

# The disease severity index for inflammatory bowel disease is associated with psychological symptoms and quality of life, and predicts a more complicated disease course

Akhilesh Swaminathan<sup>1,2</sup>  | Dali Fan<sup>2</sup> | Grace M. Borichevsky<sup>1</sup> | Thomas C. Mules<sup>2</sup>  | Esther Hirschfeld<sup>1</sup> | Chris M. Frampton<sup>1</sup> | Andrew S. Day<sup>3</sup>  | Corey A. Siegel<sup>4</sup> | Richard B. Geary<sup>1,2</sup> 

<sup>1</sup>Department of Medicine, University of Otago, Christchurch, New Zealand

<sup>2</sup>Department of Gastroenterology, Christchurch hospital, Christchurch, New Zealand

<sup>3</sup>Department of Paediatrics, University of Otago, Christchurch, New Zealand

<sup>4</sup>Inflammatory Bowel Disease Centre, Section of Gastroenterology and Hepatology, Dartmouth Hitchcock Medical Centre, Lebanon, New Hampshire, USA

## Correspondence

Dr. Akhilesh Swaminathan, Department of Medicine, University of Otago, Christchurch, 2 Riccarton Avenue, Christchurch, New Zealand.

Email: [swaak389@student.otago.ac.nz](mailto:swaak389@student.otago.ac.nz)

## Funding information

New Zealand Society of Gastroenterology; Royal Australasian College of Physicians

## Summary

**Background:** The Disease Severity Index (DSI) is a novel tool to predict disease severity in inflammatory bowel disease (IBD). However, its ability to predict disease complications and the presence of psychosocial comorbidity is unclear.

**Aims:** To assess prospectively associations between the DSI and psychological symptoms, quality-of-life (QoL) and disease outcomes in an IBD cohort.

**Methods:** Patients with IBD undergoing ileocolonoscopy were followed prospectively for 12 months. DSI, psychological symptoms (perceived stress (PSS-10), depression (PHQ-9), anxiety (GAD-7)) and QoL (IBDQ-32) scores were assessed at baseline. Logistic regression identified variables predicting a complicated IBD course at 12 months (composite outcome of need for escalation of biological/immunomodulator for disease relapse, recurrent corticosteroid use, IBD-related hospitalisation and surgery). Receiver operating characteristics (ROC) analysis identified optimal DSI thresholds predicting a complicated disease course and multivariable logistic regression assessed the risk of reaching this outcome.

**Results:** One hundred and seventy-two patients were recruited (100 Crohn's disease, 91 female). Median DSI was 21 (IQR 11–32) and 97 patients had endoscopically active disease at baseline. The DSI was significantly higher in patients with symptoms of moderate–severe stress (PSS-10 > 14,  $p < 0.01$ ), depression (PHQ-9  $\geq 10$ ,  $p < 0.01$ ), anxiety (GAD-7  $\geq 10$ ,  $p < 0.05$ ) and impaired quality-of-life (IBDQ-32 < 168,  $p < 0.01$ ). Only the baseline DSI (OR 1.05,  $p < 0.01$ ) and endoscopically active disease (OR 6.12,

**Abbreviations:** DSI, Disease Severity Index; IBD, inflammatory bowel disease; QoL, quality-of-life; PSS-10, perceived stress scale; PHQ-9, patient health questionnaire-9; GAD-7, generalised anxiety disorder 7-item scale; IBDQ-32, inflammatory bowel diseases questionnaire; ROC, receiver operating characteristics; IQR, interquartile range; OR, odds ratio; CD, Crohn's disease; UC, ulcerative colitis; HRQoL, health-related quality-of-life; NIDA-IBD, new indicators of disease activity in inflammatory bowel disease; BMI, body mass index; CT, computed tomography; MRI, magnetic resonance imaging; CRP, C-reactive protein; fCal, faecal calprotectin; SES-CD, simple endoscopic score for Crohn's disease; UCEIS, ulcerative colitis endoscopic index of severity; HBI, Harvey-Bradshaw index; CDAI, Crohn's disease activity index; SCCAI, simple clinical colitis activity index; AUROC, area under the receiver operating characteristic curve.

The Handling Editor for this article was Dr Cynthia Seow, and it was accepted for publication after full peer-review.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Alimentary Pharmacology & Therapeutics* published by John Wiley & Sons Ltd.

$p < 0.01$ ) were associated with a complicated IBD course. A DSI  $> 23$  was strongly predictive of a complicated IBD course (OR 8.31,  $p < 0.001$ ).

**Conclusions:** The DSI is associated with psychological distress, impaired QoL and predicts a more complicated disease course in patients with IBD.

## 1 | INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic, progressive intestinal disorders for which there is no cure.<sup>1</sup> Individuals with IBD follow a heterogeneous disease course. Whilst some with this disease have an indolent course of illness, others experience significant morbidity including the need for IBD-related hospitalisation and surgery.<sup>2,3</sup> Patients with IBD also experience higher rates of stress, anxiety and depression compared with those without IBD.<sup>4-7</sup> Thus, the overall burden of IBD is vast and has significant impacts on health-related quality of life (HRQoL).<sup>8,9</sup>

Predicting the overall severity of illness in IBD is a challenging concept for both clinicians and patients. A true measure of IBD severity needs to encompass indicators of current disease activity, markers of poor long-term outcomes such as previous medication failures and IBD-related surgery, and the impact of the disease on the patient.<sup>10</sup> The disease severity index (DSI) was developed using conjoint analysis methodology, based on expert opinions of IBD clinicians (Table S1).<sup>11</sup> The goal of this tool is to incorporate measures of IBD activity (biomarkers and endoscopic/radiological indices), clinical prognostic markers, a history of IBD-related complications and patient-reported outcomes to estimate overall disease severity. This instrument aims to stratify individuals from low to a high disease burden to better characterise overall disease severity as opposed to disease activity at a moment in time.

Given the importance of psychosocial health for patients with IBD it is important that prognostic scores can identify patients at risk for reduced/altered mental health. This prospective study investigated the associations of the DSI with symptoms of psychological illness and HRQoL. This study also aimed to assess the use of the DSI in predicting long-term IBD-related outcomes.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient selection

Patients with IBD undergoing ileocolonoscopy within the Canterbury or West Coast regions of New Zealand were prospectively recruited into the new indicators of disease activity in IBD (NIDA-IBD) study between April 2019 and September 2020.<sup>12</sup> Eligible study participants were aged 16 years or older and had an established diagnosis of CD or UC.

