Digestive Diseases and Sciences (2023) 68:596–607
https://doi.org/10.1007/s10620-022-07639-w

ORIGINAL ARTICLE

A Method Using Longitudinal Laboratory Data to Predict Future Intestinal Complication in Patients with Crohn's Disease

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Received: 12 May 2022 / Accepted: 20 July 2022 / Published online: 20 September 2022

Abstract

Background Stenosis, fistulization, and perforation of the bowel are severe outcomes which can occur in patients with Crohn's disease. Accurate prediction of these events may enable clinicians to alter treatment strategies and avoid these outcomes.

Aims To study the correlation between longitudinal laboratory testing and subsequent intestinal complications in patients with Crohn's disease.

Methods An observational cohort of patients with Crohn's disease at a single center were analyzed between 01/01/1994 and 06/30/2016. A complication was defined as the development of an intestinal fistula, stenosis, or perforation. Exploratory analysis using Cox regression was performed to select the best statistical method to represent longitudinal laboratory data. Cox regression was used to identify laboratory variables independently associated with the development of a subsequent complication. A clinical scoring tool was designed.

Results In 246 patients observed over a median of 5.72 years, 134 complications occurred. Minimum or maximum value in a preceding window period of one year was most strongly associated with subsequent complication. A Longitudinal Laboratory score of ≥ 2 (maximum albumin level < 39 g/L $= 1$, maximum mean cell volume < 88 fL $= 1$, minimum platelet count $> 355 \times 10^9$/L $= 1$, minimum C reactive protein > 5 mg/L $= 1$) was 62% sensitive and 91% specific in identifying patients who develop a subsequent complication.

Conclusion A consistent reduction in serum albumin and mean cell volume, and a consistent increase in platelet count and C reactive protein were associated with a subsequent complication in patients with Crohn's disease. Longitudinal laboratory tests may be used as described in this paper to provide a rational for earlier escalation of therapy.

Keywords Biomarkers · Crohn's disease · Inflammatory bowel diseases · Stenosis · Perforation · Fistula

Introduction

Crohn's disease is a chronic inflammatory condition of the human gastrointestinal tract of undetermined etiology. It is characterized by a relapsing and remitting course [1] and by significant morbidity from chronic abdominal pain, diarrhea, perianal abscess and fistula formation, bowel stenosis and obstruction, internal fistulization, and bowel perforation [2–7].

Medical therapy (corticosteroids, immunomodulatory medications, and biologic medications) controls symptoms, and may reduce the risk of long-term complications of Crohn's disease. These treatments have been demonstrated to reduce evidence of active Crohn's disease when measured by the Crohn's disease activity index (CDAI) and by endoscopic assessment of bowel mucosa [8–17].

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There is observational evidence that anti-TNF therapy is associated with a reduction in the rates of intestinal surgery [18], and conflicting evidence that azathioprine and 6-mercaptopurine are associated with a reduction in the rates of intestinal surgery, or stenotic or penetrating complications [3, 4, 18–21]. Immunomodulatory therapy in Crohn's disease carries a significant side effect profile. For patients without significant symptoms from their Crohn's disease, a decision to embark on long-term immunomodulatory therapy is made weighing up potential medication side effects, against the likelihood of a reduction in severity of Crohn's disease symptoms, and the risk of development of a future complication.

Features of a patient's clinical presentation and early disease course allow some prediction of the likelihood of a subsequent poor clinical course. Age < 16 years at diagnosis, perianal disease at diagnosis, and requirement for corticosteroids to control the first flare of disease are published, validated, and widely used predictors of a poor outcome [22, 23]. Additionally, there are published data demonstrating an association between NOD2 genotype and development of stenotic or penetrating complications [24], and active smoking with penetrating complications [25].

Published predictors of poor outcome suffer from low discriminatory power in identifying patients who are likely to follow a complicated disease course, and from non-uniformity of outcome measure. Further stratification of patients into those more and less likely to follow a poor clinical course would allow improved tailoring of medical therapy, and better management.

Longitudinal laboratory testing is a routine part of the management of patients with Crohn's disease. Testing is performed to assess inflammatory status, nutritional status, and to monitor for side effects from prescribed medications. These results contain objective clinical information which may provide useful prediction of future disease course. Published literature associating laboratory testing and long-term outcome in Crohn's disease demonstrate an association between both a high CRP and a high platelet count at diagnosis, with subsequent intestinal surgery [23, 26]. There are also recently published data demonstrating an association between longitudinal laboratory testing (serum albumin, platelet count, serum urea level, and mean cell hemoglobin concentration) and subsequent outcome [27]. However, the optimum way to interpret longitudinal laboratory data when predicting future outcome is far from clear.

This study aimed to define a simple and useful clinical tool for interpreting longitudinal laboratory data in patients with Crohn's disease. This was done through the assessment of the correlation between longitudinal laboratory testing and subsequent development of luminal complications, specifically bowel stenosis, bowel perforation, or intra-abdominal fistula formation in patients with Crohn's disease.

Patients and Methods

Study Design

This was a single-center observational longitudinal cohort study. All patients with a diagnosis of Crohn's disease made between 1st January 1994 and 31st March 2008, managed at the Inflammatory Bowel Diseases Unit at the Royal Brisbane and Women's Hospital (RBWH, Brisbane, Australia), were invited to participate in the research programme. Serological, epidemiological, clinical, and genetic data were recorded at baseline, and further clinical data were recorded longitudinally until 30th June 2016.

