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Crohn's Disease Activity Index and Vienna Classification – Is It Worthwhile to Calculate before Surgery?

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Key Words
Crohn's disease · Crohn's disease activity index · Vienna classification · Surgery

Abstract
Background: Crohn's disease (CD) patients with increased disease activity may reveal an increased risk for perioperative complications. The 'Crohn's disease activity index' (CDAI) and the 'Vienna classification' (VC) were developed for standardized disease activity estimations. The significance of these scores to predict extent, type and early outcome of surgery in CD patients was analyzed. ***Methods:*** In 179 surgically treated CD patients, the CDAI and VC were assessed from a prospective database. Relations of the scores with CD risk factors, type, number, location and complications of surgery were analyzed. ***Results:*** VC behavior and location subtypes were associated with distinct types of surgery (i.e. 'strictureplasty' in 'stricturing disease', 'colon surgery' in 'colon involvement'), but not with surgery type and extent or outcome. Surgery extent (i.e. with 5 vs. 3 'surgical sites' 425 ± 25 vs. 223.3 ± 25) and complications (357.1 ± 36.9 (with) vs. 244.4 ± 13 (without)) were associated with elevated CDAI levels; however, nicotine abuse remained the only significant risk factor for perioperative complications after multiple logistic regression. ***Conclusion:*** The significance of VC or CDAI for predicting the extent of surgery or complications is limited. None of the tested variables except preoperative nicotine abuse influenced the likelihood for perioperative complications.

M. Rentsch and A. Beham contributed equally to this work.

Introduction

More than two thirds of patients with Crohn's disease (CD) require surgery during their lifetime [1]. This situation is made more serious by an increased risk for perioperative complications and re-operations among these patients when compared to a general patient population. For this reason, a preoperative score, which would allow the prediction of the extent of surgery required, the perioperative risk, and the likelihood of disease recurrence would be extremely valuable [2].

Quantification and scoring systems, such as the CD activity index (CDAI) of Best and the Vienna classification (VC) [3–5] (fig. 1) have been introduced. These are intended for the estimation of CD severity in clinical practice, mainly for evaluation of conservative, medical treatment [3, 6–8]. Whereas the VC aims to identify patient subgroups with increased risk factors, such as age at disease onset (A), location (L) and behavior characteristics (B) [5, 9], the CDAI is a calculated index, combining patients vital

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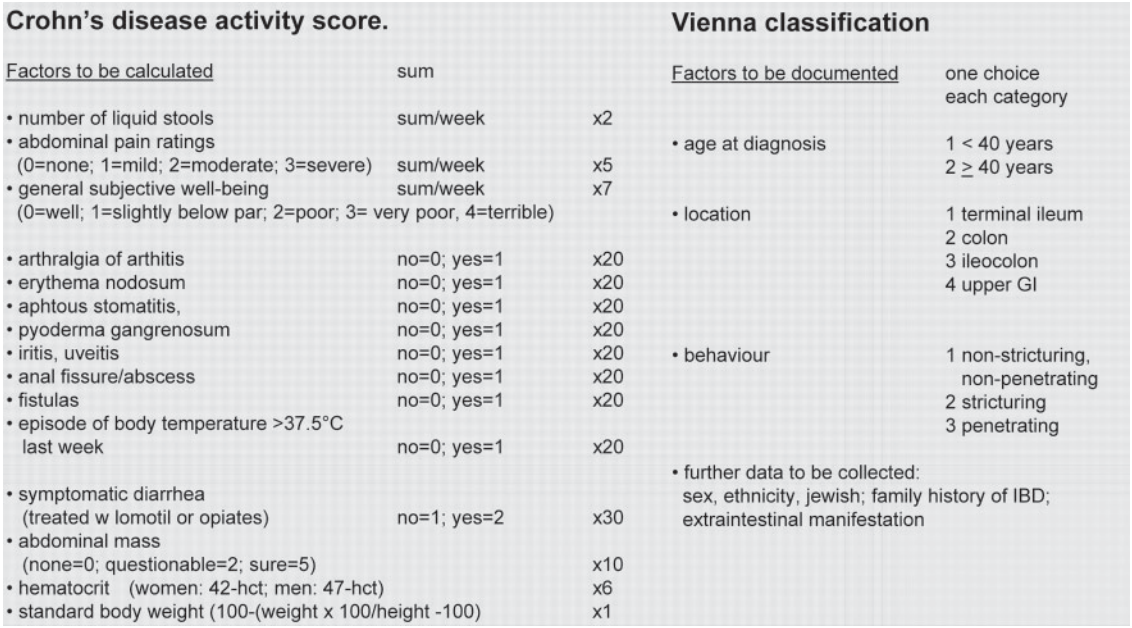

