Journal of Crohn's and Colitis, 2015, 1–8
doi:10.1093/ecco-jcc/jjv127
Original Article

Original Article

Risk Matrix for Prediction of Disease Progression in a Referral Cohort of Patients with Crohn's Disease

Peter L. Lakatos[a], Nora Sipeki[b], Gyorgy Kovacs[b], Eszter Palyu[b], Gary L. Norman[c], Zakera Shums[c], Petra A. Golovics[a], Barbara D. Lovasz[a], Peter Antal-Szalmas[d], Maria Papp[b]

[a]1st Department of Medicine, Semmelweis University, Budapest, Hungary [b]Institute of Medicine, Department of Gastroenterology, University of Debrecen, Clinical Center, Debrecen, Hungary [c]Inova Diagnostics, Inc., San Diego, CA, USA [d]Department of Laboratory Medicine, University of Debrecen, Clinical Center, Debrecen, Hungary

Corresponding author: Peter Laszlo Lakatos, MD, DSc, 1st Department of Medicine, Semmelweis University, 2A Koranyi S, H-1083 Budapest, Hungary. Tel/Fax: 36-1-4591500; Email: lakatos.peter_laszlo@med.semmelweis-univ.hu

Abstract

Background: Early identification of patients with Crohn's disease (CD) at risk of subsequent complications is essential for adapting the treatment strategy. We aimed to develop a prediction model including clinical and serological markers for assessing the probability of developing advanced disease in a prospective referral CD cohort.

Methods: Two hundred and seventy-one consecutive CD patients (42.4% males, median follow-up 108 months) were included and followed up prospectively. Anti-*Saccharomyces cerevisiae* antibodies (ASCA IgA/IgG) were determined by enzyme-linked immunosorbent assay. The final analysis was limited to patients with inflammatory disease behaviour at diagnosis. The final definition of advanced disease outcome was having intestinal resection or disease behaviour progression.

Results: Antibody (ASCA IgA and/or IgG) status, disease location and need for early azathioprine were included in a 3-, 5- and 7-year prediction matrix. The probability of advanced disease after 5 years varied from 6.2 to 55% depending on the combination of predictors. Similar findings were obtained in Kaplan–Meier analysis; the combination of ASCA, location and early use of azathioprine was associated with the probability of developing advanced disease ($p < 0.001$, log rank test).

Conclusions: Our prediction models identified substantial differences in the probability of developing advanced disease in the early disease course of CD. Markers identified in this referral cohort were different from those previously published in a population-based cohort, suggesting that different prediction models should be used in the referral setting.

Keywords: Serological antibodies; ASCA; Crohn's disease; disease progression; referral cohort; azathioprine

1. Introduction

Crohn's disease (CD) is a multifactorial chronic inflammatory disease of the gastrointestinal tract. It runs a variable disease course, yet the majority of patients eventually develop penetrating or stricturing complications leading to repeated surgery and disability.[1]

Studies on the natural history of CD provide important data on its course and may help to identify clinical predictors of disease progression. Some years ago, Peyrin-Biroulet et al.[2] published a systematic review of the natural history of CD in population-based cohorts and concluded that available data did not suggest a significant change in disease course, with approximately half of patients

requiring surgery within 10 years after diagnosis. Furthermore, the authors stated that the impact of changes in monitoring and treatment paradigms with increased and earlier use of immunosuppressants and biological agents on the natural history of the disease was poorly understood.

Interestingly, an increasing proportion of patients were diagnosed with uncomplicated disease behaviour in recent population-based cohorts; e.g. in a study from New Zealand >70% of CD patients had inflammatory disease at diagnosis, while only 23 and 40% of these progressed to complicated disease 5 and 10 years after diagnosis, respectively.[3] Similarly, the rate of initial inflammatory disease behaviour was as high as 68 and 75% in CD patients from Western and Eastern Europe, respectively, in the most recent EpiCom study,[4] with only 10% of all patients presenting with perianal involvement.

