Risk matrix for prediction of disease progression in a referral cohort of patients with Crohn's disease

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Title page

Risk matrix for prediction of disease progression in a referral cohort of patients with Crohn's disease
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List of abbreviations: ASCA: anti-*Saccharomyces cerevisiae* antibody, AZA: azathioprine, BT: bacterial translocation, CD: Crohn's disease, CRP: C-reactive protein, ECCO: European Crohn's and Colitis Organisation, EIM: extraintestinal manifestations, ELISA: enzyme-linked immunosorbent assay, HBI: Harvey–Bradshaw Index, HR: hazards ratio, IBD: inflammatory bowel diseases, Ig: immunoglobulin, IQR: inter quartile range, LPS: lipopolysaccharide, PSC: primary sclerosing cholangitis, UC: ulcerative colitis, 95%CI: 95% confidence interval, TNF: tumor necrosis factor

ABSTRACT

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

Patient and methods: 271 consecutive CD patients (42.4% males, median follow-up: 108 months) were included and followed-up prospectively. Anti-*Saccharomyces cerevisiae* antibodies (ASCA IgA/IgG) antibodies were determined by enzyme-linked immunosorbent assay (ELISA). The final analysis was limited to patients with inflammatory disease behaviour at diagnosis. The final definition for advanced disease outcome was having intestinal resection or disease behaviour progression.

Results: ASCA (IgA and/or IgG) status, disease location, and need for early azathioprine (AZA) were included in a 3-, 5- and 7-year prediction matrix. The probabilities 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 for AZA was associated with the probability to develop advanced disease (pLogRank<0.001).

Conclusion: 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 referral setting.

Word count 222

Key words: serologic antibodies, ASCA, Crohn's disease, disease progression, referral cohort, azathioprine

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 surgeries and disability [1].

Studies on the natural history of CD provide important data on its course and may help to identify clinical predictors for disease progression. Some years ago, *Peyrin-Biroulet et al.* published a systematic review of the natural history of CD in population based-cohorts[2] 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 the 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 [3]. >70% of CD patients had inflammatory disease at diagnosis, while only 23% and 40% of those progressed to complicated disease after 5- and 10 years after the diagnosis, respectively. Similarly, the rate of initial inflammatory disease behaviour was as high as 68% and 75% in CD patients from Western and Eastern Europe in the most recent EpiCom study [4] with only 10% of all patients presenting with perianal involvement.

Therefore, early stratification of patients became utmost important 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, an 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 ileo-colonic 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 pediatric-onset CD runs a more aggressive course, with more extensive disease location, more upper gastrointestinal involvement, more active disease, growth failure, and need for more aggressive medical therapy in predominantly referral-center 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 serologic (anti-*Saccharomyces cerevisiae* antibody [ASCA] positivity) variables that was able to predict the risk of disease outcome 5- and 10 years after the diagnosis. However, similarly to the previous French [5] approach need for immunosuppressants was defined as 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 early aggressive treatment strategy as a possible predictor of disease progression.

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

MATERIAL AND METHODS

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 (inter quartile range [IQR], 19-33) seen in one tertiary IBD referral center of Hungary (Department of Gastroenterology, Institute of Internal Medicine, University of Debrecen) were included between January 1, 2005 and June 1, 2010 and were followed-up until October 1, 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 (EIM) (for example, arthritis: peripheral and axial; ocular manifestations: conjunctivitis,

uveitis, iridocyclitis; skin lesions: erythema nodosum, pyoderma gangrenosum; and hepatic manifestations: primary sclerosing cholangitis [PSC]), frequency of flare-ups (frequent flare-up: >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 center (the actual interval varies between 3–6 months). In addition, 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. The start of immunosupressive or anti-TNFs was indicated by the same 3 IBD specialists throughout the study period by using the ECCO guidelines, the center'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).

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 AZA need was defined as need of AZA within 3 years from the diagnosis.

Serological Analysis

Blood samples were obtained at enrolment from each patient and were frozen at -80°C until testing. All the serological assays were performed in a blinded fashion without prior knowledge of the patients' diagnosis or other clinical information. In 40.2% of the patients the sampling was done at early stages of the disease (duration of disease less than two years) and in 59.8% of patients with >2 years disease duration. The overall disease duration at sampling was 3 years (median [IQR]: 0-8 years).

