-Based Nested Case-Control Study in China. *J Am Heart Assoc* 2016; **5** [PMID: 27815265 DOI: 10.1161/jaha.116.004534]

84 **Deng Y**, Li G, Chang D, Su X. YKL-40 as a novel biomarker in cardio-metabolic disorders and inflammatory diseases. *Clin Chim Acta* 2020; **511**: 40-46 [PMID: 33002471 DOI: 10.1016/j.cca.2020.09.035]

85 **Kastrup J**. Can YKL-40 be a new inflammatory biomarker in cardiovascular disease? *Immunobiology* 2012; **217**: 483-491 [PMID: 21601307 DOI: 10.1016/j.imbio.2011.04.007]

86 **Di Rosa M**, Malaguarnera L. Chitinase 3 Like-1: An Emerging Molecule Involved in Diabetes and Diabetic Complications. *Pathobiology* 2016; **83**: 228-242 [PMID: 27189062 DOI: 10.1159/000444855]

87 **Rathcke CN**, Vestergaard H. YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. *Inflamm Res* 2006; **55**: 221-227 [PMID: 16955240 DOI: 10.1007/s00011-006-0076-y]

88 **Li F**, Liu A, Zhao M, Luo L. Astrocytic Chitinase-3-like protein 1 in neurological diseases: Potential roles and future perspectives. *J Neurochem* 2023; **165**: 772-790 [PMID: 37026513 DOI: 10.1111/jnc.15824]

89 **Russo C**, Valle MS, Casabona A, Malaguarnera L. Chitinase Signature in the Plasticity of Neurodegenerative Diseases. *Int J Mol Sci* 2023; **24** [PMID: 37047273 DOI: 10.3390/ijms24076301]

90 **Amaral Pedroso L**, Nobre V, Dias Carneiro de Almeida C, da Silva Praxedes MF, Sernizon Guimarães N, Simões E Silva AC, Parreiras Martins MA. Acute kidney injury biomarkers in the critically ill. *Clin Chim Acta* 2020; **508**: 170-178 [PMID: 32413402 DOI: 10.1016/j.cca.2020.05.024]

91 **Sandokji I**, Greenberg JH. Plasma and Urine Biomarkers of CKD: A Review of Findings in the CKiD Study. *Semin Nephrol* 2021; **41**: 416-426 [PMID: 34916002 DOI: 10.1016/j.semnephrol.2021.09.003]

92 **Montgomery TA**, Xu L, Mason S, Chinnadurai A, Lee CG, Elias JA, Cantley LG. Breast Regression Protein-39/Chitinase 3-Like 1 Promotes Renal Fibrosis after Kidney Injury *via* Activation of Myofibroblasts. *J Am Soc Nephrol* 2017; **28**: 3218-3226 [PMID: 28679671 DOI: 10.1681/ASN.2017010110]

93 **Kocyigit I**, Gungor O, Dogan E, Karadavut S, Karakukcu C, Eroglu E, Orscelik O, Unal A, Dogan A, Sipahioglu MH, Tokgoz B, Oymak O. The serum YKL-40 level is associated with vascular injury and predicts proteinuria in nephrotic syndrome patients. *J Atheroscler Thromb* 2015; **22**: 257-264 [PMID: 25253160 DOI: 10.5551/jat.26385]

94 **Richter B**, Roslind A, Hesse U, Nordling J, Johansen JS, Horn T, Hansen AB. YKL-40 and mast cells are associated with detrusor fibrosis in patients diagnosed with bladder pain syndrome/interstitial cystitis according to the 2008 criteria of the European Society for the Study of Interstitial Cystitis. *Histopathology* 2010; **57**: 371-383 [PMID: 20840668 DOI: 10.1111/j.1365-2559.2010.03640.x]

95 **Wang P**, Song J, Qian D. CTX-II and YKL-40 in early diagnosis and treatment evaluation of osteoarthritis. *Exp Ther Med* 2019; **17**: 423-431 [PMID: 30651816 DOI: 10.3892/etm.2018.6960]

96 **Cui B**, Chen Y, Luo F, Lin S, Liu H, Huang Y, Zhou Y, Tian Y, Yin G, Xie Q. Clinical value of YKL-40 in patients with polymyositis/dermatomyositis: A cross-sectional study and a systematic review. *J Clin Lab Anal* 2022; **36**: e24605 [PMID: 35837962 DOI: 10.1002/jcla.24605]