Fig. 1. Overview of both analyzed CD scoring systems. Whereas the CDAI represents clinical and subjective patient data reflecting the disease activity, the VC theoretically would allow conclusions on disease activity by identifying risk groups according to their macroscopic disease appearance (stricturing, perforating, and involvement of the upper GI tract).

parameters (i.e. temperature, body weight, white blood cell count), clinical findings (abscess/fistula, abdominal mass, body weight/temperature) and medical history (extraintestinal symptoms), reflecting general disease activity. It may be misleading to apply these two indices to decision making involving patient's awaiting surgery. In the preoperative environment, clinical parameters may be altered by previous drug treatment [10–12], changes in the disease pattern may occur [9], and diagnostic findings may underestimate the true extent of the disease [13]. Therefore, the aim of the present study is to analyze the accuracy of both scores in predicting the intra-operative extent of the disease, the amount and technique of surgical therapy required, and early postoperative outcome.

Methods

The study population consisted of patients referred for surgical treatment to the Department of surgery at the University of Regensburg and registered in a prospective database. Measures of disease activity and extent, verified pre-operatively and during surgery, were analyzed retrospectively. All surgeries and intraoperative assessments were performed by ten experienced surgeons.

Subgroups were categorized according to age, disease location and behavior (structuring, perforating or the combination of both). General patient characteristics, including family history, general clinical status, medical history (current medication) and preoperative findings, as well as surgical interventions, and immediate surgical outcomes (perioperative complications) were recorded (table 1). Nicotine abuse was defined as any nicotine abuse at the time of surgery.

Diagnostic Techniques

Leading diagnoses were ascertained instantly before surgery with one or a combination of common diagnostic techniques [range 1–8, median 3 diagnostic techniques], depending on the certainty of the results. Definite diagnoses were obtained with ultrasound (57%), endoscopy (56%), intestinal contrast X-ray (50%), computed tomography (33%), abdominal X-ray examination (20%), barium enema (10.6%), and magnetic resonance imaging (9%).

Analyses were focused on the determination of the CDAI and the VC. We did depart from the original VC in one instance: patients were classified regardless of *first* or *recurrent* surgery for CD at the time of admission in our unit. Patients without surgical treatment and patients with non-Crohn-related diseases undergoing surgery were excluded from statistical analyses.

Only patients with complete prospectively determined CDAI were considered for analyses. Since the prospective CDAI documentation was incomplete in 50 patients (i.e. patients with exclusively perianal disease), data on VC (174 patients), and CDAI (124 patients) were separately calculated.

Table 1. Registered data within the patient population

Patient history and diagnostic procedures	Preoperative assessment	Intra-/postoperative assessment
General data Age Onset of disease Gender	CDAI	emergency surgery elective surgery repeat surgery resection/strictureplasty
Disease-specific risk factors Nicotine abuse NSAID Oral contraceptives Mycobacteria tuberculosis Immunization to measles	VC	surgery location stomach duodenum jejunum ileum ileocecum ascendending colon transverse colon descending colon rectosigmoid colon
Diagnostic procedures Ultrasound X-ray abdomen Small bowel enema Colonography CT scan MRI Biopsy	disease localizaton esophageus/stomach duodenum/jejunum ileum ileocecum ascending colon transverse colon descending colon rectosigmoid colon perianal disease	preexisting anastomosis fistula drainage seton placement advancement flap abscess drainage
	pre-existing complications stenosis ileus abscess (intra-/extra-abdominal) fistulae entero-enteral entero-cutaneous entero-vesical entero-genital other hemorrhage malignancy	perioperative complications anastomotic leakage peritonitis sepsis wound infection/ dehiscence infection (other) hemorrhage bowel obstruction early recurrence abscess fistula thrombembolic event death

Note that 170 patients have been analyzed after exclusion of surgical procedures without relation to CD and in 124 patients CDAI data were obtained for statistical evaluation.

Statistical Analyses

Descriptive and univariate analyses were performed to summarize the data. Categorical variables were compared between subgroups with the χ^2 or Fisher's exact test. Correlations among variables were assessed by calculation of the Spearman coefficient. CDAI values were tested for presence of normal distribution and compared with the Student t test or one-way ANOVA.