Ethical approval for the study was obtained through the Royal Brisbane and Women's Hospital ethics committee. All participating patients consented to take part in the research programme.

The methodology of this study followed the STROBE guidelines for the performance of observational studies [28].

Patients were observed from 2 years prior to the date of diagnosis of Crohn's disease, to the end of their clinical contact with our unit, or until development of a complication, whichever came first.

Definitions

A complication was defined as the first observation of an intestinal fistula, stenosis, or perforation. This observation could be made at surgery, on macroscopic examination of a surgical specimen, at colonoscopy or gastroscopy, on computed tomography (CT) scan, on magnetic resonance imagining (MRI) scan, or in the case of enterocutaneous fistulae, on clinical examination. This study focused on luminal complications and hence perianal fistulae were not included in the outcome definition. The definition of each complication is outlined in Table 1.

Inclusion and Exclusion Criteria

All included patients met criteria for a diagnosis of Crohn's disease [29]. These were consistent with the Lennard–Jones criteria; however, patients who did not undergo surgery, and therefore did not have a transmural surgical specimen for examination, were not required to demonstrate evidence of transmural bowel involvement. For these patients evidence of chronic mucosal bowel inflammation (lymphocytic infiltration of the lamina propria, presence of granulomas, or crypt architectural distortion) in a typical distribution (ileal only, or non-continuous colonic) was considered adequate for diagnosis. All early clinical information was reviewed to confirm that diagnostic criteria were met. Patients who did

Table 1 Identification of internal penetrating or stricturing complications

Complication	Modality	
Stenosis	Endoscopy	Narrowing of lumen unable to be passed by endoscope
	Surgery	Macroscopic stenosis identified at surgery or on pathological specimen
	Radiology	Luminal narrowing with prestenotic dilation to greater than 2.5 cm
Perforation	Surgery	Phlegmon or extraluminal collection
	Radiology	Phlegmon, extraluminal collection, free air under the diaphragm
Fistula	Endoscopy	Internal opening of fistula visible
	Surgery	Macroscopic fistula between two hollow viscera or the skin, identified at surgery or on pathological specimen
	Radiology	Fistula tract evident between two hollow viscera or the skin
	Clinical examination	Cutaneous fistula tract evident on skin (not perianal)

not have 5 years of follow-up data available, and patients without laboratory data, were excluded from the cohort. Patients who suffered a complication within 30 days of diagnosis were also excluded from the cohort. This exclusion was made considering that the goal of this study is to identify a laboratory testing profile that predicts the future development of a complication. The make-up of this cohort is therefore designed so that clinicians managing similar patients will have time to consider giving treatment that may alter future disease course.

Laboratory Data

Laboratory data were obtained by matching identities to data from four sources: AUSLAB (all laboratory results performed in public hospitals across Queensland 1st January 1999 to present), PARIS (a historical database which records all laboratory results performed in public hospitals in Brisbane 1st January 1985–1st January 1999), Queensland Medical Laboratories (QML, private laboratory database covering all of Queensland 1st January 1995 to present), and Sullivan and Nicolaides Pathology (SNP, private laboratory database covering all of Queensland 1st January 2001—present). QML and SNP are the two major private pathology providers in Queensland. Patient data were matched by surname, first-name, date of birth (DOB), and gender.

CRP, (mg/L), erythrocyte sedimentation rate (ESR, mm/h), hemoglobin level (g/L), mean cell volume (MCV, fL), white blood cell count (WCC, $\times 10^9$/L), platelet count ($\times 10^9$/L), neutrophil count ($\times 10^9$/L), fecal calprotectin (mcg/g feces), ferritin (mcg/L), alanine transferase (ALT, IU/L), and albumin (g/L) were analyzed. Values reported below the lowest detectable level were considered equal to zero, while values reported above the highest detectable level were considered equal to that highest detectable level. These considerations were most important for CRP which had a lower limit of detection of 5 mg/L in the 1990s, reducing to 2 mg/L in 2006.

Statistical Analysis

Correlation between laboratory variables and complications was evaluated using Cox proportional hazard analysis. Laboratory data were transformed into a time standardized dataframe, with representative values at each time point for each variable, and an interval between time points of 10 days. The data were aligned by time to event. The data were represented at each time point by the median, minimum, maximum, area under the curve, and last value of all values in a preceding observation window. Repeated analysis was performed with differing observation windows of 30, 60, 90, 180, 365, and 720 days. Where no data existed in the observation window, data were filled using the last value carried forward. Varying observation windows and varying representative statistical methods were tested to determine which window period and which statistical method carried the most association with the development of a complication.

To assess the longitudinal predictive value of the data, multiple Cox regression models were built with varying event horizons. This is a variation of a statistical method employed in stock market analysis, 'long horizon predictive regression' [30]. For an event horizon of 3 months, all data recorded within 3 months of an event or of censoring were removed. The remaining data were then assessed for their correlation with complications that occur 3 months (the event horizon) after the last analyzed time point. This method allows demonstration of how long prior to an event a signal predictive of complication exists in the data.