Detection of anti-microbial antibodies

The presence of anti-*Saccharomyces cerevisiae* antibodies (ASCA) IgA, 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 as positive. The results were documented in absolute values and in frequency of positivity.

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

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.

Statistical analysis

Continuous variables were summarized as medians [interquartile range (IQR)] according to their homogeneity. The predictive potential of the different models for predicting advanced outcome according to the 2 pre-set definitions were tested by both cross sectional analysis after pre-set time-points at 3-, 5- and 7 years after the diagnosis and also in time-dependent models. We developed two different models. In the first model we replicated 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 limited number of cases we limited the final model to the combination of 3 variables. This was based on the result from the univariate chi-square tests where age at diagnosis was not significant. In the second step, since the predictive potential was better 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 rather a treatment decision 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 substituting early steroid requirement by 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 in both univariate and multivariate logistic regression testing. Variables with a $p<0.2$ were selected for multiple testing [17]. In addition, Kaplan-Meier survival curves were plotted for analysing the association between the combination of clinical variables, serological antibodies and complicated disease outcomes during follow-up with LogRank test. A 2-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.

RESULTS

At diagnosis, 79.7% of the CD patients had inflammatory behaviour and 45% had ileocolonic disease (see 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 had at least one resective surgery at last follow-up. Total exposures to steroids, AZA or anti-TNFs were 88.2%, 73.8% and 41.7%, respectively.

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

The association between clinical and serologic 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 for 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**, p=NS 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%. Similar findings were obtained Kaplan-Meier analysis, where the combination of ASCA, location and early AZA was associated with the probability to develop advanced disease (pLogRank<0.001, **Figure 2.**),

DISCUSSION

The present study has shown that the disease course may be predicted in referral CD patients in a complex model including disease phenotype, serologic 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 to the population-based setting.

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 published from 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 referral center 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 2 steroid courses or steroid dependency, the need for immunosuppressive treatment, disabling chronic symptoms, hospitalization, or surgery. Using this definition, 3 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, the clinical importance of these factors is clearly different, and there is little doubt that the start of immunosuppressive therapy rather represents a treatment strategy decision 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.

In a Belgian referral cohort study, ileo-colonic 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 behavior 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 a complex perianal disease, any colonic resection, two or more small-bowel resections (or a single small bowel resection measuring 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 are all predictors of disease behavior change in our previous referral CD cohort study [6]. Furthermore, progression towards complicated disease was also more rapid in those with small bowel compared to colonic disease ($p<0.001$) in a New Zealand cohort [3], and perianal disease was a significant predictor of change in CD behavior (HR: 1.62, $p<0.001$). Thus, patients with small bowel involvement should be observed especially closely.

In addition, biomarkers including serologic 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 UC, they have also been associated with prediction of aggressive disease phenotype and a faster progression towards complicated disease, need for surgery [21].

Finally, treatment strategy has also changed in the last decade. Monitoring became tighter together with earlier introduction of immunomodulator therapy. Relatively recent population-based reports from Wales and Hungary [22]reported that

early AZA use may be associated with reduced need for resective surgery and delayed the time to first operation in a population-based CD cohort after matching on propensity scores in the later study. Although, 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 on symptomatic relapse and clinical remission rates even though the need for perianal surgery was lower (4% versus 18%, p=0.036) in the study by the GETAID group. 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 for 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 an 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 the 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 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, app. 36% developed advanced outcome after 5 years according to the original definition including the need for

immunosuppressives in the definition. 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 number of positive risk factors demonstrating a good discriminative potential of the tool to assess 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 the diagnosis although stability of these markers has been previously demonstrated [27]. Patient management in CD has changed significantly in the last decade including tight monitoring quicker access to imaging (e.g. availability of CT and MRI), increased and earlier access to anti-TNFs and also surgery techniques especially in referral centers that could have potentially affected the probability of developing advanced outcomes and surgery rates in CD. Therefore, results from our study may not be generalized to patient cohorts outside IBD centers and with a 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 advanced disease outcome including only high impact clinical scenarios. In addition, the access to biological therapy in Hungary is one of the best in Middle-Eastern Europe currently with more than 2500 IBD patients on anti-TNF therapy equaling app 9% in CD[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 centers that serve as tertiary referral centers for IBD and the exposure of anti-TNFs in these centers is high, app. 40%[29]. Thus we believe that our cohort is representative to high volume IBD centers from other parts of the world applying an early aggressive treatment and tight monitoring strategy and after validation from an independent cohort from another geographic region results may be generalized to this setting. Finally, the decision to start AZA and anti-TNFs were uniform and IBD specialists in the center followed the European, 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 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 referral setting.