In a second step, variables were re-evaluated by general multifactorial analysis of variances and stepwise logistic regression. $p < 0.05$ was considered significant. Analyses were carried out with SPSS statistical software, version 13.0 (SPSS® Inc., Chicago, Ill., USA).

Results

General Patient Characteristics

One hundred and ninety-eight patients with the diagnosis of CD were treated in our department between June 1992 and July 2000. The demographic data are summarized in table 2. 39% of the patients had surgery elsewhere previous to admission, 17% had undergone intestinal resection. No patients were submitted for secondary surgical treatment of postoperative complications.

Table 2. General patient characteristics

Patients admitted, total		198
Surgery/medical management		177 (88.9%)/21 (11.1%)
Gender, men:women		80:97
Age at surgery, years	median, min/max	M: 32,5; 14/61 W: 34,0; 16/70
Age at first diagnosis, years	median, min/max	M: 25,0; 11/60 W: 25,0; 8/57
Repeat surgery		69 (39.7%)
Emergency		11 (6.4%)
Medication before surgery, patients	steroids	103 (59.2%)
	azathioprin	17 (9.8%)
	5-ASA	77 (44.3%)
	anti-TNF	0
	ciprofloxacin	11 (6.3%)
	metronidazole	17 (9.8%)
	combined drug therapy	79 (45.4%)

Surgical procedures are listed in detail in table 3. In 5 patients, laparotomy was indicated due to causes unrelated to CD. Specifically, indications were (a) mechanical bowel obstruction after prior surgery (3 patients); (b) cholecystitis (1 patient), and (c) an incarcerated incisional hernia (1 patient). These patients were excluded from further analysis. 65 patients presented as emergencies (GI bleeding: 3 patients, Crohn-related mechanical obstruction: 12 patients, intra- or extra-abdominal abscesses: 22 and 28 patients, respectively), 11 of whom required acute surgical therapy. Resections were performed in 138 patients, vs. 15 patients with strictureplasties (two strictureplasties in 2 patients, five in 1 patient; table 3).

Table 3. Characterization of surgical procedures and surgical site (multiplicity of sites included)

	Patients/percentages
Emergency surgery	11/6.4
Elective surgery	160/93.6
Repeat surgery	67/39
Resection:strictureplasty	151/82.5:15/8.8
Stoma (ileostoma)	8/4.7
Fistula drainage	13/7.6
Seton placement	13/7.6
Advancement flap	2/1.2
Abscess drainage	22/12.9
Surgical site	
Stomach	0
Duodenum	2/1.2
Jejunum/ileum	23/13.5
Ileocecum	91/53.2
Ascendending colon	19/11.1
Transverse colon	17/9.9
Descending colon	9/5.3
Recto-sigmoid	27/15.8
Preexisting anastomosis	13/7.6

Medical Therapy

Medical therapy prior to surgery included corticosteroids in 59.2% of the patients, 5-ASA in 44.3%, azathioprine in 9.8%. No patient received 6-mercaptopurine or anti-TNF-α treatment. 6.3% were treated with ciprofloxacin and 9.8% with metronidazole. There were no differences in the CDAI scores of patient groups treated with different medical therapies.

Of note, corticosteroid medication was used in 77% of the patients with disease location proximal to the ileum (vs. 55% under corticosteroid therapy overall, $p = 0.03$, χ^2) and in 71.4% of the patients with stricturing disease behavior (vs. 53.4% patients without strictures, $p = 0.02$; χ^2 and logistic regression). In contrast, patients without CD proximal to the ileum more frequently received azathioprine (22 vs. 7.4% overall, $p = 0.018$, χ^2). Ciprofloxacin (9.5%) and metronidazole (14%) were predominately used in patients with intra-abdominal abscess formation ($p < 0.006$; χ^2 and logistic regression).

Table 4. Relation between preoperative and intraoperative findings according to the VC as assessed by χ^2 test and Spearman correlation

Vienna classification factor		Presence		Surgical intervention yes/no		χ^2	Spearman correlation
Location	1	yes	138	yes	117	<0.0001	0.491
		no	36	no	57		
	2	yes	98	yes	45	<0.0001	0.416
		no	76	no	129		
	3	yes	97	yes	127	0.206	–0.096
		no	77	no	47		
	4	yes	27	yes	27	<0.0001	0.431
		no	147	no	148		
Behavior	1	yes	38	yes	100[a]	0.005	0.231
		no	136	no	74		
	2	yes	138	yes	138	0.002	0.277
		no	36	no	36		
	3	yes	106	yes	67[b]	<0.0001	0.620
		no	68	no	107		
	X	yes	137	yes	67[b]	<0.0001	0.529
		no	37	no	107		

[a] Surgical interventions without fistula excision or abscess drainage.
[b] Exclusively surgical interventions with fistula excision or abscess drainage.
X = Combined structuring and perforating disease behaviour, not classifiable in VC.