Therefore, early stratification of patients became of the utmost importance to avoid negative outcomes and considerable emphasis has been placed in recent years on the determination of important predictive factors. In one of the early approaches, an initial need for steroid use, age below 40 years and the presence of perianal disease were associated with the development of disabling disease in the landmark paper by Beaugerie et al.[5] However, the definition of disabling outcome was complex and included the need to start immunosuppressives. Multiple studies reported a more rapid progression towards complicated disease in CD patients with small bowel or perianal disease.[3,6] In another Belgian study, besides perianal lesions, the early need for steroids and ileocolonic location, but not age below 40 years, were identified as predictive markers for the development of disabling disease (according to the predefined criteria) at 5 years.[7] In addition, according to available data paediatric-onset CD runs a more aggressive course, with more extensive disease location, more upper gastrointestinal involvement, more active disease, growth failure and the need for more aggressive medical therapy in predominantly referral centre studies,[8–10] with some exceptions.[11]

Recently, the IBSEN group[12] has developed a population-based risk assessment model based on complex evaluation of clinical (age at onset, location and early steroid requirement) and serological (anti-*Saccharomyces cerevisiae* antibody [ASCA] positivity) variables that was able to predict the risk of disease outcome 5 and 10 years after diagnosis. However, similarly to the previous French[5] approach, the need for immunosuppressants was defined as an adverse outcome. In contrast, in an earlier study by our group, early aggressive immunosuppressive therapy was associated with a reduction in surgical rates in a population-based study[13] from Hungary, even after fitting the model on propensity scores. Almost certainly, future complex prediction models should assess the value of an early aggressive treatment strategy as a possible predictor of disease progression.

Early identification of CD patients at risk of subsequent complications is essential for adapting the treatment strategy in everyday clinical practice, especially in CD patients followed up at referral inflammatory bowel disease (IBD) centres. Therefore, the aim of the present study was to develop a prediction model including clinical and serological markers for assessing the probability of developing advanced disease during medium-term follow-up in a prospective referral CD cohort.

2. Methods

2.1. Patient population

A total of 271 well-characterized, unrelated, consecutive CD patients with a complete clinical follow-up {male/female, 120/140; median age at presentation, 25 years (interquartile range [IQR]), 19–33} seen in one tertiary IBD referral centre in Hungary (Department of Gastroenterology, Institute of Internal Medicine, University of Debrecen) were included between 1 January 2005 and 1 June 2010 and were followed up until 1 October 2013. Blood samples and detailed clinical phenotypes were captured at inclusion.

The clinical characteristics of the patients at diagnosis are presented in Table 1. Diagnosis of IBD was based on the Lennard-Jones criteria.[14] The disease phenotype (age at onset, duration, location and behaviour) was determined according to the Montreal classification.[15] Blood samples and detailed clinical phenotypes were captured at inclusion. Clinical data were determined by thorough review of patients' medical records, which had been collected in a uniform format. Medical records that documented the disease phenotype, presence of extraintestinal manifestations (e.g. arthritis [peripheral and axial]; ocular manifestations [conjunctivitis, uveitis, iridocyclitis]; skin lesions [erythema nodosum, pyoderma gangrenosum]; and hepatic manifestations [primary sclerosing cholangitis]), frequency of flare-ups (frequent flare-up was >1 clinical relapse/year),[16] medication use (e.g. steroid, immunosuppressive and/or biological use at any time), need for surgery (resections), the presence of familial IBD, smoking habits and perianal involvement were retrospectively analysed for the period prior to the prospective follow-up and prospectively thereafter.

In Hungary, a follow-up visit is usually scheduled for every 6 months at a specialized gastroenterology centre (the actual interval varies between 3 and 6 months). In addition, a harmonized, mandatory, tight monitoring strategy is requested and regularly controlled by the National Health Fund (OEP) in anti-tumour necrosis factor (TNF)-exposed patients, including Crohn's disease activity index-perianal disease activity index (CDAI-PDAI) assessment, laboratory evaluation (including C-reactive protein [CRP]) at least every 3 months and endoscopy/imaging at least every 12 months. The start of immunosuppressive or anti-TNF treatment was indicated by the same three IBD specialists throughout the study period by using the European Crohn's and Colitis Organisation (ECCO) guidelines, the centre's treatment policy and prescription regulations. Follow-up was terminated if there was no further record available. Median follow-up from diagnosis was 108 months (IQR, 65–178).

2.2. Definitions of advanced disease

Two definitions were used for advanced disease: (1) having intestinal resection or progression in disease behaviour; and (2) having intestinal resection, progression in disease behaviour or need for thiopurines (IBSEN definition). Early need for azathioprine (AZA) was defined as need of AZA within 3 years from diagnosis.

2.3. Serological analysis

Blood samples were obtained at enrolment from each patient and were frozen at −80°C until testing. All serological assays were

Table 1. Clinical characteristics of the referral cohort with Crohn's disease (CD).