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FIGURE LEGENDS

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

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

TABLES

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

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Table 4. Risk matrix showing advanced 5-year outcome according to the original definition in referral CD patients with non-stricturing and non-penetrating disease behavior (B1) at diagnosis after changing the location grouping.

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

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%**

Table 2. Association between clinical, serologic variables and advanced disease outcome after 3-, 5- and 7 years after the 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)	mulivariate 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[3]	0.001	3.41 (1.59-7.29)	0.19		0.99		0.42		-	
Early AZA[4]	*		<0.001	3.30 (1.92-	0.002	2.50 (1.41-	<0.001	2.64 (1.54-	0.001	2.62 (1.46-

				5.64)		**1.91)**		**4.52)**		**4.67)**
total AZA	*		**0.004**	**2.64 (1.33-5.24)**	**0.31**		**0.13**		**-**	
ASCA either	**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	**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] Early steroid needs was defined as need of steroid within 30 days from the diagnosis

[4] Early AZA need was defined as need of AZA within 3-years from the diagnosis

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

AZA: azathioprine

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

ASCA (IgA and/or IgG)	Early steroid* requirement	Colon location at diagnosis (L2+L3)	Ileal or upper GI 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%

*within 30 days from diagnosis

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

Table 4. Risk matrix showing advanced 5-year outcome according to the original definition in referral CD patients with non-stricturing and non-penetrating disease behavior (B1) at diagnosis after changing the location grouping.

ASCA either (IgA or IgG)	Early steroid* requirement	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%

*within 30 days from diagnosis

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

Table 5. Association between 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 the diagnosis in referral CD patients with non-stricturing and non-penetrating (B1) disease behavior at diagnosis.

ASCA (IgA and IgG)	Early AZA* requirement	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%