Recruited study participants completed IBD-related symptoms, psychological symptom and HRQoL questionnaires.<sup>13-16</sup> Stool samples were collected for faecal biomarker analyses in the week prior to ileocolonoscopy. Demographics, clinical history and venous blood

samples for biomarker analyses were collected during baseline interviews. The DSI was calculated for each participant at the time of ileocolonoscopy. After 6 months, repeat symptom and HRQoL questionnaires were completed. Questionnaires were completed using the Research Electronic Data Capture software (REDCap, Vanderbilt, USA).<sup>17</sup> This study was conducted in accordance with the World Medical Assembly Declaration of Helsinki and was approved by the New Zealand Health and Disability Ethics Committee (18/NTA/197).

### 2.2 | Demographic data, disease activity and disease severity index assessment

Demographics and clinic data collected at recruitment included age, sex, ethnicity, body mass index (BMI), comorbid illnesses, medication use, year of IBD diagnosis, disease type (CD or UC) and phenotype according to Montreal classification,<sup>18</sup> current and previous IBD medications, IBD-related hospitalisations in the last year, previous strictures noted on cross-sectional imaging (computed tomography, CT; or magnetic resonance imaging, MRI of the small bowel) in the last year, and previous bowel resections. The faecal and blood biomarkers that were analysed included full blood count, albumin, C-reactive protein (CRP) and faecal calprotectin (fCal).

Baseline endoscopic disease activity was assessed by the Gastroenterologist performing the patient's ileocolonoscopy trained in using the Simple Endoscopic Score for Crohn's Disease (SES-CD) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) for patients with CD and UC, respectively.<sup>19,20</sup> For the SES-CD, scores of 0-2 were used for disease remission, 3-6 for mild, 7-15 for moderate and  $\geq 16$  for severe disease activity.<sup>21</sup> For the UCEIS, scores of 0-1 were used for disease remission, 2-4 for mild, 5-6 for moderate and 7-8 for severe disease activity.<sup>22</sup>

For CD, the Harvey-Bradshaw Index (HBI) and Crohn's disease activity index (CDAI) were used to assess patient symptoms.<sup>23,24</sup> An HBI  $> 4$  and CDAI  $> 150$  signified clinical activity.<sup>25</sup> For UC, the simple clinical colitis activity index (SCCAI) was used, with a score  $> 5$  signifying clinical activity.<sup>26</sup>

DSI scores were calculated based on the established index (Table S1).<sup>11</sup> The highest possible total score for either CD or UC was 100.

### 2.3 | Assessment of psychological symptoms and HRQoL

The Perceived Stress Scale (PSS-10) was used to assess for stress and a PSS-10  $\geq 14$  was indicative of moderate to high-stress

symptoms.<sup>13</sup> Symptoms of depression and anxiety were assessed using the Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7) questionnaires, respectively.<sup>14,15</sup> A PHQ-9  $\geq 10$  and GAD-7  $\geq 10$  were indicative of severe symptoms of depression and anxiety, respectively. HRQoL was assessed using the Inflammatory Bowel Disease Questionnaire-32 (IBQ-32), with scores  $< 169$  indicative of a poor QoL.<sup>16,27-29</sup>

## 2.4 | Assessment of IBD-related outcomes

All study participants were followed prospectively for 12 months to assess for disease complications. A composite outcome of the need for prospective escalation of biological agent/immunomodulator due to clinical disease relapse, recurrent corticosteroid use, IBD-related hospitalisation and surgery over the 12 months following recruitment defined a complicated disease course.

## 2.5 | Statistical analysis

### 2.5.1 | Associations of DSI with psychological symptoms, HRQoL and disease activity

Descriptive statistics were used to assess patient demographics, disease characteristics, disease and symptom activity, and disease-related outcome measures. Only participants who had completed all study questionnaires were analysed. Spearman's rank correlation coefficient was used to determine correlations between the DSI and symptom scores (HBI and SCCAI), endoscopic disease activity (SES-CD and UCEIS), biomarkers (fCal), psychological symptoms (PSS-10, PHQ-9 and GAD-7) and HRQoL (IBDQ-32 at baseline and at 6 months). Subgroup analyses were performed within groups based on the IBD sub-type (CD or UC). Differences in DSI between individuals with and without symptoms of significant stress, depression, anxiety, impaired HRQoL and endoscopically active disease were compared using the Mann-Whitney *U* test. Receiver operating characteristics (ROC) curves assessed the precision of the DSI in predicting significant symptoms of stress, depression, anxiety and impaired HRQoL at baseline.

### 2.5.2 | Assessing the utility of the DSI in predicting a complicated IBD course

Univariable logistic regression was used to identify baseline variables that were associated with a complicated IBD course. Variables reaching a pre-determined significance of  $p < 0.01$  were incorporated into a multivariable logistic regression model to predict this outcome. ROC analyses determined the optimum DSI value that predicted a complicated IBD course at 12 months. A final multivariable logistic regression model to predict a complicated IBD course was developed using both a continuous DSI score and the

optimum DSI threshold coded as a categorical variable. Sub-group analyses using this final prediction model were subsequently performed in patients with CD and UC separately, and in a subset of patients with baseline inactive or mildly active disease (SES-CD  $< 7$  or UCEIS  $< 5$ ).

Statistical analyses were performed using the SPSS 28 statistical package (IBM Corp., Armonk, NY). Graphs from this data were created using the GraphPad Prism 9 Package (GraphPad Software, Inc., San Diego, CA).

## 3 | RESULTS

### 3.1 | Description of study participants

A total of 172 participants were included in this analysis (CD,  $n = 100$ ; UC,  $n = 72$ ). Further details regarding the characteristics of study participants are included in Table 1 and Table S2. The indication for ileocolonoscopy was recorded as either surveillance (CD,  $n = 57$ ; UC,  $n = 41$ ) or to assess/ascertain current disease activity (CD,  $n = 43$ ; UC,  $n = 31$ ).

### 3.2 | Correlations of DSI with symptoms, HRQoL and faecal biomarkers

The DSI score was significantly correlated with baseline IBD activity including symptoms (HBI,  $r_s = 0.43$ ,  $p < 0.01$ ; CDAI,  $r_s = 0.59$ ,  $p < 0.01$ ; SCCAI,  $r_s = 0.75$ ,  $p < 0.01$ ), endoscopic disease activity (SES-CD,  $r_s = 0.59$ ,  $p < 0.01$ ; UCEIS,  $r_s = 0.73$ ,  $p < 0.01$ ) and fCal (all IBD,  $r_s = 0.47$ ,  $p < 0.01$ ; CD,  $r_s = 0.33$ ,  $p < 0.05$ ; UC,  $r_s = 0.65$ ,  $p < 0.01$ ). The DSI positively correlated (Table 2) with symptoms of stress (PSS-10,  $r_s = 0.21$ ,  $p = 0.01$ ;  $n = 148$ ), depression (PHQ-9,  $r_s = 0.31$ ,  $p < 0.01$ ;  $n = 156$ ) and anxiety (GAD-7,  $r_s = 0.17$ ,  $p = 0.03$ ;  $n = 157$ ) and inversely correlated with IBDQ-32 at baseline ( $r_s = -0.57$ ,  $p < 0.01$ ;  $n = 172$ ) and at 6 months of follow-up ( $r_s = -0.37$ ,  $p < 0.05$ ;  $n = 45$ ).