A formal Cox regression model was then designed using the optimum observation window and optimum representative statistical value for laboratory data, in addition to clinical and genetic data points. This model was built using a selected event horizon. For this model each variable was correlated with complication using univariate Cox regression. Variables with a p value of association < 0.2 were then entered into a multivariate model in a stepwise fashion, retaining those with independent correlation ($p < 0.05$) in

a multivariate model. The model was corrected for potential confounders by including the following variables in the analysis: age at diagnosis, gender, Montreal classification disease location at diagnosis [31], perianal disease at diagnosis, smoking status at diagnosis, NOD2 genotype, intravenous steroids given for first disease flare, thiopurine use, biologic use (infliximab or adalimumab), and methotrexate use. Medication use was coded depending on whether it was used continuously through the observation window (2), partially (1), or not used (0). Finally, continuous variables were converted to categorical variables to produce a model which presents the data in a way that is most easily interpretable by clinicians at the bedside.

All analysis was performed in the R statistical computing environment [32] (version 3.6.3).

Results

Demographics

377 patients were assessed. 62 were lost to follow-up, 2 had inadequate laboratory data, and 67 patients suffered a complication within 30 days of diagnosis and were excluded. 246 patients contributed data for analysis. Demographics are shown in Table 2. Patients were observed a median of 5.72 years [intra-quartile range (IQR) 2.57–9.28 years]. 66 patients suffered a bowel stenosis after a median 3.46 years (IQR 1.06–6.74 years) of observation, 30 patients suffered a bowel perforation or fistula formation after a median 2.92 years (IQR 0.87–6.18 years) of observation, and 38 patients suffered a combination event (bowel stenosis and bowel perforation or fistula formation) after a median 3.35 years (IQR 1.00–6.03 years) of observation. 112 patients suffered no complication over the observation period. 201/246 patients underwent testing for their NOD2 genotype. Median blood testing frequency was between 0 and 6.19 times per year while under observation, depending on the variable (Table 3).

Determination of Statistical Method

Exploratory analysis of variables demonstrated a marked variation in correlation with complication, depending on the statistical method used to represent each variable (Fig. 1). There was a general trend for variables to be more strongly associated with complications as the event horizon reduced. For most variables correlation was significant with an event horizon as long as 720 days. Using 365 days as the window period, either maximum (albumin, hemoglobin, ferritin, MCV) or minimum (white cell count, neutrophil count, platelet count, ALT, CRP, ESR, fecal calprotectin) value observed over the window period was the statistical method most strongly correlated with outcome.

Using the selected statistical method determined for each variable, further analysis was performed comparing differing window periods. Correlation with outcome was generally strongest with a window period of 365 days

Table 2 Demographics (at diagnosis unless stated otherwise)

Variable	Proportion
Gender (female)	139/246 (0.57)
Age*	30.3 (22.9–39.9)
Montreal disease location	
L1	96
L2	54
L3	96
Perianal disease	25/246 (0.1)
IV steroids given	37/246 (0.15)
Smoker	19/189 (0.1)
Smoker ever	117/243 (0.48)
Family history of IBD (any)	68/242 (0.28)
Family history of IBD (1st degree relative)	32/242 (0.13)
Thiopurine use**	194/246 (0.79)
Biologic use**	107/246 (0.43)
Methotrexate use**	55/246 (0.22)
NOD2 status***	
Homozygote	7/201 (0.03)
Compound heterozygote	11/201 (0.05)
Heterozygote	52/201 (0.26)
Wildtype	131/201 (0.65)

*Median and intra-quartile range

**Medication use at any time through observation period

***NOD2 status: homozygotic for one of the following three NOD2 variants—rs2066844, rs2066845, rs2066847. Compound hetereozygotic for two of these variants

Table 3 Frequency of laboratory testing per patient per year—median and intra-quartile range

Variable	Median tests per year
Platelet count	6.19 (2.96–10.45)
Hemoglobin level	6.19 (2.96–10.45)
Mean cell volume	5.94 (2.98–10.66)
Neutrophil count	5.94 (2.98–10.66)
White cell count	5.92 (2.85–10.66)
Serum albumin	5.52 (2.61–9.85)
ALT	5.24 (2.55–9.85)
CRP	4.2 (2.02–8.04)
ESR	3.7 (1.66–6.76)
Serum ferritin	1.51 (0.6–3.69)
Fecal calprotectin	0 (0–1.74)