	CD patients (n = 271)
Males/females	42.4/47.6%
Median follow-up (IQR), months	108 (65–178)
Inflammatory behaviour at diagnosis	79.7%
Ileocolonic disease at diagnosis	45.0%
Complicated disease behaviour at last follow-up	52.0%
At least one resective surgery at last follow-up	41.1%
Total steroid exposure	88.2%
Total azathioprine exposure	73.8%
Total anti-TNF exposure	41.7%

performed in a blinded fashion without prior knowledge of the patient's diagnosis or other clinical information. Sampling was done at early stages of the disease (duration of disease less than 2 years) in 40.2% of the patients the and after a disease duration of more than 2 years of in 59.8% of patients. The overall disease duration (median) at sampling was 3 years (IQR 0–8 years).

2.4. Detection of antimicrobial antibodies

The presence of ASCA IgA and ASCA IgG in serum was determined by enzyme-linked immunosorbent assay (ELISA) (QUANTA Lite™, Inova Diagnostics, San Diego, CA) according to the manufacturers' instructions. The results are presented as arbitrary units, and values above the cut-off of 25 units were considered positive. The results were documented in absolute values and in frequency of positivity.

All the serological assays were performed in a blinded fashion without prior knowledge of the patient's diagnosis or other clinical information.

2.5. Ethical considerations

The regional and national committee [DEOEC RKEB/IKEB 3515-2011, 3880/2012/EKU (59/PI/2012)] for research ethics approved the study protocol. Each patient was informed of the nature of the study and signed an informed consent form.

2.6. Statistical analysis

Continuous variables were summarized as median (IQR) according to their homogeneity. The predictive potential of the different models for predicting advanced outcome according to the two pre-set definitions were tested both by cross-sectional analysis after pre-set time-points at 3, 5 and 7 years after the diagnosis and in time-dependent models. We developed two different models. In the first model we replicated a matrix model with the original variables and outcome definition reported by the IBSEN group[12] in our referral cohort, both after the pre-set time-points and in the time-dependent model. However, because of the limited number of cases we limited the final model to the combination of three variables. This was based on the results of univariate χ^2 tests, in which age at diagnosis was not significant. In the second step, since the predictive potential was improved by grouping the location as colon only vs ileal involvement ($p_{\text{advanced disease for L2 vs other}} = 0.002$), we repeated the testing after changing the location grouping. In addition, our group has shown that early AZA therapy is a treatment decision rather than a negative outcome and may predict surgical outcome in the population-based setting[13] and early AZA need in the present study was associated with advanced disease in every model. Therefore, in the third step we developed a new model and analysed the outcomes after replacing early steroid requirement with early AZA requirement and used a modified advanced disease definition (excluding the need for AZA). In addition, the association between possible risk factors and the modified advanced 5-year outcome definition were assessed by both univariate and multivariate logistic regression testing. Variables with $p < 0.2$ were selected for multiple testing.[17] In addition, Kaplan–Meier survival curves were plotted to analyse the association between the combination of clinical variables, serological antibodies and complicated disease outcomes during follow-up with the log rank test. A two-sided probability value <0.05 was considered to be statistically significant. For statistical analysis, GraphPadPrism 6 (San Diego, CA) and SPSS 20.0 (SPSS Inc., Chicago, IL) programs were used.

3. Results

3.1. Clinical characteristics

At diagnosis, 79.7% of the CD patients had inflammatory behaviour and 45% had ileocolonic disease (Table 1). Disease progression during follow-up was significant, with 52% of the patients progressing to complicated disease behaviour and 41.1% of the patients having at least one resective surgery at the last follow-up. Total exposures to steroids, AZA and anti-TNFs were 88.2, 73.8 and 41.7%, respectively.

3.2. Predicting advanced disease during follow-up in referral CD patients with non-stricturing and non-penetrating disease behaviour at diagnosis

The association between clinical and serological variables and advanced outcome at 3, 5 and 7 years by either the original definition or the modified definition is summarized in Table 2. Location (colon vs ileal involvement), early AZA need and ASCA positivity were identified as independent predictors of advanced outcome. The original model, including ASCA (IgA and/or IgG), disease location and early need for steroids but not age at onset, was of low discriminative potential to predict advanced outcome in this referral CD cohort at 5 years if the original definition was used (Table 3). In addition, a lack of separation among the groups was observed in the time-dependent model (Figure 1, not significant for ASCA positive vs negative subgroups).