### 3.3 | Associations of DSI with significant symptoms of stress, depression, anxiety, impaired HRQoL and endoscopic disease activity

The DSI was elevated in individuals with severe depressive (median DSI 27 (IQR, 21–42) vs 19 (IQR, 7–29);  $U = 1652$ ,  $p < 0.01$ ) and anxiety (median DSI 27 (IQR, 19–39) vs 21 (IQR, 8–32);  $U = 1606$ ,  $p = 0.04$ ) symptoms, with moderate or severe stress symptoms (median DSI 26 (IQR, 14–40) vs 18 (IQR, 6–27);  $U = 1914$ ,  $p < 0.01$ ), and in those with a poor HRQoL (median DSI 31 (IQR, 21–46) vs 13 (IQR, 6–22),  $U = 1311$ ,  $p < 0.01$ ) at baseline (Figure 1). The baseline DSI predicted for the presence of moderate-to-high stress (AUROC<sub>PSS-10</sub> = 0.64,  $p < 0.01$ ), severe depressive (AUROC<sub>PHQ-9</sub> = 0.68,  $p < 0.01$ ), and severe anxiety (AUROC<sub>GAD-7</sub> = 0.62,  $p = 0.04$ ) symptoms, and poor HRQoL (AUROC<sub>IBDQ-32</sub> = 0.82,  $p < 0.01$ ) at baseline.

TABLE 1 Description of demographics, clinical phenotype, symptoms and IBD-related complications in the NIDA-IBD cohort

	All IBD (n = 172)	CD (n = 100)	UC (n = 72)
Mean Age (SD, years)	47.0 (15)	45.2 (14)	49.5 (14)
Female participants (%)	91 (52.9)	53 (53.0)	38 (52.8)
Median time since IBD diagnosis (range, years)	13.0 (5.0–22.0)	13.0 (6.0–21.0)	11.5 (4.0–23.5)
NZ European ethnicity (%)	169 (98.3)	100 (100)	69 (95.8)
Montreal classification of IBD(%)			
A1		7 (7)	0 (0)
A2		75 (75)	19 (26)
A3		18 (18)	53 (74)
L1		18 (18)	
L2		21 (21)	
L3		61 (61)	
B1		60 (60)	
B2		20 (20)	
B3		20 (20)	
Perianal disease		17 (17)	
E1			6 (8.3)
E2			33 (45.8)
E3			33 (45.8)
Endoscopically active IBD (SES-CD >2, UCEIS ≥2, %)	97 (56.4)	62 (62.0)	35 (48.6)
Endoscopically inactive/mildly active IBD (SES-CD <7, UCEIS <5, %)	131 (76.2)	72 (72.0)	59 (81.9)
Endoscopically moderate/severely active IBD (SES-CD ≥7, UCEIS ≥5, %)	41 (23.8)	28 (28.0)	13 (18.1)
Active symptoms at baseline (HBI >4, CDAI >150, SCCAI >5; %)	97 (56.4)	61 (61.0)	36 (20.9)
Median DSI (IQR)	21.0 (11.0–32.0)	20.5 (10.0–27.0)	24.5 (12.3–48.5)
Median IBDQ-32 (IQR)	169.0 (134.5–196.0)	164.0 (132.5–194.3)	177.0 (138.3–200.8)
Median PSS-10 (IQR) <sup>a</sup>	15.5 (10.0–20.0)	17.0 (10.0–20.5)	14.0 (10.0–19.0)
Median PHQ-9 (IQR) <sup>b</sup>	6.0 (2.0–11.0)	7.0 (2.0–12.0)	4.0 (1.0–9.3)
Median GAD-7 (IQR) <sup>c</sup>	4.0 (1.0–7.0)	4.0 (1.0–8.0)	3.5 (0.0–7.0)
Current use of biological therapies (%)	37 (21.5)	27 (27.0)	10 (13.9)
Clinical relapse requiring biological/immunomodulator escalation at 12 months (%)	37 (21.5)	20 (20.0)	17 (23.6)
Recurrent corticosteroid use at 12 months (%)	10 (5.8)	3 (3.0)	7 (9.7)
IBD related hospitalisation at 12 months (%)	16 (9.3)	10 (10.0)	6 (8.3)
IBD related surgery at 12 months (%)	10 (5.8)	7 (7.0)	3 (4.2)
Complicated IBD course 12 months (%)	49 (28.5)	29 (29.0)	20 (27.8)

Abbreviations: CD, Crohn's disease; CDAI, Crohn's disease activity index; DSI, Disease severity index; GAD-7, generalised anxiety disorder 7-item scale; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; IBDQ-32, inflammatory bowel diseases questionnaire; IQR, interquartile range; PHQ-9, patient health questionnaire 9; PSS-10, perceived stress scale; SCCAI, simple clinical colitis activity index; SD, standard deviation; SES-CD, simple endoscopic score for CD; UC, ulcerative colitis; UCEIS, ulcerative colitis endoscopic index of severity.

<sup>a</sup>Complete data available for PSS-10 for  $n = 148$  (CD,  $n = 81$ ; UC,  $n = 67$ ).

<sup>b</sup>Complete data available for PHQ-9 for  $n = 156$  (CD,  $n = 94$ ; UC,  $n = 62$ ).

<sup>c</sup>Complete data available for GAD-7 for  $n = 157$  (CD,  $n = 95$ ; UC,  $n = 62$ ).