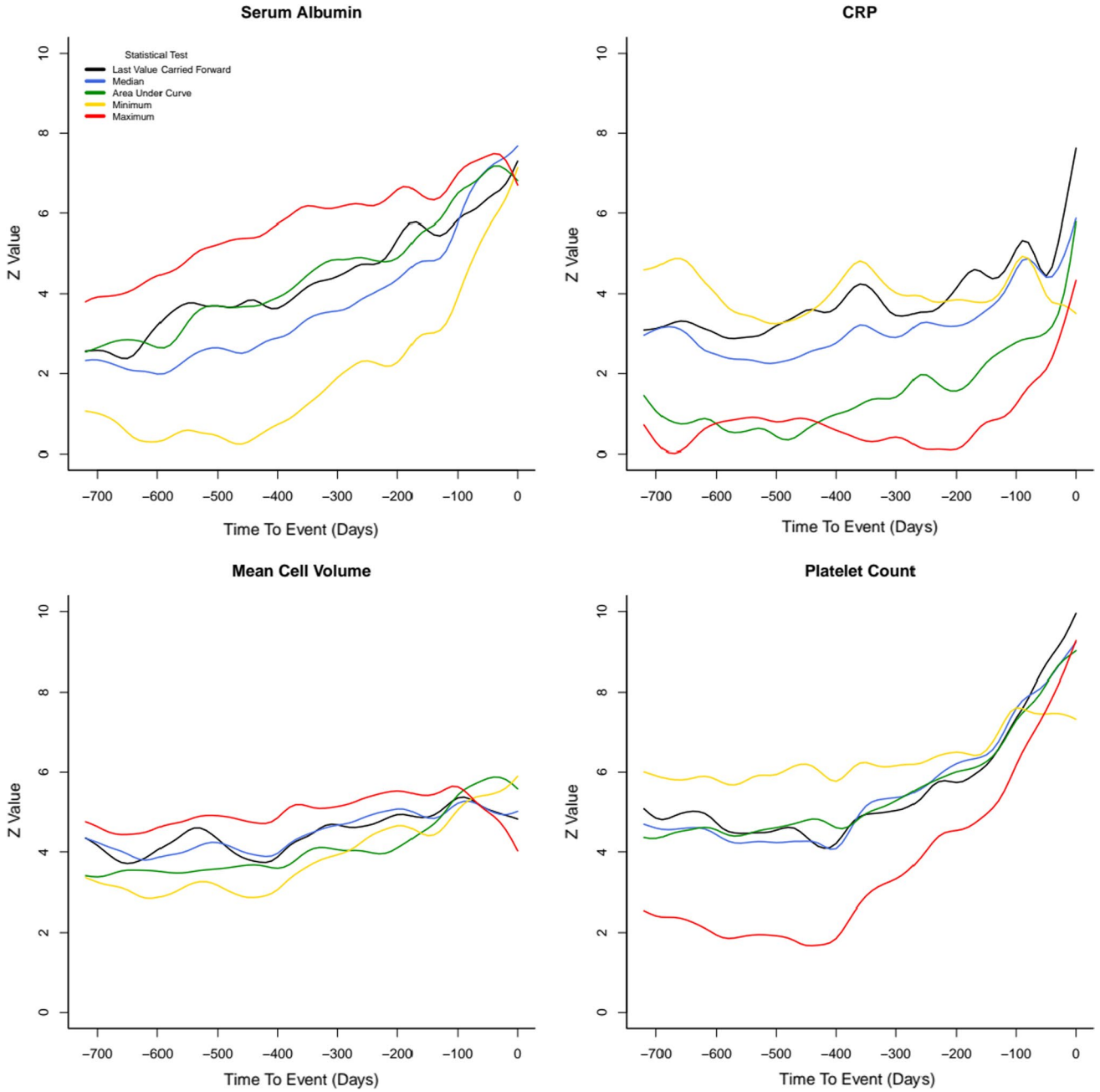

Fig. 1 *Z* value for univariate cox proportional hazard analyses of association between complication and laboratory variable (albumin, CRP, MCV, and platelet count), using varying statistical methods to represent the laboratory variable. The event horizon decreases from 720 to 0 days from left to right in each graph. For variables that tend to rise with illness (CRP, platelet count), minimum value during window period was the representative statistic most strongly associated with complication. For variables that tend to fall with illness (albumin, hemoglobin, mean cell volume), maximum value was most strongly associated with complication

(Fig. 2). The correlation of each variable with outcome using minimum value (white cell count, neutrophil count, platelet count, ALT, CRP, ESR, fecal calprotectin) or maximum value (albumin, hemoglobin, ferritin, MCV) observed in a window period of 365 days is shown in Fig. 3.

Correlation with Outcome

Univariate correlation of confounding variables and complication using Cox regression is shown in Table 4. Variables with a p value of < 0.2 were then entered into a multivariate Cox regression model along with laboratory variables. From