97 **Zhou PM**, Fu LX, Chen T, Wang L, Lu YH. Elevated YKL-40 serum levels in patients with chronic spontaneous urticaria. *Ann Allergy Asthma Immunol* 2019; **123**: 404-405 [PMID: 31330242 DOI: 10.1016/j.anai.2019.07.009]

98 **Pourani MR**, Abdollahimajd F, Zargari O, Shahidi Dadras M. Soluble biomarkers for diagnosis, monitoring, and therapeutic response assessment in psoriasis. *J Dermatolog Treat* 2022; **33**: 1967-1974 [PMID: 34369253 DOI: 10.1080/09546634.2021.1966357]

99 **Tizaoui K**, Yang JW, Lee KH, Kim JH, Kim M, Yoon S, Jung Y, Park JB, An K, Choi H, Song D, Jung H, Ahn S, Yuh T, Choi HM, Ahn JH, Kim Y, Jee S, Lee H, Jin S, Kang JG, Koo B, Lee JY, Min KM, Yoo W, Rhyu HJ, Yoon Y, Lee MH, Kim SE, Hwang J, Koyanagi A, Jacob L, Park S, Shin JI, Smith L. The role of YKL-40 in the pathogenesis of autoimmune diseases: a comprehensive review. *Int J Biol Sci* 2022; **18**: 3731-3746 [PMID: 35813465 DOI: 10.7150/ijbs.67587]

100 **Ning L**, Shan G, Sun Z, Zhang F, Xu C, Lou X, Li S, Du H, Chen H, Xu G. Quantitative Proteomic Analysis Reveals the Deregulation of Nicotinamide Adenine Dinucleotide Metabolism and CD38 in Inflammatory Bowel Disease. *Biomed Res Int* 2019; **2019**: 3950628 [PMID: 31179321 DOI: 10.1155/2019/3950628]

101 **Pieczarkowski S**, Kowalska-Deptuch K, Kwinta P, Wędrychowicz A, Tomasik P, Stochel-Gaudyn A, Fyderek K. Serum concentrations of fibrosis markers in children with inflammatory bowel disease. *Folia Med Cracov* 2020; **60**: 61-74 [PMID: 32658213 DOI: 10.24425/fmc.2020.133487]

102 **Shi Y**, He W, Zhong M, Yu M. MIN score predicts primary response to infliximab/adalimumab and vedolizumab therapy in patients with inflammatory bowel diseases. *Genomics* 2021; **113**: 1988-1998 [PMID: 33872704 DOI: 10.1016/j.ygeno.2021.04.011]

103 **Vind I**, Johansen JS, Price PA, Munkholm P. Serum YKL-40, a potential new marker of disease activity in patients with inflammatory bowel disease. *Scand J Gastroenterol* 2003; **38**: 599-605 [PMID: 12825867 DOI: 10.1080/00365520310000537]

104 **Qin X**. Why is damage limited to the mucosa in ulcerative colitis but transmural in Crohn's disease? *World J Gastrointest Pathophysiol* 2013; **4**: 63-64 [PMID: 23946890 DOI: 10.4291/wjgp.v4.i3.63]

105 **Tsuruha J**, Masuko-Hongo K, Kato T, Sakata M, Nakamura H, Sekine T, Takigawa M, Nishioka K. Autoimmunity against YKL-39, a human cartilage derived protein, in patients with osteoarthritis. *J Rheumatol* 2002; **29**: 1459-1466 [PMID: 12136906]

106 **Verheijden GF**, Rijnders AW, Bos E, Coenen-de Roo CJ, van Staveren CJ, Miltenburg AM, Meijerink JH, Elewaut D, de Keyser F, Veys E, Boots AM. Human cartilage glycoprotein-39 as a candidate autoantigen in rheumatoid arthritis. *Arthritis Rheum* 1997; **40**: 1115-1125 [PMID: 9182922 DOI: 10.1002/art.1780400616]