The DSI was elevated in individuals with endoscopically active IBD at baseline (median DSI 28 (IQR, 19–41) vs 12 (IQR, 5–21);  $U = 1271$ ,  $p < 0.001$ ). An elevated DSI was also observed in

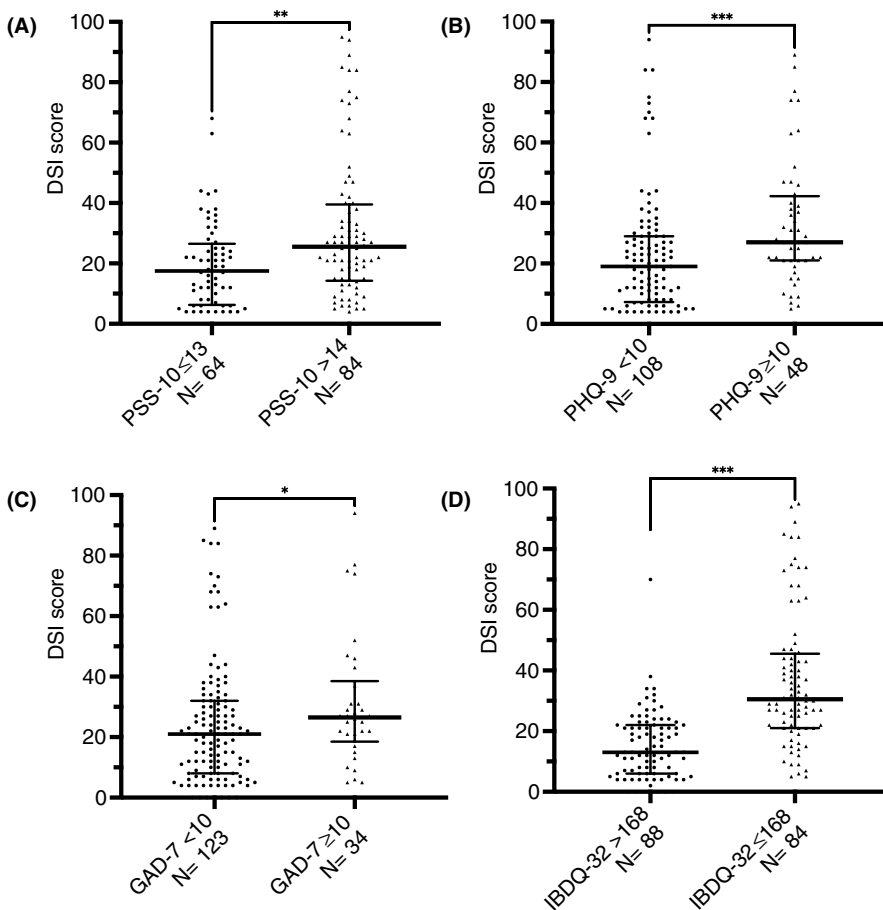
individuals with endoscopically active CD (median DSI 25 (IQR, 17–31) vs 9 (IQR, 5–19);  $U = 371$ ,  $p < 0.001$ ) and UC (median DSI 49 (IQR, 29–74) vs 13 (IQR, 4–25);  $U = 140.5$ ,  $p < 0.001$ ).

**TABLE 2** Spearman rank correlations of disease severity index (DSI) with clinical symptoms (HBI and CDAI for CD, SCCAI for UC), faecal calprotectin (fCal), endoscopic activity (SES-CD and UCEIS), psychological symptoms (perceived stress, PSS-10; depression, PHQ-9; anxiety, GAD-7) and health-related quality of life (IBDQ-32) at baseline

Domain	Comparisons	All IBD		CD		UC	
		Spearman's r	N	Spearman's r	N	Spearman's r	N
Symptoms	DSI vs HBI			0.43 <sup>***</sup>	100		
	DSI vs CDAI			0.59 <sup>***</sup>	100		
	DSI vs SCCAI					0.75 <sup>***</sup>	72
Biomarkers	DSI vs fCal	0.47 <sup>***</sup>	172	0.33 <sup>***</sup>	100	0.65 <sup>***</sup>	72
	Endoscopic activity	DSI vs SES-CD		0.59 <sup>***</sup>	100		
	DSI vs UCEIS					0.73 <sup>***</sup>	72
Psychological symptoms and quality of life	DSI vs IBDQ-32	-0.57 <sup>***</sup>	172	-0.55 <sup>***</sup>	100	-0.70 <sup>***</sup>	72
	DSI vs PSS-10	0.21 <sup>*</sup>	148	0.25 <sup>*</sup>	81	0.26 <sup>*</sup>	67
	DSI vs PHQ-9	0.31 <sup>**</sup>	156	0.42 <sup>***</sup>	94	0.33 <sup>**</sup>	62
	DSI vs GAD-7	0.17 <sup>*</sup>	157	0.18	95	0.25 <sup>*</sup>	62

Abbreviations: CDAI, Crohn's disease activity index; HBI, Harvey-Bradshaw index; IBDQ-32, inflammatory bowel diseases questionnaire; SES-CD, simple endoscopic score for Crohn's disease; UCEIS, ulcerative colitis endoscopic index of severity.

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .



**FIGURE 1** The disease severity index (DSI) was associated with the presence of symptoms of significant stress (A, perceives stress scale, PSS-10), depression (B, patient health questionnaire, PHQ-9), anxiety (C, generalised anxiety disorder scale, GAD-7) and impaired quality of life (D, inflammatory bowel diseases questionnaire, IBDQ-32) at baseline. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

### 3.4 | Use of DSI in predicting a complicated IBD course

A total of 49 study participants (29 CD and 20 UC) reached the composite outcome of complicated IBD at 12 months.

#### 3.4.1 | Univariable and multivariable logistic regression

Univariable logistic regression was used on baseline clinical variables that were associated with a complicated IBD course at

12 months (Table 3). Of the eight variables that were subsequently included in a multivariable logistic regression model (for factors meeting a pre-defined significance value of  $p < 0.01$  on univariable regression), only the  $DSI_{\text{continuous}}$  (OR = 1.05; 95% CI 1.01–1.07;  $p = 0.01$ ) and endoscopically active IBD at baseline (SES-CD >2, UCEIS  $\geq 2$ ; OR = 6.12; 95% CI 1.85–20.26;  $p < 0.01$ ) were associated with a complicated IBD course (Table 3). These two variables were used in the final multivariable model to predict a complicated IBD course at 12 months.

Using this final prediction model, the  $DSI_{\text{continuous}}$  was associated with a complicated disease course in all patients with IBD (OR = 1.05, 95% CI 1.03–1.08), independent of the presence of endoscopically active IBD. This was also seen in subgroup analyses of only patients

with CD (OR = 1.10, 95% CI 1.04–1.16) and UC (OR = 1.06, 95% CI 1.02–1.10).