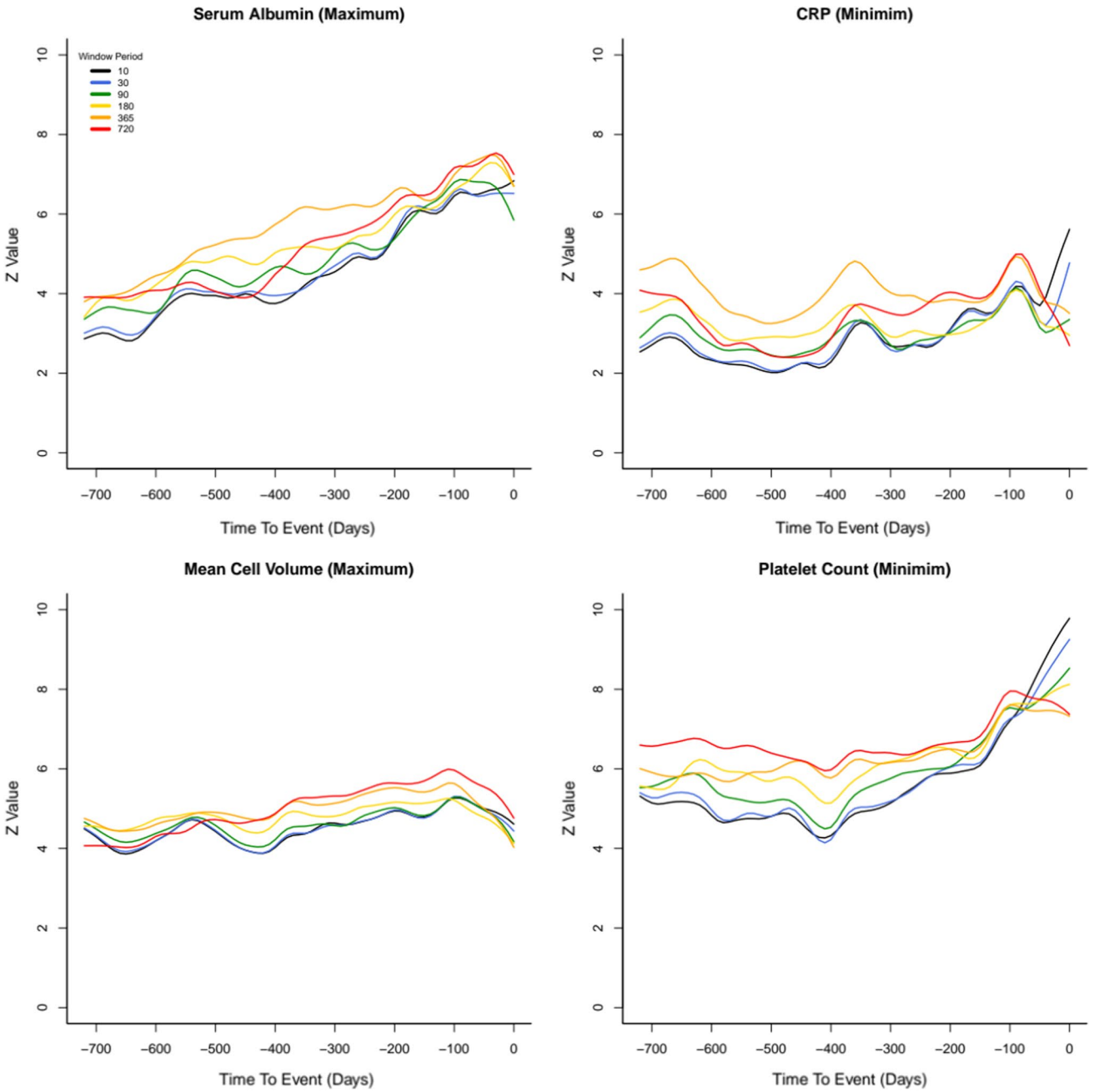

Fig. 2 *Z* value for univariate cox proportional hazard analyses of association between complication, and the selected statistical method to represent laboratory variables (albumin, CRP, MCV, and platelet count), with a varying window period. The event horizon decreases from 720 to 0 days from left to right. 365 days is the window period that is most consistently correlated with complication

exploratory analyses 365 days was selected as the best event horizon with which to derive a multivariate Cox regression model. A final model was built that retained all variables that maintained independent correlation with complication (Table 5).

Continuous variables (minimum or maximum values during a 365-day window period) were then converted to categorical variables by determining the cut-off point with the strongest association with complication. For maximum albumin level this was < 39 g/L, for minimum CRP > 26 mg/L, for minimum platelet count > 355×10^9/L, and for maximum MCV < 88 fL. (Fig. 4). The CRP analysis demonstrated there was little difference in significance of association between minimum CRP and complication if a lower cut-off was selected. A lower cut-off is more sensitive for identifying systemic inflammation, and for this reason minimum

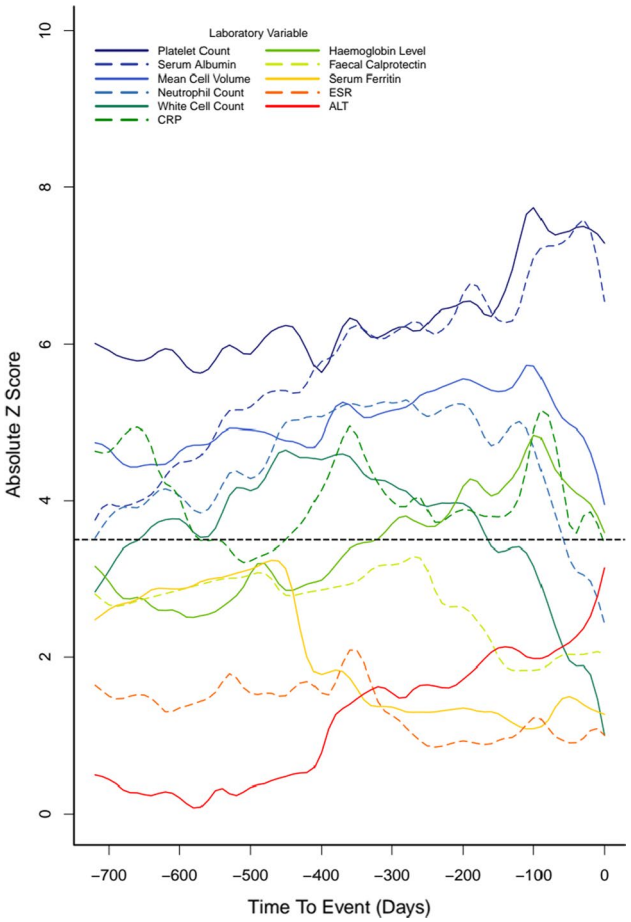

Fig. 3 *Z* scores for univariate cox proportional hazard analyses of each pathology test, each modeled independently using minimum (white cell count, neutrophil count, platelet count, ALT, CRP, ESR, fecal calprotectin) or maximum (albumin, hemoglobin, ferritin, MCV) of values from a 365-day window period prior to each time point. The event horizon decreases from 720 to 0 days from left to right. Values above the dashed line survive Bonferroni correction

CRP > 5 mg/L was selected as the cut-off for this variable. The remaining three variables had a clear optimum cut-off value that was retained.