Age/Gender

The median age of our study group (95 women and 79 men) at the time of surgery was 34.0 years (17–62) and 31.5 years (17–58), respectively. 27.6% were older than 40 years and 9.2% younger than 20 years. At primary diagnosis, 14.9% of the patients were older than 40 years. CDAI levels were equal in both age groups (see table 5). In addition, no significant relation between age (</≥40 years, classification parameter A) and preoperative disease location (classification parameter L) was detectable. Nevertheless, higher age was associated with an elevated ratio of patients with stricturing disease (50 vs. 25.4%, p = 0.002; Spearman correlation 0.235). Gender had no impact on the investigated parameters.

Location of Disease

Location 1 (ileum plus spillover to cecum) was diagnosed in the majority of the patients (n = 139). This number includes patients who had a previous ileocecal resection. All 97 patients, who presented with colon involvement, had a diseased terminal ileum (L3). CD spreading proximal to the ileum was detectable in 27 patients. In all regions, the primarily diagnosed disease location revealed a significant relation with the surgically treated locations ($p < 0.0001$; table 4). This was reconfirmed by stepwise logistic regression. However, the Spearman coefficients revealed weak positive correlations between pre- and intraoperatively determined locations (table 4).

Stratification of the patients into the four VC disease location subgroups revealed no differences in CDAI. However, multiplicity of disease locations was accompanied by a high CDAI variation. CDAI levels ranged between 223.3 ± 25.4 and 425.0 ± 24.8 for subgroups with 1–5 or more sites of surgery and a significantly higher CDAI was associated with 5 vs. 3 locations ($p = 0.07$, χ^2). Since certain patient subgroups obviously required a different intensity of medical treatment, we hypothesized that the CDAI may vary in VC subgroups. However, no differences in CDAI values were observed in the VC location subgroups.

Behavior of Disease

56 patients presented with stricturing vs. 105 patients with penetrating disease behavior. 37 patients showed neither strictures nor penetrations. However, 24 patients had combinations of strictures and penetrations, and were, therefore, not represented by the VC. As expected, significantly ($p < 0.001$) more strictureplasties were performed in patients with stricturing disease behavior and with involvement of the upper gastrointestinal tract (vs. other bowel regions) (table 4). Interestingly, stratification according to behavior factors (3) revealed an elevated CDAI (463 ± 21, table 5) in patients with the simultane-

Table 5. CDAI variations in dependence of clinical situation

Clinical situation	Status		CDAI	p value
Age <40 years	yes		242 ± 14	0.29
	no		279 ± 28	
VC location 4	yes		263 ± 41	0.91
	no		249 ± 13	
VC behavior 3	yes		256 ± 18	0.79
	no		243 ± 17	
Ileus	yes		271 ± 51	0.67
	no		249 ± 13	
Presence of fistulas	yes		255 ± 19	0.89
	no		246 ± 16	
Multiple independent fistula systems	yes	1 system	253 ± 21	
		2 systems	227 ± 52	
		3 or more s.	463 ± 21	0.128
	no		246 ± 16	
Extraintestinal manifestation	yes	1 location	255 ± 29	
		2 locations	393 ± 110	0.293
	no		244 ± 13	
Surgery upper GI tract	yes		280 ± 35	0.32
	no		245 ± 13	
Surgery colon	yes	1 site	277 ± 33	0.125
		2	345 ± 50	
		3 or more	369 ± 75	
	no		229 ± 14	
Surgery multiple sites	yes	1	246 ± 18	
		2	261 ± 30	0.07 (5 vs. 1 site) and 0.04 (5 vs. 3 sites)
		3	223 ± 25	
		4	241 ± 51	
		5 or more	425 ± 25	
	no		212 (2 pat.)	
Emergency	yes		207 ± 43	0.431
	no		253 ± 13	

CDAI given as mean ± SEM, p values calculated by use of Student's t test or one-way ANOVA after rank transformation of non-normally distributed CDAI values. Note that none of the factors had any impact on short-term postoperative outcome.

ous presence of three or more different fistulae (i.e. enterocutaneous plus enteroenteral plus enterovaginal), however without significance in comparison to patients with less than three fistulae.