### 3.4.2 | Significance of the DSI in predicting a complicated IBD course

Receiver operating characteristic curve analysis (Figure 2) identified that a DSI threshold of 23 best predicted a complicated IBD course (sensitivity 84%, specificity 72%,  $AUROC_{DSI>23} = 0.84$ ,  $p < 0.01$ ). The addition of fCal to this model did not improve its predictive ability ( $AUROC_{DSI+fCal} = 0.85$ ,  $p_{\text{diff}} > 0.05$ ). When analysed separately, the optimum DSI threshold identified through

**TABLE 3** Univariable and multivariable analyses for baseline factors associated with the composite study outcome at 12 months (escalation of biologic/immunomodulator due to clinical relapse, corticosteroid use, IBD related hospitalisation and surgery)

Univariable analysis			Multivariable analysis	
Variable	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age	0.99 (0.96–1.01)	0.22		
Female vs male	0.55 (0.28–1.09)	0.09		
UC vs CD	1.06 (0.54–2.08)	0.86		
Time since diagnosis of IBD	0.96 (0.92–0.99)	0.02		
Current steroids	3.73 (1.62–8.62)	<0.01*	0.78 (0.18–3.20)	0.71
Steroids in last year	3.96 (1.97–7.94)	<0.01*	1.97 (0.61–6.32)	0.26
Biological use	2.74 (1.28–5.84)	<0.01*	1.71 (0.61–4.77)	0.31
Thiopurine use	0.60 (0.30–1.18)	0.14		
Opioid use	0.61 (0.13–2.99)	0.54		
Anti-depressant use	1.25 (0.54–2.88)	0.61		
Depression (established diagnosis)	1.88 (0.67–5.27)	0.23		
Anxiety (established diagnosis)	1.63 (0.51–5.26)	0.41		
Concurrent irritable bowel syndrome	1.28 (0.37–4.45)	0.70		
Smoker	2.60 (0.79–8.56)	0.12		
Previous bowel surgery	1.65 (0.77–3.54)	0.20		
IBDQ-32	0.98 (0.97–0.99)	<0.01*	1.00 (0.98–1.03)	0.82
PSS-10	1.06 (1.01–1.12)	0.02		
PHQ-9	1.08 (1.03–1.14)	<0.01*	1.06 (0.95–1.17)	0.31
GAD-7	1.04 (0.98–1.11)	0.23		
$DSI_{\text{continuous}}$	1.07 (1.04–1.09)	<0.01*	1.05 (1.01–1.07)	0.01**
Subjectively active IBD at baseline (HBI >4, SCCAI >5)	3.75 (1.76–8.00)	<0.01*	0.99 (0.29–3.33)	0.99
Objectively active IBD at baseline (SES-CD >2, UCEIS $\geq 2$ )	10.48 (3.88–28.26)	<0.01*	6.12 (1.85–20.26)	<0.01**

Abbreviations: CD, Crohn's disease; DSI, disease severity index; GAD-7, generalised anxiety disorder 7-item scale; HBI, Harvey-Bradshaw index; IBD, inflammatory bowel disease; IBDQ-32, inflammatory bowel diseases questionnaire; PHQ-9, patient health questionnaire-9; PSS-10, perceived stress scale; SCCAI, simple clinical colitis activity index; SES-CD, simple endoscopic score for CD; UC, ulcerative colitis; UCEIS, UC endoscopic index of severity.

\*Selected for multivariable analysis ( $p < 0.01$  on univariable regression analyses); \*\*Selected for final multivariable prediction model for a complicated IBD course ( $p < 0.05$ ).

ROC analyses, was 22 in patients with CD (sensitivity 83%, specificity 72%,  $AUROC_{\text{DSI-CD}} = 0.83$ ,  $p < 0.01$ ) and 29 in patients with UC (sensitivity 95%, specificity 75%,  $AUROC_{\text{DSI-UC}} = 0.90$ ,  $p < 0.01$ ). There was no significant difference in the performance of the DSI in predicting the study outcome between individuals with CD and UC ( $AUC_{\text{difference}} = 0.08$ ,  $p > 0.05$ ). A DSI threshold of 23 performed similarly in predicting a complicated IBD course in individuals with CD (sensitivity 76%, specificity 75%) and UC (sensitivity 95%, specificity 62%).

Univariable and multivariable logistic regression using a DSI threshold of 23 as a categorical variable confirmed that only the baseline DSI and the presence of endoscopically active IBD were significantly associated with a complicated IBD course. Using this prediction model, individuals who had a baseline DSI  $>23$  had a significantly increased risk of having a complicated IBD course at 12 months (OR = 8.31; 95% CI, 3.38–20.46;  $p < 0.001$ ) (Figure 2). This association remained consistent on subgroup analysis of individuals with CD (OR = 6.95, 95% CI 2.34–20.69) and UC (OR = 19.45, 95% CI 2.24–168.90).

Of the 131 individuals with endoscopically inactive or mild disease activity (SES-CD  $< 7$ , UCEIS  $< 5$ ) at baseline, 24 had a complicated IBD course (20 of these individuals had a DSI  $> 23$ ). Using the final multivariable prediction model (Figure 3), a DSI  $> 23$  was associated with a significantly elevated risk of having a complicated IBD course at 12 months even in individuals with inactive or mild disease activity at baseline (OR = 11.75; 95% CI, 3.47–39.81;  $p < 0.001$ ).

## 4 | DISCUSSION

Currently available measures of IBD activity focus on specific snapshots in time and do not encompass the complete burden of illness.<sup>30</sup>

This observation led to the development of the DSI, which aims to gauge the overall severity of IBD and the long-term risk of disease complications. Given the significant psychological impacts associated with IBD,<sup>6</sup> disease severity scores such as the DSI could also be able to predict the presence of underlying psychological diagnoses. This prospective observational study found that the DSI was associated with symptoms of moderate to severe stress, severe depression and anxiety and a poor HRQoL. Using a cut-off score of  $>23$ , this study showed that baseline DSI strongly predicted individuals at high risk of experiencing a complicated disease course over the following 12 months, including clinical relapse requiring escalation of disease-modifying medications, IBD-related hospitalisation and surgery. These findings thus highlight the clinical utility of the DSI in identifying individuals at risk of IBD-related complications and concomitant psychological diagnoses.

Patients with IBD carry a substantial psychological burden, which can have negative impacts on their disease state and overall quality of life.<sup>6,7</sup> Previous studies have reported elevated levels of psychological stress being associated with impaired HRQoL and preceding flares of IBD.<sup>4,31</sup> Anxiety and depression have been independently associated with clinical relapse in IBD overall,<sup>32</sup> and increased risk for surgery in CD.<sup>5</sup> Unfortunately, symptoms of psychological illness are not always associated with objective markers of disease activity and can be overlooked if adhering to a strict “treat-to-target” approach to the management of IBD.<sup>33,34</sup> The targets for IBD treatment typically focus on objective markers of inflammation. While this has merit, a wider view of IBD assessment and therapeutics is required to identify and address non-inflammatory symptoms that are associated with poor quality of life.