107 **Johansen JS**, Stoltenberg M, Hansen M, Florescu A, Hørslev-Petersen K, Lorenzen I, Price PA. Serum YKL-40 concentrations in patients with rheumatoid arthritis: relation to disease activity. *Rheumatology (Oxford)* 1999; **38**: 618-626 [PMID: 10461474 DOI: 10.1093/rheumatology/38.7.618]

108 **Matsumoto T**, Tsurumoto T. Serum YKL-40 levels in rheumatoid arthritis: correlations between clinical and laborarory parameters. *Clin Exp Rheumatol* 2001; **19**: 655-660 [PMID: 11791636]

109 **Volck B**, Johansen JS, Stoltenberg M, Garbarsch C, Price PA, Ostergaard M, Ostergaard K, Løvgreen-Nielsen P, Sonne-Holm S, Lorenzen I. Studies on YKL-40 in knee joints of patients with rheumatoid arthritis and osteoarthritis. Involvement of YKL-40 in the joint pathology. *Osteoarthritis Cartilage* 2001; **9**: 203-214 [PMID: 11300743 DOI: 10.1053/joca.2000.0377]

110 **Panayi GS**. Targeting of cells involved in the pathogenesis of rheumatoid arthritis. *Rheumatology (Oxford)* 1999; **38** Suppl 2: 8-10 [PMID: 10646482]

111 **Ruel J**, Ruane D, Mehandru S, Gower-Rousseau C, Colombel JF. IBD across the age spectrum: is it the same disease? *Nat Rev Gastroenterol Hepatol* 2014; **11**: 88-98 [PMID: 24345891 DOI: 10.1038/nrgastro.2013.240]

112 **Koutroubakis IE**, Petinaki E, Dimoulios P, Vardas E, Roussomoustakaki M, Maniatis AN, Kouroumalis EA. Increased serum levels of YKL-40 in patients with inflammatory bowel disease. *Int J Colorectal Dis* 2003; **18**: 254-259 [PMID: 12673492 DOI: 10.1007/s00384-002-0446-z]

113 **Sipeki N**, Kovats P, Balogh B, Shums Z, Norman GL, Antal-Szalmas P, Papp M. P288 Gut barrier failure biomarkers in IBD: Is there anything new beyond "The Wall"? *JCC* 2020; **14**: S296 [DOI: 10.1093/ecco-jcc/jjz203.417]

114 **Sipeki N**, Norman GL, Shums Z, Veres G, Lakatos PL, Antal-Szalmas P, Papp M. P152 Reconsidering the prognostic value of traditional serologic antibodies in Crohn's disease – immunoglobulin classes to take the centre stage. *JCC* 2017; **11**: S153-S154 [DOI: 10.1093/ecco-jcc/jjx002.278]

115 **Pabst O**. New concepts in the generation and functions of IgA. *Nat Rev Immunol* 2012; **12**: 821-832 [PMID: 23103985 DOI: 10.1038/nri3322]

116 **Brandtzaeg P**. Update on mucosal immunoglobulin A in gastrointestinal disease. *Curr Opin Gastroenterol* 2010; **26**: 554-563 [PMID: 20693891 DOI: 10.1097/MOG.0b013e32833dccf8]

117 **Papp M**, Sipeki N, Vitalis Z, Tornai T, Altorjay I, Tornai I, Udvardy M, Fechner K, Jacobsen S, Teegen B, Sumegi A, Veres G, Lakatos PL, Kappelmayer J, Antal-Szalmas P. High prevalence of IgA class anti-neutrophil cytoplasmic antibodies (ANCA) is associated with increased risk of bacterial infection in patients with cirrhosis. *J Hepatol* 2013; **59**: 457-466 [PMID: 23639483 DOI: 10.1016/j.jhep.2013.04.018]

118 **Wiest R**, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology* 2005; **41**: 422-433 [PMID: 15723320 DOI: 10.1002/hep.20632]

119 **Saab S**, Hernandez JC, Chi AC, Tong MJ. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *Am J Gastroenterol* 2009; **104**: 993-1001; quiz 1002 [PMID: 19277033 DOI: 10.1038/ajg.2009.3]

120 **McGuckin MA**, Eri R, Simms LA, Florin TH, Radford-Smith G. Intestinal barrier dysfunction in inflammatory bowel diseases. *Inflamm Bowel Dis* 2009; **15**: 100-113 [PMID: 18623167 DOI: 10.1002/ibd.20539]