Extent of Surgery

101 patients (58%) revealed a multifocal disease pattern (2–6 locations) that could not be represented by a precise VC categorization.

When the CDAI was analyzed according to the extent of surgical therapy, only the necessity of surgery at more five or more vs. three locations (resection and strictureplasty) was associated with a markedly higher score (table 5).

Perioperative Complications

No lethal complications were noted. Perioperative complications (table 6) occurred in 10.5% of the patients, with 4.1% displaying anastomotic leakage. Three patients

Table 6. Perioperative complications

Complication	Number/ percent
Anastomotic leakage	7/4.1
Peritonitis	3/1.8
Sepsis	0/ND
Wound infection/dehiscence	2/1.2
Infection (other)	7/4.0
Hemorrhage	0/ND
Bowel obstruction	0/ND
Early recurrence	
Abscess	
Fistula	2/1.2
Thrombembolic event	1/0.6
Death	0/ND
Total	22/13.2

(1.8%) developed a generalized peritonitis. Early fistula recurrence appeared in 2 (1.2%) and wound dehiscence in 4 (2.4%) patients. Half of the patients with complications presented with two or more complications at once.

The average CDAI of patients with complications (overall 340.9 ± 27.9) and with complications requiring revision surgery (353.2 ± 34.9) was elevated in comparison to patients without complications (240.2 ± 13.6, $p < 0.05$). Analogously, patients with postoperative anastomotic leakage revealed significantly elevated CDAI levels (357.1 ± 36.9 vs. 244.4 ± 13.2, $p < 0.05$). However, multivariate calculations abolished the significant differences in CDAI in patients with or without postoperative complications.

χ^2 calculations showed significant ($p < 0.05$) associations of VC behavior types 1, 3, and combined stricturing plus perforating disease with later perioperative complications. Moreover, corticoid medication ($p = 0.025$), resection surgery performed at the ileocecal region ($p = 0.02$), combined disease pattern (0.24) and nicotine abuse ($p = 0.003$) were significantly associated with anastomotic leakage. After stepwise logistic regression, however, nicotine abuse remained the only significant variable increasing the risk for postoperative anastomotic leakage ($p = 0.037$) and perioperative complications in general ($p = 0.004$).

Discussion

In the present study we evaluated, the usefulness of the 'VC' and the 'CDAI', when applied preoperatively to CD patients, in predicting the extent and type of surgery required and the risk of early surgical complications. Both instruments have been predominately applied to patients who are treated medically, but not surgically [3–5].

In general, quantification of CD activity may be problematic, due to the frequently complex disease appearance. Any information about the disease aggression would be useful for a multimodal treatment concept including medical pretreatment, surgical strategy and postoperative maintenance therapy, balancing quality of life [14], requirement of side effect charged drug therapy vs. the probability for surgery [10, 15, 16], including the risk of recurrence and re-operation [10, 17]. Precise information on the surgery-associated risk is of fundamental importance to the patient [2].

The examined classifications are based on different types of Crohn's-associated data, and are therefore not comparable. Whereas the CDAI includes numerous subjective and clinical data (vital parameters, body weight, abscess/intra-abdominal mass), the VC focuses on morphological characteristics of the disease. Therefore, we presumed that by quantificating the CDAI in certain VC subgroups we would be most likely to identify patient subgroups with increased CDAI, who were particularly prone to increased disease extent and perioperative risk.

Preoperative medical therapy, i.e. corticosteroids, may decrease disease activity and subjective complaints, and therefore, interfere with the reliability of the VC and the CDAI. Bowel strictures and inflammatory changes may rapidly resolve [12, 18], which may change the phenotypic disease appearance [9]. Since nearly 60% of our patients received steroids preoperatively, we cannot exclude that drug treatment interfered our observations. However, the diagnostic procedures in our study immediately preceded surgery, and the majority of patients with different intra- vs. preoperative disease extent and location consistently revealed more diseased locations intraoperatively. Furthermore, since corticosteroid therapy had no effect on the CDAI in our patients, it is unlikely that corticosteroids acted as disease-resolving agent and significantly affected our results. The evidently low number of patients on azathioprine at the time of surgery in our study may be explained by our center policy with restrictive use of azathioprine (and 6-mercaptopurine) and complete avoidance of anti-TNF treatment for remission maintenance therapy [19].