*Early AZA need was defined as need of AZA within 3-years from the diagnosis

[1] need for surgery and disease behaviour change

FIGURES

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

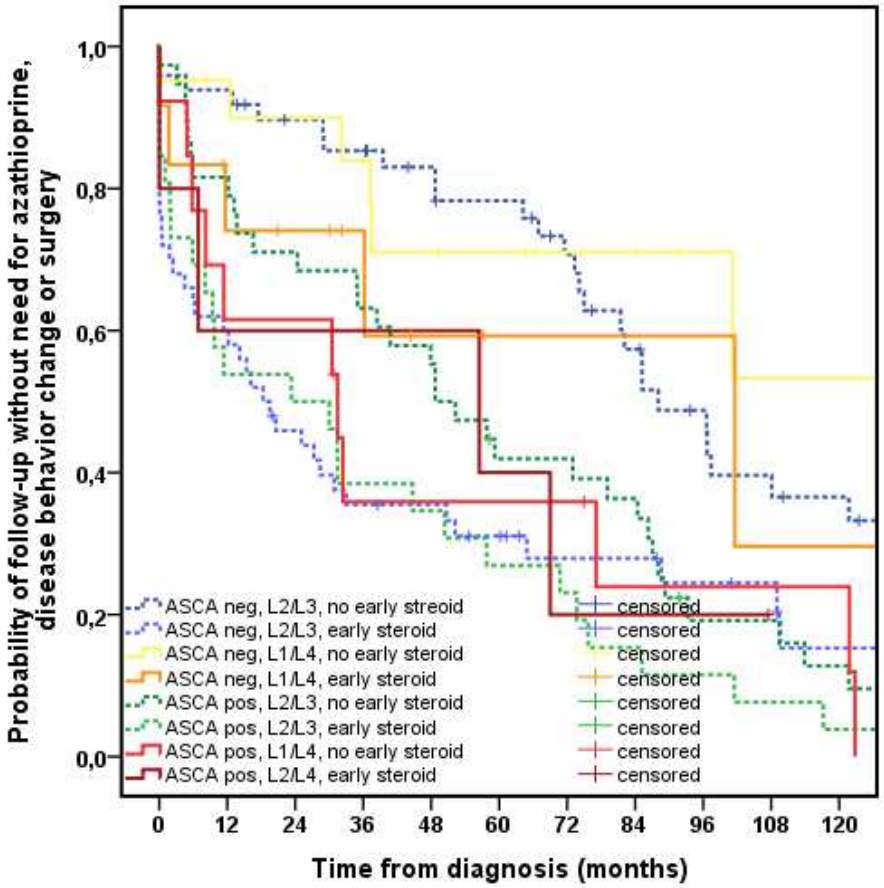
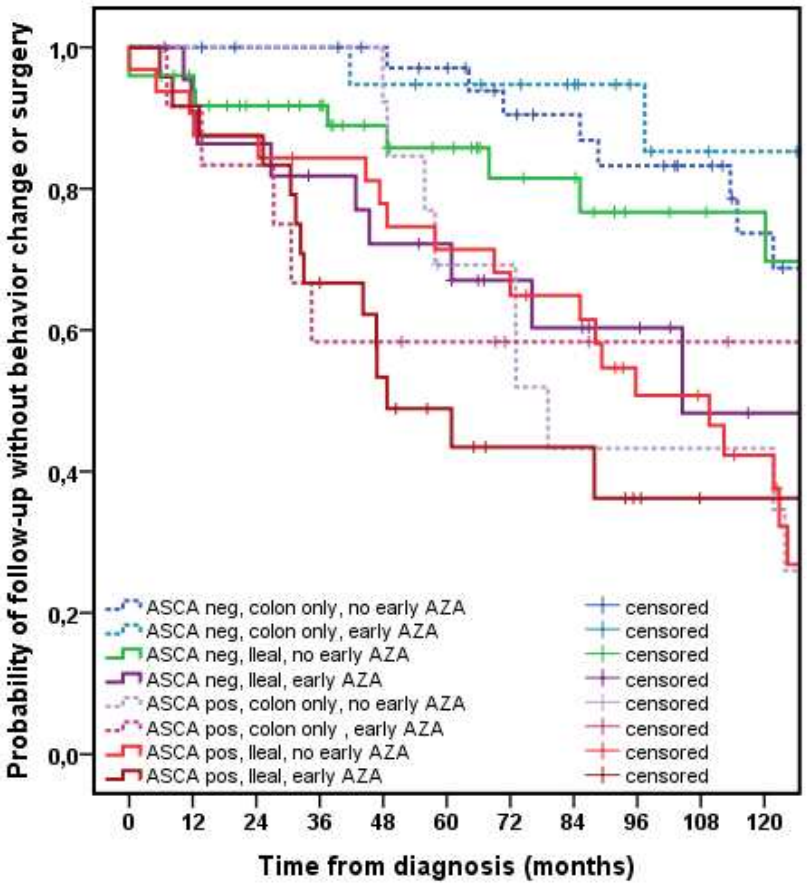
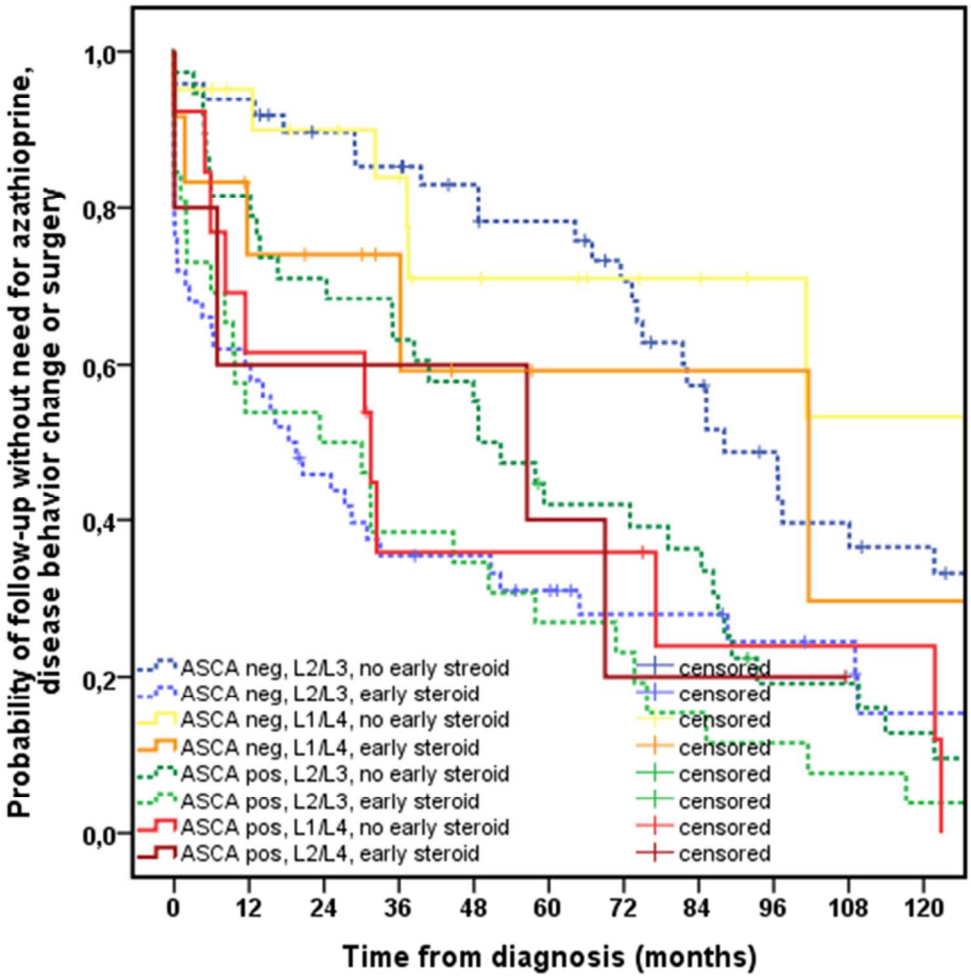