Longitudinal Laboratory Scoring Tool

From these data a consistently abnormal laboratory variable is defined as a variable that, over the previous 365 days, is always recorded above (CRP 5 mg/L, Platelet count 355×10^9/L) or below (albumin level 39 g/L, MCV 88 fL) a defined cut-off. Using these cut-off values, a simple table of incidence of complication stratified by the number of consistently abnormal laboratory variables is shown 365 days prior to complication/censoring (Table 6) and 720 days prior (Table 7). At 365 days prior, if no laboratory values were consistently abnormal, the rate of complication was 14/80 = 21%. If two or more laboratory variables were consistently abnormal, the complication rate was 51/61 = 84%. A Longitudinal Laboratory score ≥ 2 was 62% sensitive and 91% specific for the development of a future complication, with a positive predictive value of 84%, and a negative predictive value of 76%. Receiver Operating Characteristic (ROC) analysis is shown in Fig. 5, yielding an area under the curve (AUROC) of 0.808 for this clinical tool.

Discussion

Prediction of Complication

In this study of patients with Crohn's disease, consistently reduced albumin and MCV, and consistently increased platelet count and CRP were associated with subsequent development of a complication. This relationship existed up to 720 days prior to the development of a complication. This time window provides an opportunity to use these laboratory results to help identify at risk individuals, and

Table 4 Univariate correlation using Cox regression, between confounding variables and complication

Variable	coef	exp(coef)	se(coef)	*z*	Pr(>|z|)
NOD2	0.144	1.155	0.329	0.439	0.660957
Ileal disease (L1/L3)	0.729	2.074	0.243	3.004	0.002666**
Perianal disease	− 0.398	0.672	0.329	− 1.211	0.225866
Thiopurine use	− 0.088	0.916	0.226	− 0.388	0.697797
Biologic use	− 1.747	0.174	0.51	− 3.426	0.000612***
Methotrexate use	− 0.065	0.937	0.418	− 0.156	0.876261
Male gender	0.054	1.055	0.173	0.311	0.755809
Family history of IBD	− 0.117	0.89	0.13	− 0.898	0.369042
IV steroids at diagnosis	− 0.117	0.89	0.242	− 0.482	0.629545
Age at diagnosis	− 0.016	0.984	0.007	− 2.115	0.034412**
Smoking status at diagnosis	− 0.607	0.545	0.392	− 1.549	0.1213*

Significance: *$p < 0.2$; **$p < 0.05$; ***$p < 0.001$

Table 5 Final multivariable cox regression model

	coef	exp(coef)	se(coef)	*z*	Pr(>|*z*|)
Platelet count (minimum)	0.003	1.003	0.001	2.014	0.044*
Mean cell volume (maximum)	− 0.034	0.966	0.016	− 2.112	0.035*
CRP (minimum)	0.011	1.011	0.004	2.564	0.01*
Serum albumin (maximum)	− 0.092	0.912	0.028	− 3.299	0.001***
Biologic use	− 1.671	0.188	0.524	− 3.192	0.001***
Age at diagnosis	− 0.028	0.972	0.012	− 2.419	0.016*
Ileal disease location (L1 or L3)	0.649	1.914	0.297	2.187	0.029*

Laboratory variables are represented by minimum or maximum values in a 365-day window period prior to each time point. Biologic use is calculated for a 365-day window period prior to each time point. (0 = none, 1 = some, 2 = continuous)

*$p < 0.2$; **$p < 0.05$; ***$p < 0.001$

potentially implement therapy to avoid future development of a complication.

Laboratory testing for patients with Crohn's disease tends to be reactive, performed to correlate current symptoms with objective inflammatory or nutritional markers, or to assess the response of these markers to a change in therapy. This study demonstrates that these same laboratory variables can provide an objective longitudinal assessment of inflammatory and nutritional status which correlates with the future development of a complication. The striking finding that minimum (for variables that tend to rise with illness) and maximum (for variables that tend to fall with illness) were the representative variables most strongly associated with complication was unexpected. We interpret this to mean that consistently abnormal laboratory variables (no deviation toward normal values) are associated with a subsequent complication. Conversely, any return of a laboratory value toward normal over the previous year, even if a single measurement, portends a better outcome. This observation adds weight to the paradigm that in Crohn's disease, irreversible bowel damage is the result of chronic bowel inflammation.

It is also striking that the cut-offs identified in this study that are most strongly correlated with a subsequent luminal complication are not markedly deviated from values considered to be normal. This observation suggests that patients with mild inflammation also tend to progress to develop bowel damage and luminal complication, when inflammation is chronic.

We propose the following Longitudinal Laboratory Score to predict future risk of complication for patients with Crohn's disease. In patients with Crohn's disease who have not suffered a complication, assess the following four values over the preceding year: maximum albumin < 39 g/L = 1 point, maximum MCV < 88 fL = 1 point, minimum platelet count > 355×10^9/L = 1 point, minimum CRP > 5 mg/L = 1 point. Assessment may be made regardless of whether this time is prior or subsequent to the date of diagnosis. If the sum of these four values is 0, the risk of future complication is low. If the score is ≥ 2, the risk is high.

Further Observations

Fecal calprotectin was used routinely in the management of our patients from 2008, and therefore, a smaller number of observation periods had fecal calprotectin data to use for analysis. There were not enough data, and not enough statistical power, to adequately assess this biomarker, which has been shown to provide prognostic information in patients with IBD [33].