121 **Merga Y**, Campbell BJ, Rhodes JM. Mucosal barrier, bacteria and inflammatory bowel disease: possibilities for therapy. *Dig Dis* 2014; **32**: 475-483 [PMID: 24969297 DOI: 10.1159/000358156]

122 **Vrakas S**, Mountzouris KC, Michalopoulos G, Karamanolis G, Papatheodoridis G, Tzathas C, Gazouli M. Intestinal Bacteria Composition and Translocation of Bacteria in Inflammatory Bowel Disease. *PLoS One* 2017; **12**: e0170034 [PMID: 28099495 DOI: 10.1371/journal.pone.0170034]

123 **Camilleri M**, Madsen K, Spiller R, Greenwood-Van Meerveld B, Verne GN. Intestinal barrier function in health and gastrointestinal disease. *Neurogastroenterol Motil* 2012; **24**: 503-512 [PMID: 22583600 DOI: 10.1111/j.1365-2982.2012.01921.x]

124 **Fukui H**. Increased Intestinal Permeability and Decreased Barrier Function: Does It Really Influence the Risk of Inflammation? *Inflamm Intest Dis* 2016; **1**: 135-145 [PMID: 29922669 DOI: 10.1159/000447252]

125 **Pastorelli L**, De Salvo C, Mercado JR, Vecchi M, Pizarro TT. Central role of the gut epithelial barrier in the pathogenesis of chronic intestinal inflammation: lessons learned from animal models and human genetics. *Front Immunol* 2013; **4**: 280 [PMID: 24062746 DOI: 10.3389/fimmu.2013.00280]

126 **Roggenbuck D**, Reinhold D, Werner L, Schierack P, Bogdanos DP, Conrad K. Glycoprotein 2 antibodies in Crohn's disease. *Adv Clin Chem* 2013; **60**: 187-208 [PMID: 23724745 DOI: 10.1016/B978-0-12-407681-5.00006-4]

127 **Somma V**, Ababneh H, Ababneh A, Gatti S, Romagnoli V, Bendia E, Conrad K, Bogdanos DP, Roggenbuck D, Ciarrocchi G. The Novel Crohn's Disease Marker Anti-GP2 Antibody Is Associated with Ileocolonic Location of Disease. *Gastroenterol Res Pract* 2013; **2013**: 683824 [PMID: 23762038 DOI: 10.1155/2013/683824]

128 **Di Rosa M**, Distefano G, Zorena K, Malaguarnera L. Chitinases and immunity: Ancestral molecules with new functions. *Immunobiology* 2016; **221**: 399-411 [PMID: 26686909 DOI: 10.1016/j.imbio.2015.11.014]

129 **Mizoguchi E**. Chitinase 3-like-1 exacerbates intestinal inflammation by enhancing bacterial adhesion and invasion in colonic epithelial cells. *Gastroenterology* 2006; **130**: 398-411 [PMID: 16472595 DOI: 10.1053/j.gastro.2005.12.007]

130 **Erzin Y**, Uzun H, Karatas A, Celik AF. Serum YKL-40 as a marker of disease activity and stricture formation in patients with Crohn's disease. *J Gastroenterol Hepatol* 2008; **23**: e357-e362 [PMID: 17725598 DOI: 10.1111/j.1440-1746.2007.05121.x]

131 **Lakatos PL**, Sipeki N, Kovacs G, Palyu E, Norman GL, Shums Z, Golovics PA, Lovasz BD, Antal-Szalmas P, Papp M. Risk Matrix for Prediction of Disease Progression in a Referral Cohort of Patients with Crohn's Disease. *J Crohns Colitis* 2015; **9**: 891-898 [PMID: 26188353 DOI: 10.1093/ecco-jcc/jjv127]

132 **Kawada M**, Chen CC, Arihiro A, Nagatani K, Watanabe T, Mizoguchi E. Chitinase 3-like-1 enhances bacterial adhesion to colonic epithelial cells through the interaction with bacterial chitin-binding protein. *Lab Invest* 2008; **88**: 883-895 [PMID: 18490894 DOI: 10.1038/labinvest.2008.47]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com