The predictive potential was not much better if the need for AZA was excluded from the advanced disease definition (data not shown).

The predictive potential of the model was not much better after changing the location grouping both with the original definition (Table 4) and with the modified definition of advanced outcome after excluding need for AZA from the advanced outcome definition (data not shown).

The combination of ASCA (IgA and IgG) status, disease location and need for early AZA was associated with advanced outcome by using the modified definition of advanced disease (need for surgery and disease behaviour change). The probabilities of advanced disease 5 years after diagnosis varied from 6.2 to 55% depending on the combination of predictors (Table 5). The 3- and 7-year ASCA-based model resulted in probabilities of advanced disease ranging from 0 to 45.5% and from 11.1 to 64.7%, respectively. Similar findings were obtained by Kaplan–Meier analysis, in which the combination of ASCA, location and early AZA was associated with the probability of developing advanced disease ($p_{\text{logrank}} < 0.001$, Figure 2).

4. Discussion

The present study has shown that the disease course may be predicted in referral CD patients by the use of a complex model including disease phenotype and serological and treatment variables. We have also confirmed that different models are necessary for the prediction of disease outcomes in referral CD cohorts with different predictors compared with the population-based setting.

2 The risk factors – location, ASCA, early steroid requirement and early azathioprine therapy – identified for developing disease complication (in the present study the final definition was a change in disease behaviour or surgery) in patients with initial uncomplicated disease were in line with factors identified in previous population-based[3,12,13] or referral cohort[5–7,18] studies. Of note, however, there is a significant variance in the definition of adverse outcome in the published literature. In the French study,[5] performed in a tertiary

Table 2. Association between clinical, serological variables and advanced disease outcome 3, 5 and 7 years after diagnosis according to the different outcome definitions.

	IBSEN advanced disease outcome[1] at 5 years		Advanced disease outcome[2] at 3 years		Advanced disease outcome[2] at 7 years		Advanced disease outcome[2] at 5 years, univariate		Advanced disease outcome[2] at 5 years	
	p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	Univariate *p* value	OR (95% CI)	Multivariate *p* value	OR (95% CI)
Gender	0.41		0.20		0.29		0.24		–	
Age at onset	0.42		0.15		0.34		0.25		–	
Location, IBSEN (colon and ileocolon)	0.71		0.48		0.03	0.44 (0.20–0.92)	0.21		–	
Location, colon only vs ileal involvement	0.002	0.42 (0.24–0.74)	<0.001	0.26 (0.13–0.50)	<0.001	0.28 (0.15–0.53)	<0.001	0.27 (0.14–0.49)	<0.001	0.29 (0.15–0.55)
Early steroid need[3]	0.001	3.41 (1.59–7.29)	0.19		0.99		0.42		–	
Early AZA need[4]	*		<0.001	3.30 (1.92–5.64)	0.002	2.50 (1.41–1.91)	<0.001	2.64 (1.54–4.52)	0.001	2.62 (1.46–4.67)
Total AZA	*		0.004	2.64 (1.33–5.24)	0.31		0.13		–	
ASCA, either IgA or IgG	0.001	2.65 (1.48–4.76)	<0.001	3.44 (1.81–6.56)	0.002	2.66 (1.40–5.07)	0.001	2.74 (1.47–5.11)	0.04	2.03 (1.03–3.96)
ASCA, both IgA and IgG	0.005	2.23 (1.27–3.92)	<0.001	2.88 (1.69–4.91)	<0.001	2.87 (1.62–5.07)	<0.001	3.02 (1.75–5.20)	0.002	2.52 (1.42–4.49)
Smoking	0.31		0.15		0.85		0.25		–	

[1]Having intestinal resection, progression in disease behaviour or need for thiopurines (IBSEN definition).

[2]Having intestinal resection or progression in disease behaviour.

[3]Need for steroid within 30 days from diagnosis.

[4]Need for azathioprine (AZA) within 3 years from diagnosis.

*AZA is included in the advanced outcome definition by the IBSEN group.

Table 3. Risk matrix showing advanced 5-year outcome according to the original definition[1] in referral Crohn's disease patients with non-stricturing and non-penetrating disease behaviour (B1) at diagnosis.

ASCA (IgA and/or IgG)	Early steroid requirement[2]	Colon location at diagnosis (L2 + L3)	Ileal or upper gastrointestinal tract location (L1 + L4)
ASCA positive	Yes	72.5%	66.7%
	No	50.0%	53.3%
ASCA negative	Yes	69.6%	75.0%
	No	16.7%	30.0%

[1]Having intestinal resection, progression in disease behaviour or need for thiopurines (IBSEN definition).
[2]Within 30 days from diagnosis.
ASCA, anti-*Saccharomyces cerevisiae* antibodies.