Figure 2. Probability of developing of advanced disease outcome according to the modified definition in the referral CD cohort in patients with non-stricturing and non-penetrating disease behaviour (B1) at diagnosis.





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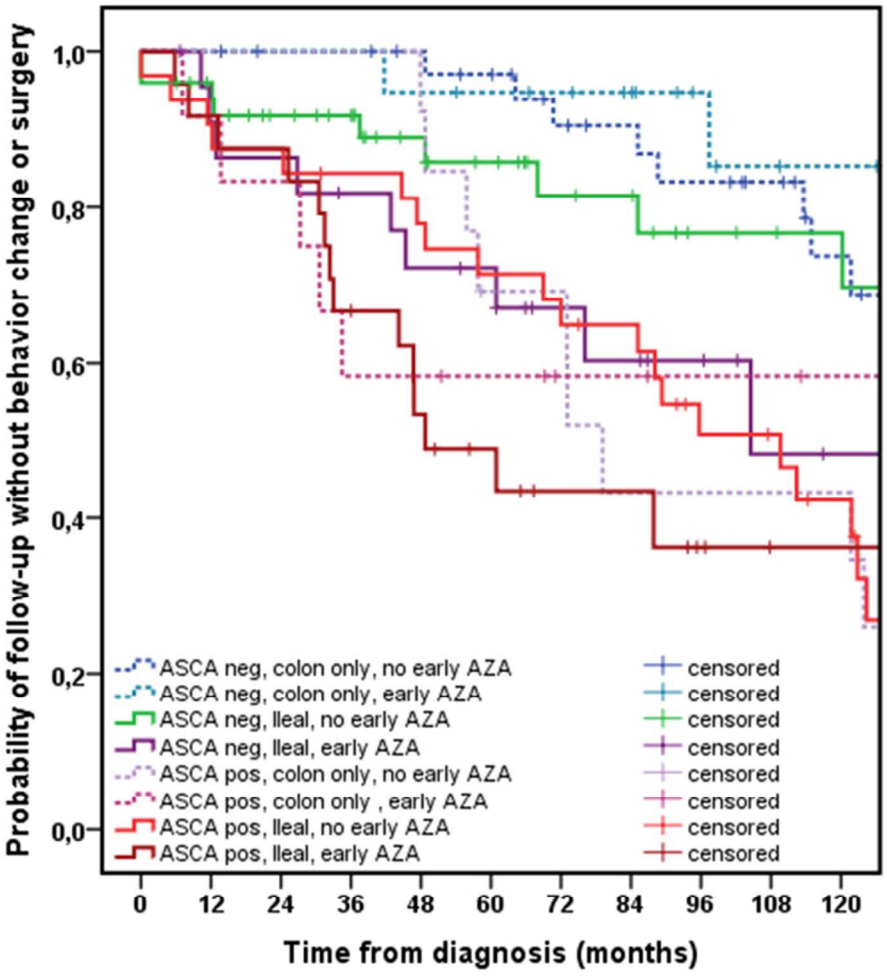

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