In patients with Crohn's disease, thiopurine and methotrexate use increases MCV, while folate or B12 deficiency increases MCV, and iron deficiency decreases MCV. The correlation of a decreased MCV with complication in this study may be a consequence of either of these factors—worse disease leading to both complication and iron deficiency/microcytosis, or immunosuppressive use causing less severe disease and also increasing MCV.

The dominant observed complication in this study was bowel stenosis. The absolute rate and relative proportion of intra-abdominal stenosis, perforation, and fistula formation in our cohort is similar to published cohorts when represented by cumulative Montreal phenotype classification [5, 7, 31, 34]. We believe that this is representative of the spectrum of long-term complications suffered by patients with Crohn's disease, and that therapy initiated with the goal of preventing the development of long-term complications would be given predominantly to prevent bowel stenosis.

Objectivity in Outcome Assessment

Intestinal surgery is a commonly used endpoint in longitudinal studies of Crohn's disease [4, 18, 19]. We elected to use the development of a complication, and not the performance of intestinal surgery, as our primary endpoint in this study. We feel the decision to perform surgery may be

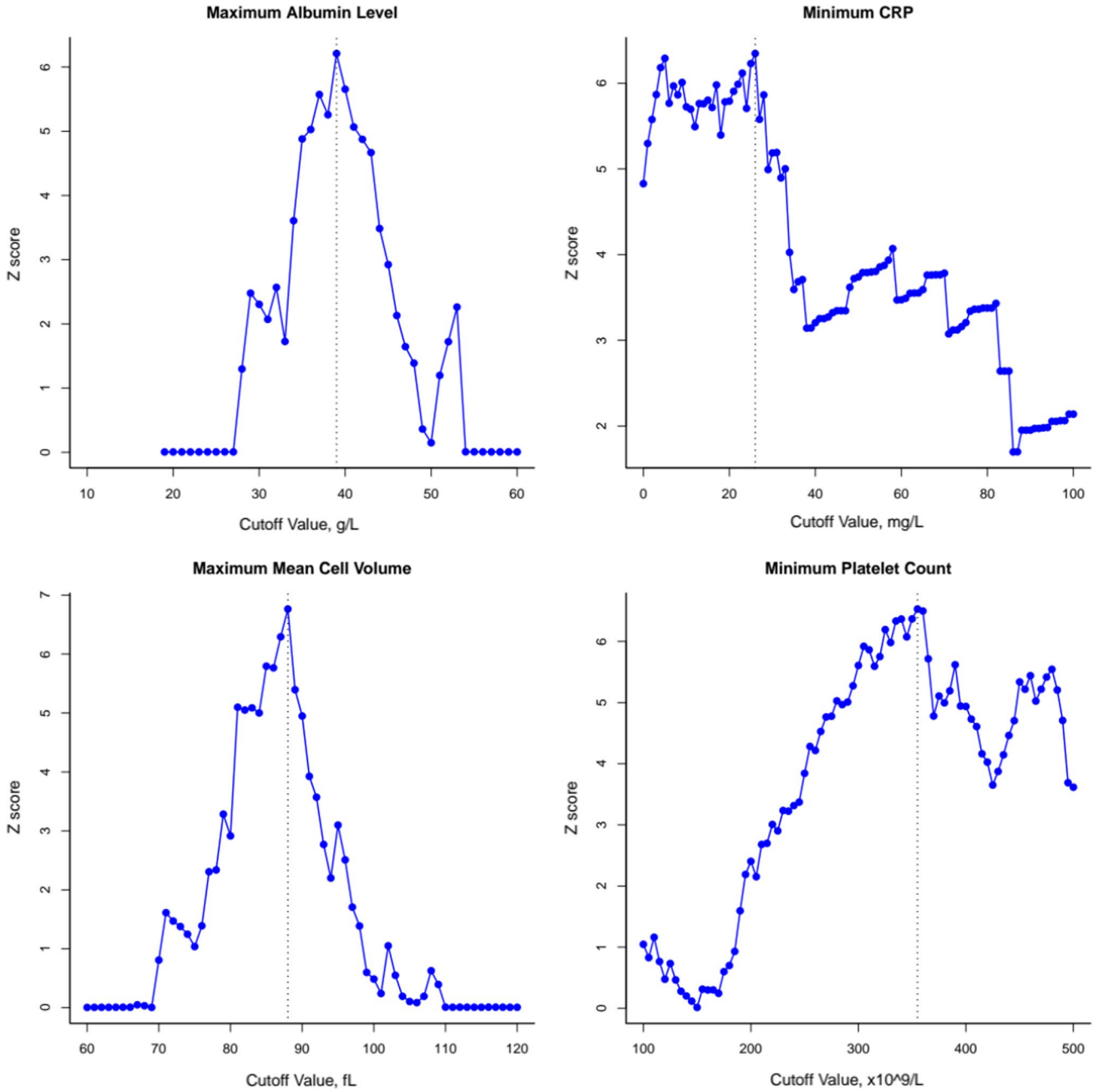

Fig. 4 *Z* score for univariate cox regression of laboratory variables categorized above or below a cut-off. The cut-off used varies along the *x* axis, and the vertical dotted line represents the cut-off value which gives the strongest association with complication

influenced by subjective factors (physician and surgeon opinion of what a reasonable indication for surgery is, patient agreement to undergo surgery) and may not be a truly objective marker of outcome. This is demonstrated by varied rates of intestinal surgery in cohorts of patients with Crohn's disease, across time periods and across geographic location [4, 35]. The international IBD community has proposed a more objective definition of long-term outcome in Crohn's disease, the Lémann score [36]. This score assigns a numeric representation of outcome based on the observation of stenosis, perforation, and fistulization made at ileocolonoscopy, gastroscopy, surgery, on examination of macroscopic histological specimens, clinical examination, and cross-sectional imaging. It is complex and has not yet been routinely taken up in observational Crohn's disease research to date. However, it, or a simplified variation, is likely to provide a more objective and standardized measure of longitudinal outcome in