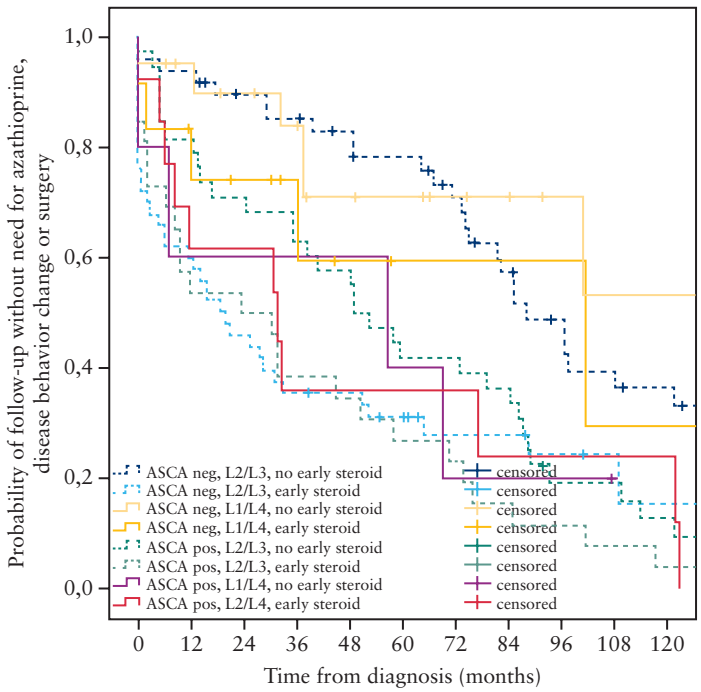

Figure 1. Probability of developing advanced disease outcome according to the original definition in referral Crohn's disease patients with non-stricturing and non-penetrating disease behaviour (B1) at diagnosis.

Table 4. Risk matrix showing advanced 5-year outcome according to the original definition[1] in referral Crohn's disease patients with non-stricturing and non-penetrating disease behaviour (B1) at diagnosis after changing the location grouping.

ASCA (either IgA or IgG)	Early steroid requirement[2]	Only colon location at diagnosis (L2 + L3)	Ileal location at diagnosis (L1 + L4)
ASCA positive	Yes	58.3%	80.0%
	No	63.6%	58.3%
ASCA negative	Yes	73.7%	70.4%
	No	22.6%	26.1%

[1]Having intestinal resection, progression in disease behaviour, or need for thiopurines (IBSEN definition).
[2]Within 30 days from diagnosis.
ASCA, anti-*Saccharomyces cerevisiae* antibodies.

referral centre in 1123 patients, adverse outcome was defined as fulfilling at least one of the following criteria within the first 5 years after the diagnosis: the need for more than two steroid courses or steroid dependency; the need for immunosuppressive treatment; disabling chronic symptoms; hospitalization; or surgery. Using this definition, three risk factors at diagnosis were found to be independently associated with a disabling 5-year course of disease: age <40 years; presence of perianal disease; and requirement for steroids. However, these factors differ clearly in clinical importance and there is little doubt that the start of immunosuppressive therapy represents a treatment strategy decision rather than a negative outcome. However, the discriminative potential of the model was low, as the chance for disabling outcome in this referral CD cohort was approximately 90% in the first 5 years of the disease.

3 In a Belgian referral cohort study, ileocolonic location, perianal lesions and the need for steroids for the first flare, but not age below 40 years, were identified as predictive markers for developing disabling disease at 5 years.[7] In the same study, stricturing behaviour

Table 5. Association between anti-*Saccharomyces cerevisiae* antibody (ASCA) IgA and IgG positivity, disease location and need for early azathioprine (AZA) with the probability of developing advanced disease outcome at 5 years according to the modified definition[1] after diagnosis in referral Crohn's disease patients with non-stricturing and non-penetrating (B1) disease behaviour at diagnosis.

ASCA (IgA and IgG)	Early AZA requirement[2]	Only colon location at diagnosis (L2)	Ileal location at diagnosis (L1, L3, L4)
ASCA positive	Yes	50.0%	55.0%
	No	30.8%	29.0%
ASCA negative	Yes	11.1%	22.2%
	No	6.2%	18.8%

[1]Need for surgery and disease behaviour change.
[2]Need for AZA within 3 years from diagnosis.