Tools that assess the multiple facets contributing to psychological comorbidity can be cumbersome to employ in clinical practice. The findings of this study suggest that the DSI could provide

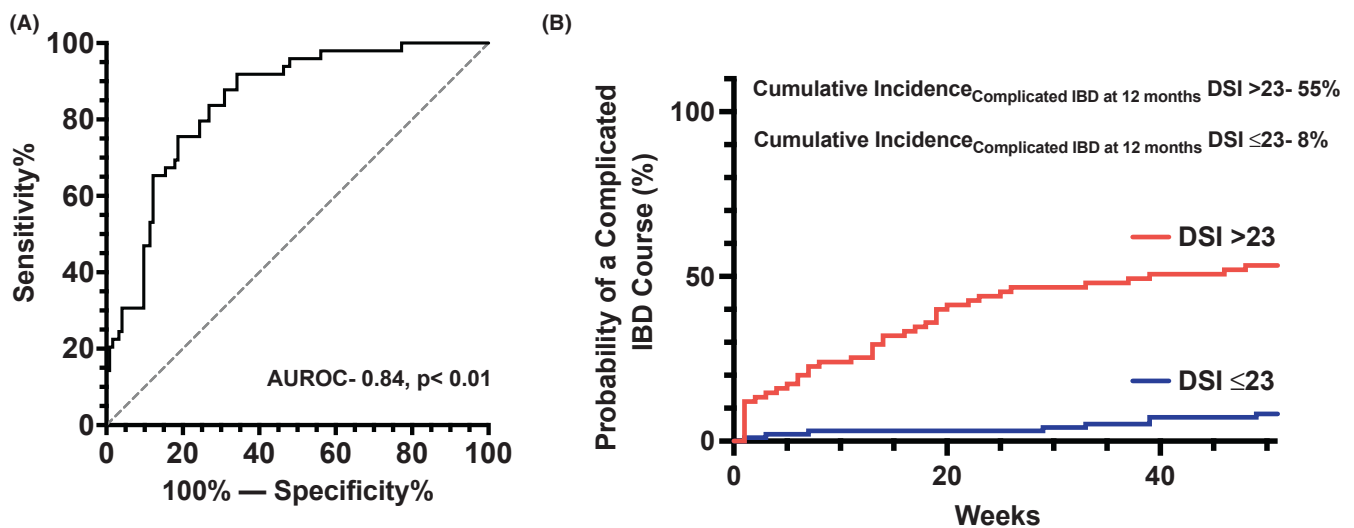
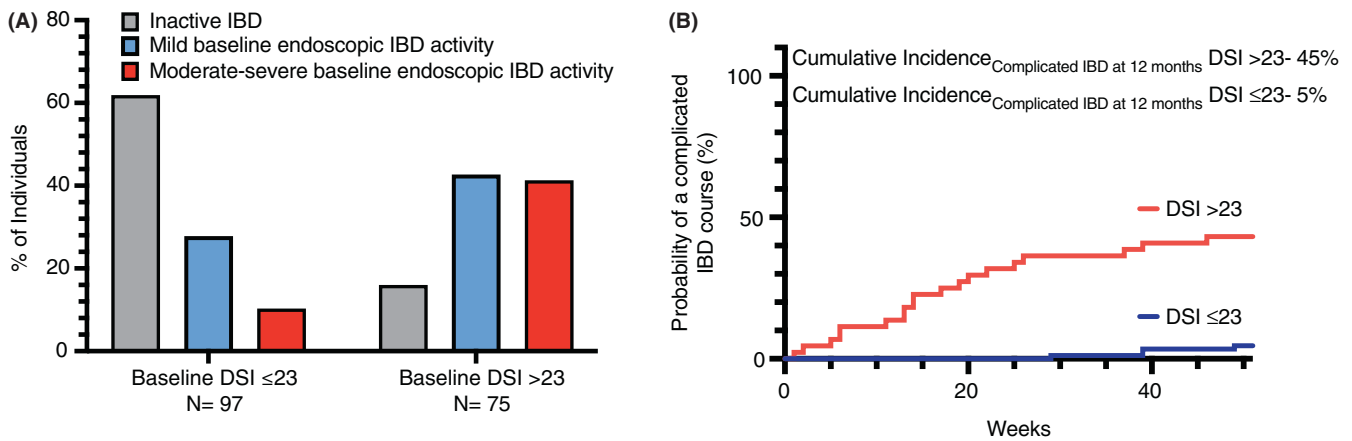


FIGURE 2 The disease severity index (DSI) accurately predicts for individuals who develop a complicated IBD course at 12 months (A) and a baseline DSI  $> 23$  was associated with a significant increase in risk of developing a complicated IBD course at 12 months (B).



**FIGURE 3** Degree of baseline inflammatory bowel disease (IBD) endoscopic disease activity stratified by baseline disease severity index (DSI)  $>23$  (A). Amongst individuals with inactive or mildly active disease at baseline, an elevated DSI  $>23$  was associated with a significant increase in risk of developing a complicated IBD course at 12 months (B). Inactive IBD = simple endoscopic score for Crohn's disease (SES-CD)  $<3$  or ulcerative colitis endoscopic index of severity (UCEIS)  $<2$ . Mild IBD = SES-CD  $<7$ , UCEIS  $<5$ . Moderate-severe IBD = SES-CD  $\geq 7$ , UCEIS  $\geq 5$ .

a more holistic assessment of overall IBD severity and prognosis and could also identify individuals with symptoms of significant psychological distress. The early detection and management of psychological problems could potentially have a significant impact on reducing a patient's suffering and also costs associated with health-care utilisation.<sup>35,36</sup>

Determining IBD prognosis is a challenge given the heterogeneous nature of this condition.<sup>2</sup> The true burden of IBD involves disease-specific complications, the impact on patients' HRQoL and the overall effects of this illness on the healthcare system. Reliably predicting prognosis assists in a personalised approach to care.<sup>37</sup> Current tools to forecast the course of IBD include clinical variables from longitudinal cohorts<sup>38-41</sup> and non-invasive biomarkers that can predict an aggressive course of illness but are not yet cost-effective for widespread clinical use.<sup>42-44</sup> The DSI can be calculated by clinicians using data routinely collected during each IBD re-staging assessment, does not require the use of additional resources and offers similar capabilities to currently available blood-based prognostic markers.<sup>44</sup> Thus, the DSI is a cost-effective and useful tool that can be aligned with "routine" IBD assessment. Interestingly, the addition of fCal did not provide additional prognostic benefit in this cohort.