Table 6 Rate of complication stratified by number of consistently abnormal laboratory results

Number of consistently abnormal laboratory results	No complication	Complication	Proportion
0	66	14	0.18
1	35	18	0.34
2	6	22	0.79
3	4	12	0.75
4	0	17	1

Laboratory results are CRP, MCV, platelet count, and albumin level. Analysis performed with a 365-day event horizon

Table 7 Rate of complication stratified by number of consistently abnormal laboratory results

Number of consistently abnormal laboratory results	No complication	Complication	Proportion
0	75	23	0.23
1	28	22	0.44
2	3	19	0.86
3	2	9	0.82
4	0	2	1

Laboratory results are CRP, MCV, platelet count, and albumin level. Analysis performed with a 720-day event horizon

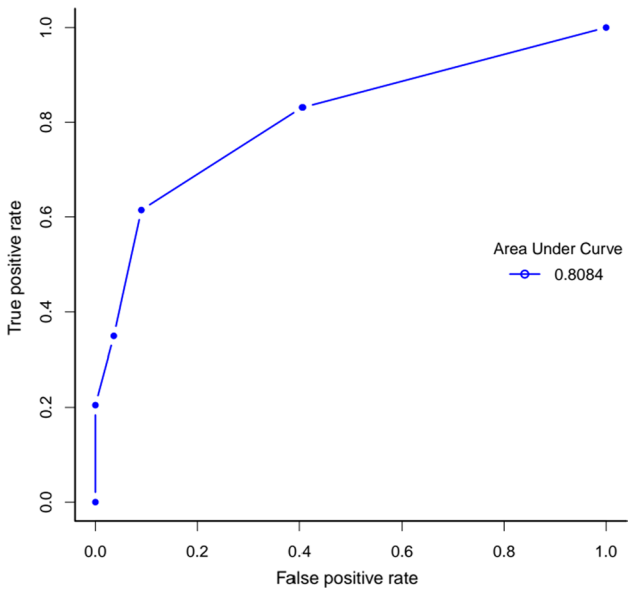

Fig. 5 Receiver Operating Characteristic (ROC) curve for the Longitudinal Laboratory Scoring Tool in predicting a subsequent complication

Crohn's disease than the performance of surgery. This may translate more objectively between patients across time periods and geographic location, and allow closer comparison between different research cohorts.

Weaknesses in Study Design

This was an observational study and so was inherently subject to bias. We have attempted to minimize bias through study design, although acknowledge that unidentified bias may have influenced the observed associations.

Delay in the diagnosis of perforation, fistula, or stenosis could mean that the observed association between abnormal tests and complication may be due to an undiagnosed complication being present when the tests were performed. This would reduce this study to observe that patients with a complication have abnormal laboratory values. We consider the study design minimized this risk. By analyzing event horizon data, we were able to describe a correlation between data at a time point, and the occurrence of a complication up to 2 years into the future.

Many of our patients suffered a complication at diagnosis or early in their disease course. These patients were excluded from analysis, as we considered that we wanted to observe clinically useful trends in the data. Patients with a complication at diagnosis have a very short time window to take therapy with the hope of preventing any complication. The observations in this study are therefore only applicable to patients who have not yet suffered a complication of their Crohn's disease.

Our hospital provides both secondary and tertiary IBD care to a wide area of south-east Queensland. Given that all patients who are ultimately diagnosed with Crohn's disease as defined by the Lennard–Jones criteria require a specialist referral, consultation, and appropriate investigations, the cohort described in this study is likely to reflect patients seen across the wider population of Queensland, and other jurisdictions of similar ethnicity.

Finally, there was significant exploratory analysis performed to determine the most useful way to assess longitudinal laboratory data. This may have led to over-fitting of the regression model, and overestimation of the utility of laboratory variables to provide an assessment of the future risk of disease complication. The proposed Longitudinal Laboratory score requires validation in an external cohort.

Conclusion

Consistently reduced serum albumin and MCV, and consistently increased CRP and platelet count are associated with future development of complications in patients with Crohn's disease. These laboratory changes are observed up to two years prior to the development of a complication. In addition to recognized markers of poor outcome in Crohn's disease, longitudinal laboratory tests may be assessed as

described in this paper and used to provide a rationale for timely escalation of therapy.

Author Contributions JRI conception and design of study, acquisition of data, analysis and interpretation of data, drafting and revising of article, and final approval of version to be submitted. AL analysis and interpretation of data, revision of article, and final approval of version to be submitted. EF, KH, and LS acquisition of data, revision of article, and final approval of version to be submitted. CM analysis and interpretation of data, revision of article, and final approval of version to be submitted. GRS conception and design of study, acquisition of data, analysis and interpretation of data, revising of article, and final approval of version to be submitted.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. No specific funding was received for this work.

Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest Authors have the following conflicts of interest to declare: GRS has worked on advisory boards for and received consulting fees from Abbvie, Janssen, Ferring, Takeda, and Amgen. JRI has received speaking fees from Janssen. AL, EF, CM, HK, and LS have no conflict of interest to declare.

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