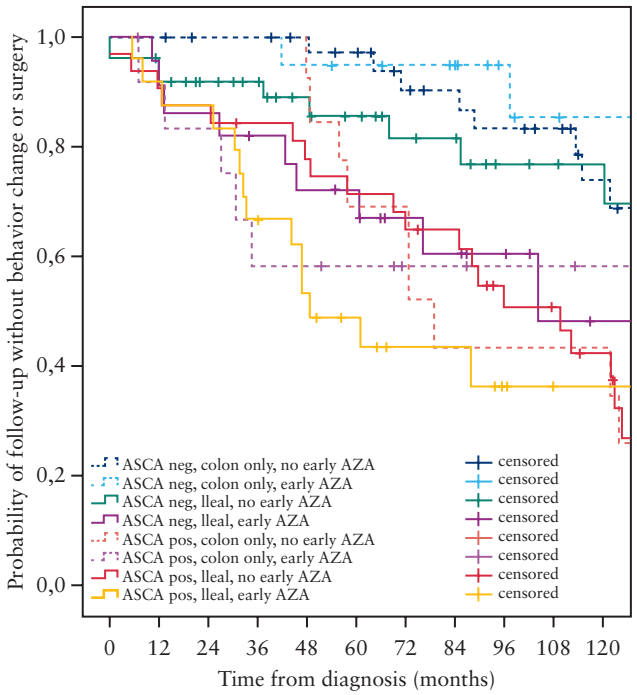

Figure 2. Probability of developing advanced disease outcome according to the modified definition in the referral Crohn's disease cohort in patients with non-stricturing and non-penetrating disease behaviour (B1) at diagnosis.

and weight loss at diagnosis were independently associated with the time to development of severe disease. However, the definition of adverse outcome was different. The authors focused on more objective factors and the definition included the presence of at least one of the following criteria: the development of complex perianal disease; any colonic resection; two or more small-bowel resections (or a single small bowel resection more than 50 cm in length); or the construction of a definite stoma. Similarly, perianal disease, small bowel disease, smoking, prior steroid use, early AZA or AZA/biological therapy were all predictors of disease behaviour change in our previous referral CD cohort study.[6] Furthermore, progression towards complicated disease was also more rapid in those with small bowel compared with colonic disease ($p < 0.001$) in a New Zealand cohort,[3] and perianal disease was a significant predictor of change in CD behaviour (hazard ratio 1.62, $p < 0.001$). Thus, patients with small bowel involvement should be observed especially closely.

4 In addition, biomarkers, including serological markers, especially ASCA, were linked to complicated disease behaviour and CD-related surgery in previous referral CD cohorts and in a meta-analysis.[18–20] Furthermore, in CD, but not in ulcerative colitis, they have also been associated with prediction of aggressive disease phenotype and faster progression towards complicated disease and the need for surgery.[21]

5 Finally, the treatment strategy has also changed in the last decade. Monitoring has become tighter and immunomodulator therapy has been introduced earlier. Relatively recent population-based studies in Wales and Hungary [13,22] reported that early AZA use may be associated with reduced need for resective surgery and a delay in the time to first operation in a population-based CD cohort after matching for propensity scores in the later study. Two recent controlled trials from the French and Spanish IBD groups[23,24] investigating the clinical benefit of systematic early introduction of AZA failed to show a short-term benefit for symptomatic relapse and clinical remission rates even though the need for perianal surgery was lower (4 vs 18%, $p = 0.036$) in the study by the GETAID group.[23] Thus, whether azathioprine has the potential for disease modification in early CD remains controversial. Interestingly, in the present referral cohort, early AZA use was not preventive of advanced outcome in initially B1 patients. Of note, however, this reflects, at least partly, the differences in the cohort setting, and a high percentage of patients in the present referral cohort were treated with anti-TNFs.