Clinicians face uncertainty over stratifying which patients will benefit most from a step-up versus top-down approach to their IBD management. The findings of this study suggest that the DSI could potentially aid in the decision-making around the escalation or de-escalation of medical therapies, especially in patients with objectively inactive or mild disease activity.

A significant limitation of this study is that it was conducted at a single tertiary centre with a predominately Caucasian population, thus the current findings may not be more widely generalisable. Furthermore, only patients referred for ileocolonoscopy were included, which may have resulted in selection bias through the exclusion of patients with asymptomatic inflammation. Despite this limitation, over half of the patients included in this study came

forward for ileocolonoscopy for colonic dysplasia surveillance. These individuals were asymptomatic or had low disease activity and were more reflective of a wider cross-section of patients with IBD than only those with symptomatic disease or current IBD flares. This study did not include patients with CD who were having radiological assessments of disease activity meaning inflammation proximal to the distal ileum, proximal small bowel strictures, transmural inflammation and penetrating disease were likely missed. This may have also led to some underreporting of the DSI for CD, which includes a stricture assessment. To help mitigate this, each patients' clinical health record was reviewed for radiological assessments of the small intestine within 12 months of recruitment. Ultimately, the processes utilised in this study reflected "real world" use of a predictive tool such as the DSI when carried out during a patients' disease assessment visit in a resource-constrained health service such as in New Zealand.

In this study, the clinical utility of the DSI in predicting a complicated IBD course was similar between individuals with CD and UC. Sub-group logistic regression and ROC analyses stratified by IBD sub-type confirmed similar performance characteristics of the DSI in predicting the study outcome. Although a degree of collinearity was seen between the presence of endoscopically active IBD and DSI score, the finding of a significant association between the DSI and a complicated IBD course whilst using the final multivariable model confirmed that this index independently predicted the study outcome.

The optimal DSI thresholds for predicting a complicated IBD course did vary between individuals with CD and UC in this cohort. This may be due, in part, to differences in the indices that contribute to the DSI between these IBD sub-types. Given the sample size included in this study, the number of outcome events observed, and for ease of use of this tool for clinical practice, patients with CD and UC were combined in the ROC analyses and final logistic regression model in predicting a complicated IBD course. Future multi-centre studies exploring the prognostic utility of the DSI would highlight



the appropriateness of having a universal DSI threshold for all individuals with IBD as opposed to disease-specific set-points.

The DSI is a promising tool to help prognosticate the course of illness in patients with IBD, however, it requires further validation before widespread use. This process would ideally require a large multi-centre prospective study to assess medium and long-term IBD-related complications with follow-up spanning beyond the 12-month period included in this study. Further investigation is also required on the performance of the DSI for CD and UC, when assessed separately, in comparison with patient-reported outcome measures and disease-related endpoints. These analyses would clarify whether these indices should be pooled for clinical use or be reviewed independently by IBD subtype. Larger studies evaluating the DSI would also assess the reproducibility of the co-variables used in the final multivariable models in this study in predicting a complicated IBD course. Furthermore, the inter- and intra-observer reliability of scoring the DSI and the impact of the longitudinal change of the DSI for an individual in predicting disease-related endpoints require more in-depth assessment.

In summary, this study showed that the DSI encompasses the psychosocial impact of IBD and could be used as a more holistic disease assessment tool for clinicians. A higher DSI should prompt clinicians not only to optimise medical therapy but also to consider significant psychological symptoms in their patients with IBD, enabling appropriate assessments, referrals or treatments. The current report also shows that the DSI accurately predicts a complicated IBD course when patients were followed prospectively for 12 months. This prognostic accuracy was present independent of inflammatory activity at recruitment. In conclusion, the DSI has the potential to allow clinicians to provide more accurate and holistic patient care.

## AUTHORSHIP

*Guarantor of the article:* Akhilesh Swaminathan.

## ACKNOWLEDGEMENTS

*Declaration of funding interests:* The Royal Australasian College of Physicians Research Entry Grant and New Zealand Society of Gastroenterology Janssen Research Fellowship grant were used to establish this study. The funding sponsors were not involved in the study design, collection, analysis and interpretation of data. Open access publishing facilitated by University of Otago, as part of the Wiley - University of Otago agreement via the Council of Australian University Librarians.

## AUTHOR CONTRIBUTIONS

**Akhilesh Swaminathan:** Conceptualization (equal); data curation (lead); formal analysis (lead); funding acquisition (equal); investigation (equal); methodology (lead); project administration (lead); writing – original draft (lead); writing – review and editing (equal). **Dali Fan:** Data curation (supporting); formal analysis (supporting); investigation (supporting); writing – review and editing (supporting). **Grace Borichevsky:** Data curation (supporting); investigation (supporting);

project administration (supporting); writing – review and editing (supporting). **Thomas C Mules:** Data curation (supporting); investigation (supporting); writing – review and editing (supporting). **Esther Hirschfeld:** Data curation (supporting); investigation (supporting); project administration (supporting); writing – review and editing (supporting). **Chris Frampton:** Formal analysis (supporting); investigation (supporting); writing – review and editing (supporting). **Andrew S Day:** Funding acquisition (supporting); supervision (supporting); writing – review and editing (supporting). **Corey Siegel:** Formal analysis (supporting); methodology (supporting); writing – review and editing (supporting). **Richard B Geary:** Conceptualization (equal); formal analysis (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); supervision (lead); writing – review and editing (supporting).

## CONFLICTS OF INTEREST

A.S. has received honoraria for educational activities for Janssen (unrelated to this manuscript). A.S.D. has served on advisory boards for Janssen, Abbvie and Nestle (all unrelated to this manuscript). C.A.S. has received personal fees as a consultant to Abbvie, BMS, Lilly, Janssen, Pfizer, Prometheus, Takeda, Trellus Health; speaker fees for activities sponsored by Abbvie, Janssen, Pfizer, Takeda; grant support from Crohn's and Colitis Foundation: Leona M. and Harry B. Helmsley Charitable Trust, Abbvie, Janssen, Pfizer and Takeda (all unrelated to this manuscript). C.A.S. has equity interest as a co-founder of MiTest health, LLC (software company). Technology developed by MiTest Health, LLC has been licensed to Takeda (unrelated to this manuscript). R.B.G. has received research grants, served on advisory boards and received honoraria for educational activities for Janssen, AbbVie and Zespri (unrelated to this manuscript).