Younger, as well as older, age at first diagnosis has been identified as risk factor for CD recurrence, reflecting general disease activity [17]. However, numerous large studies failed to show any influence of age on disease recurrence [16, 20, 21]. In our study, as well, we found no as-

sociations with age and the other VC classification factors, or with CDAI levels. Reducing the cut-off value of the VC from 40 to 20 years of age, as proposed earlier [17], had no influence on the findings.

CD activity may be determined by disease location, multiplicity of locations, disease behavior (perforating/fistulizing), and inflammatory activity [16, 22–26]. Both, the VC and CDAI, would thus theoretically allow a prediction of intraoperative findings. However, our analyses revealed no associations between the VC or the CDAI and intraoperative findings. Although a larger number of locations requiring surgical therapy (5 vs. 3), was reflected by an elevation of the CDAI, this trend was not linear, since no progressive increase in the CDAI was notable from 1 to 5 locations. Furthermore, patients displaying complex disease patterns with more than two independent fistulae revealed higher CDAI levels than those with single fistula. However, an aggressive disease type might be presumed in patients with CD manifestation in five different locations or with complex fistula combinations without the use of a special classification.

Although the analyses of VC categories revealed significant associations between pre- and intraoperative locations, correlations were weak, as indicated by a low Spearman coefficient. Moreover, these associations could have been expected without special classification. In addition, a clear allocation into the subgroups of the VC is not possible in patients with combined fistulizing and stricturing disease, which was present in the vast majority (78%) of patients.

Furthermore, the extent of CD surgery may be anticipated by clinical data included in the CDAI, such as WBC count and fever, abdominal mass, and the presence of abscesses/fistulae. We therefore evaluated the CDAI in patient subgroups, reflecting risk constellations for increased CD aggression [27, 28]. Although elevated CDAI scores (>200) were recognizable in the majority of the subgroups, no disease 'subtype' except 'multiple independent fistulae' was associated with significantly elevated CDAI values. This finding is not surprising, since 'subjective well-being' is considerably influenced by the presence of fistulas [14]. Both 'subjective well-being' and the presence of abscess/fistulae are heavily weighted factors (×7 and ×20; fig. 1) within the CDAI.

Surgical therapy prior to the VC and CDAI staging may have biased our results, since the specificity of diagnostic techniques preoperatively may be altered [13], and anastomoses may mature into restenoses. However, comparison of the CDAI's of patients with or without preceding surgery showed no statistical difference.

As mentioned previously, the number of strictures is often underestimated by radiographic as compared to surgical findings in CD patients [13]. Peristalsis and widening as well as distension or adhesions of the intestinal tract may mislead the examiner, who may furthermore focus on the most dominant lesion, causing him to direct less attention towards other findings [13]. Although in our study diagnoses relied on combined techniques including endoscopy, radiographic examinations, CT, MRT and ultrasound, we frequently (54.4%) found that while only a single site was diagnosed preoperatively, more sites actually required surgical therapy.

Since we had found that pre-operative classifications did not predict intraoperative disease extent in CD patients, we sought to determine whether preoperative findings could predict early postoperative complications [28–30]. With univariate comparisons, we confirmed that the following established risk factors: complex disease pattern, ileocecal resection, corticoid medication and nicotine abuse were significantly related to postoperative complications. The low overall number of complications in our study, however, may lead to underrating of relations to certain VC subfactors. Slightly elevated CDAI levels were observed along with postoperative complications, infectious complications, anastomotic leakage and pre-existing bowel obstruction. This is in agreement with the general concept that an exaggerated disease accompanies an increased perioperative risk [27]. In multivariate analyses, nicotine abuse remained the only predictive factor associated with an elevated risk for perioperative complications and anastomotic leakage, which is in accordance with the previously observed heightened risk of disease recurrence in smokers [31].

Together, the VC and the CDAI may be useful for monitoring disease activity under conservative therapy. However, they are less useful for surgical therapy planning and perioperative risk prediction. Nicotine abuse, which emerged as the most relevant risk factor for perioperative complications, for instance, does not contribute to any classification. Indications for surgery should depend on disease extent and activity, on refractoriness to medical therapy, and on pre-existing complications, such as bowel obstruction, perforation, hemorrhage, abscess formation, toxic megacolon and endoscopic proof of high-grade dysplasia [10, 14, 16, 32].

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