In the present study we wanted to exclude patients with already complicated disease and focused on identifying possible risk factors for advanced disease in the subgroup of patients with non-complicated disease behaviour (B1) at diagnosis. In previous studies, the probability of developing complications in CD was reported to be highest during the first years after diagnosis.[3,5,6] Furthermore, there is a window of opportunity in CD and clinical outcomes were better with early aggressive therapy in the first years of the disease.[25,26] Therefore, we focused on the first 3–7 years of the disease in the prediction models. During this period, 30.4, 42.8 and 52% of B1 patients developed advanced disease at 3, 5 and 7 years, respectively, according to the modified definition (disease behaviour change or need for resective surgery). Although a direct comparison with the IBSEN cohort[12] should be interpreted with caution, a much lower proportion of the patients (approximately 36%) developed an advanced outcome after 5 years according to the original definition including the need for immunosuppressives. The rate of advanced disease according to this definition was 64.5% at 5 years in this referral cohort, which reflects at least partly the different cohort setting and inherent higher disease progression rates in a referral setting. Of note, the probability of developing advanced disease during the first 5 years using the modified criteria ranged from 6.2 to 55.5% in the final model depending on the number of positive risk factors, demonstrating a good discriminative potential of the tool to assess the future risk of developing advanced disease in a given patient based on a given risk factor profile shortly after diagnosis.

The authors are aware of possible limitations of the present study. Serological markers were not measured in each patient at the time of diagnosis, although the stability of these markers has been previously demonstrated.[27] Patient management in CD has changed significantly in the last decade, including tight monitoring and quicker access to imaging (e.g. availability of computed tomography and magnetic resonance imaging), increased and earlier access to anti-TNFs and also surgery techniques, especially in referral centres, and this could have potentially affected the probability of developing advanced outcomes and surgery rates in CD. Therefore, the results of our study may not be generalized to patient cohorts outside IBD centres and with more limited access to biological therapies and less stringent patient monitoring. In contrast, the strengths of the study include tight uniform patient monitoring and the use of a more straightforward definition of advanced disease outcome that includes only high-impact clinical scenarios. In addition, access to biological therapy in Hungary is currently one of the best in Middle-Eastern Europe, with more than 2500 IBD patients on anti-TNF therapy, being approximately 9% of CD patients.[28] A harmonized, mandatory, tight monitoring strategy is requested and regularly controlled by the National Health Fund (OEP) in anti-TNF-exposed patients, including CDAI-PDAI assessment, laboratory evaluation (including CRP) at least every 3 months and endoscopy/imaging at least every 12 months. Furthermore, biological therapy is centralized in Hungary to 16 high-volume IBD centres that serve as tertiary referral centres for IBD, and exposure to anti-TNFs in these centres is high (approximately 40%).[29] Thus, we believe that our cohort is representative of high-volume IBD centres in other parts of the world that apply early aggressive treatment and tight monitoring strategy, and after validation by an independent cohort from another geographic region the results may be generalized to this setting. Finally, the decision to start AZA and anti-TNFs was uniform and the IBD specialists at the centre followed the European and Hungarian guidelines and prescription regulations.

In summary, our prediction models identified significant differences in the probability of developing advanced disease in the short and intermediate course of CD. The referral risk matrix model included ASCA IgA and/or IgG, disease location and the need for early AZA use. Markers identified in this referral cohort were different from those previously published in the population-based cohort, suggesting that different prediction models should be used for patients in the referral setting.

Acknowledgements

The study was supported by the Janos Bolyai Research Scholarship of the Hungarian Academy of Sciences, an Internal Research Grant from the University of Debrecen and an IOIBD Research Grant.

Conference presentation

P.L. Lakatos, N. Sipeki, T. Tornai, I. Földi, I. Altorjay, G.L. Norman, Z. Shums, G. Veres, P. Antal-Szalmas, M. Papp. Risk matrix for prediction of disease progression in a referral cohort of patients with Crohn's Disease. 10th Congress of the European Crohn's and Colitis Organisation (ECCO); Barcelona, Spain, 19–21 February 2015, P117.

Conflict of interest statement

GLN and ZS are employees of Inova Diagnostics, Inc., San Diego, CA.

Author contributions

PLL developed the study design, validation of data capture, performed data analysis and drafted the manuscript; NS performed serological tests, constructed the data capture database and revised the manuscript; GK and EP contributed to data capture, database construction and manuscript revision; GLN and ZS contributed to manuscript revision; PAG and BDL contributed to data analysis, manuscript drafting and revision; PA-S contributed to validation of serological analysis and manuscript revision; MP performed and validated the serological tests and contributed to data capture, database construction and drafting and revision of the manuscript.

References

1. Golovics PA, Mandel MD, Lovasz BD, Lakatos PL. Inflammatory bowel disease course in Crohn's disease: is the natural history changing? *World J Gastroenterol* 2014;**20**:3198–207.
2. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;**105**:289–97.
3. Tarrant KM, Barclay ML, Frampton CM, Gearry RB. Perianal disease predicts changes in Crohn's disease phenotype-results of a population-based study of inflammatory bowel disease phenotype. *Am J Gastroenterol* 2008;**103**:3082–93.
4. Burisch J, Pedersen N, Cukovic-Cavka S, *et al.* East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut* 2014;**63**:588–97.
5. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006;**130**:650–6.
6. Lakatos PL, Czegledi Z, Szamosi T, *et al.* Perianal disease, small bowel disease, smoking, prior steroid or early azathioprine/biological therapy are predictors of disease behavior change in patients with Crohn's disease. *World J Gastroenterol* 2009;**15**:3504–10.
7. Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. *Scand J Gastroenterol* 2008;**43**:948–54.
8. Abraham BP, Mehta S, El-Serag HB. Natural history of pediatric-onset inflammatory bowel disease: a systematic review. *J Clin Gastroenterol* 2012;**46**:581–9.

9. de Bie CI, Paerregaard A, Kolacek S, *et al*. Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUROKIDS Registry. *Inflamm Bowel Dis* 2013;**19**:378–85.
10. Pigneur B, Seksik P, Viola S, *et al*. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis* 2010;**16**:953–61.
11. Lovasz BD, Lakatos L, Horvath A, *et al*. Incidence rates and disease course of paediatric inflammatory bowel diseases in Western Hungary between 1977 and 2011. *Dig Liver Dis* 2014;**46**:405–11.
12. Solberg IC, Cvancarova M, Vatn MH, Moum B. Risk matrix for prediction of advanced disease in a population-based study of patients with Crohn's disease (the IBSEN Study). *Inflamm Bowel Dis* 2014;**20**:60–8.
13. Lakatos PL, Golovics PA, David G, *et al*. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977–2009. *Am J Gastroenterol* 2012;**107**:579–88.
14. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989;**170**:2–6; discussion 16–19.
15. Silverberg MS, Satsangi J, Ahmad T, *et al*. 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.
16. Van Assche G, Dignass A, Panes J, *et al*. 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.
17. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol* 1993;**138**:923–36
18. Papp M, Altorjay I, Norman GL, *et al*. Seroreactivity to microbial components in Crohn's disease is associated with ileal involvement, noninflammatory disease behavior and NOD2/CARD15 genotype, but not with risk for surgery in a Hungarian cohort of IBD patients. *Inflamm Bowel Dis* 2007;**13**:984–92.
19. Papp M, Lakatos PL. Serological studies in inflammatory bowel disease: how important are they? *Curr Opin Gastroenterol* 2014;**30**:359–64.
20. Zhang Z, Li C, Zhao X, *et al*. Anti-*Saccharomyces cerevisiae* antibodies associate with phenotypes and higher risk for surgery in Crohn's disease: a meta-analysis. *Dig Dis Sci* 2012;**57**:2944–54.
21. Dubinsky MC, Kugathasan S, Mei L, *et al*. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol* 2008;**6**:1105–11.
22. Ramadas AV, Gunesh S, Thomas GA, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986–2003): a study of changes in medical treatment and surgical resection rates. *Gut* 2010;**59**:1200–6.
23. Cosnes J, Bourrier A, Laharie D, *et al*. Early administration of azathioprine vs conventional management of Crohn's disease: a randomized controlled trial. *Gastroenterology* 2013;**145**:758–65 e752; quiz e714–755.
24. Panes J, Lopez-Sanroman A, Bermejo F, *et al*. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. *Gastroenterology* 2013;**145**:766–74 e761.
25. Allen PB, Peyrin-Biroulet L. Moving towards disease modification in inflammatory bowel disease therapy. *Curr Opin Gastroenterol* 2013;**29**:397–404.
26. Colombel JF, Sandborn WJ, Reinisch W, *et al*. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.
27. Rieder F, Lopez R, Franke A, *et al*. Characterization of changes in serum anti-glycan antibodies in Crohn's disease—a longitudinal analysis. *PLoS One* 2011;**6**:e18172.
28. Rencz F, Péntek M, Bortlik M, *et al*. Biological therapy in inflammatory bowel diseases: access in Central and Eastern Europe. *World J Gastroenterol*. 2015;**21**:1728–37.
29. Golovics PA, Farkas K, Sipeki N, *et al*. Accelerated treatment strategy in inflammatory bowel diseases; is it associated with a change in the disease course? *Gastroenterology* 2015;**148**: s242–s243.