## ORCID

Akhilesh Swaminathan  <https://orcid.org/0000-0003-1954-844X>

Thomas C. Mules  <https://orcid.org/0000-0002-3943-9198>

Andrew S. Day  <https://orcid.org/0000-0003-2290-7386>

Richard B. Geary  <https://orcid.org/0000-0002-2298-5141>

## REFERENCES

1. Chang JT. Pathophysiology of inflammatory bowel diseases. *N Engl J Med.* 2020;383(27):2652–64. <https://doi.org/10.1056/NEJMr2002697>
2. Verstockt B, Bressler B, Martinez-Lozano H, McGovern D, Silverberg MS. Time to revisit disease classification in IBD: is the current classification of IBD good enough for optimal clinical management? *Gastroenterology.* 2022;162:1370–82. <https://doi.org/10.1053/j.gastro.2021.12.246>
3. Verstockt B, Parkes M, Lee J. How do we predict a patient's disease course and whether they will respond to specific treatments? *Gastroenterology.* 2022;162:1383–95. <https://doi.org/10.1053/j.gastro.2021.12.245>
4. Wintjens DSJ, de Jong MJ, van der Meulen-de Jong AE, Romberg-Camps MJ, Bexx MC, Maljaars JP, et al. Novel perceived stress and life events precede flares of inflammatory bowel disease: a prospective 12-month follow-up study. *J Crohns Colitis.* 2019;13(4):410–6. <https://doi.org/10.1093/ecco-jcc/jjy177>

5. Ananthkrishnan AN, Gainer VS, Perez RG, Cai T, Cheng SC, Savova G, et al. Psychiatric co-morbidity is associated with increased risk of surgery in Crohn's disease. *Aliment Pharmacol Ther.* 2013;37(4):445–54. <https://doi.org/10.1111/apt.12195>
6. Bernstein CN, Hitchen CA, Walld R, Bolton JM, Sareen J, Walker JR, et al. Increased burden of psychiatric disorders in inflammatory bowel disease. *Inflamm Bowel Dis.* 2019;25(2):360–8. <https://doi.org/10.1093/ibd/izy235>
7. Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with inflammatory bowel disease: a systematic review. *J Psychosom Res.* 2016;87:70–80. <https://doi.org/10.1016/j.jpsychores.2016.06.001>
8. Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses—part I. *Inflamm Bowel Dis.* 2018;24(4):742–51. <https://doi.org/10.1093/ibd/izx100>
9. Knowles SR, Keefer L, Wilding H, Hewitt C, Graff LA, Mikocka-Walus A. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses—part II. *Inflamm Bowel Dis.* 2018;24(5):966–76. <https://doi.org/10.1093/ibd/izy015>
10. Peyrin-Biroulet L, Panés J, Sandborn WJ, Vermeire S, Danese S, Feagan BG, et al. Defining disease severity in inflammatory bowel diseases: current and future directions. *Clin Gastroenterol Hepatol.* 2016;14(3):348–354.e17. <https://doi.org/10.1016/j.cgh.2015.06.001>
11. Siegel CA, Whitman CB, Spiegel BMR, Feagan B, Sands B, Loftus EV Jr, et al. Development of an index to define overall disease severity in IBD. *Gut.* 2018;67(2):244–54. <https://doi.org/10.1136/gutjnl-2016-312648>
12. Swaminathan A, Borichevsky G, Hoskin T, Mules T, Day AS, Hampton M, et al. Su1917 faecal myeloperoxidase - a potential non-invasive biomarker of disease activity in inflammatory bowel disease (IBD). *Gastroenterology.* 2020;158(6):S701. [https://doi.org/10.1016/S0016-5085\(20\)32443-4](https://doi.org/10.1016/S0016-5085(20)32443-4)
13. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983;24(4):385–96.
14. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Intern Med.* 2001;16(9):606–13. <https://doi.org/10.1046/j.1525-1497.2001.016009606.x>
15. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006;166(10):1092–7. <https://doi.org/10.1001/archinte.166.10.1092>
16. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology.* 1989;96(3):804–10.
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377–81. <https://doi.org/10.1016/j.jbi.2008.08.010>
18. Silverberg MS, Satsangi J, Ahmad T, Arnott IDR, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal world congress of gastroenterology. *Can J Gastroenterol.* 2005;19(Suppl A):5A–36A. <https://doi.org/10.1155/2005/269076>
19. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc.* 2004;60(4):505–12. [https://doi.org/10.1016/S0016-5107\(04\)01878-4](https://doi.org/10.1016/S0016-5107(04)01878-4)
20. Travis SPL, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the ulcerative colitis endoscopic index of severity (UCEIS). *Gut.* 2012;61(4):535–42. <https://doi.org/10.1136/gutjnl-2011-300486>
21. Sipponen T, Nuutinen H, Turunen U, Färkkilä M. Endoscopic evaluation of Crohn's disease activity: comparison of the CDEIS and the SES-CD. *Inflamm Bowel Dis.* 2010;16(12):2131–6. <https://doi.org/10.1002/ibd.21300>
22. Xie T, Zhang T, Ding C, Dai X, Li Y, Guo Z, et al. Ulcerative colitis endoscopic index of severity (UCEIS) versus Mayo endoscopic score (MES) in guiding the need for colectomy in patients with acute severe colitis. *Gastroenterol Rep.* 2018;6(1):38–44. <https://doi.org/10.1093/gastro/gox016>
23. Best WR, Becktel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology.* 1976;70(3):439–44.
24. Harvey RF, Bradshaw JM. A simple index of CROHN'S-disease activity. *The Lancet.* 1980;315(8167):514. [https://doi.org/10.1016/S0140-6736\(80\)92767-1](https://doi.org/10.1016/S0140-6736(80)92767-1)
25. Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol.* 2010;8(4):357–63. <https://doi.org/10.1016/j.cgh.2010.01.001>
26. Walmsley R, Ayres R, Pounder R, Allan R. A simple clinical colitis activity index. *Gut.* 1998;43(1):29–32.
27. Hlavaty T, Persoons P, Vermeire S, Ferrante M, Pierik M, van Assche G, et al. Evaluation of short-term responsiveness and cut-off values of inflammatory bowel disease questionnaire in Crohn's disease. *Inflamm Bowel Dis.* 2006;12(3):199–204. <https://doi.org/10.1097/O1.MIB.0000217768.75519.32>
28. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology.* 2007;132(2):763–86. <https://doi.org/10.1053/j.gastro.2006.12.038>
29. Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, et al. A review of activity indices and efficacy end-points for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology.* 2002;122(2):512–30. <https://doi.org/10.1053/gast.2002.31072>
30. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology.* 2021;160(5):1570–83. <https://doi.org/10.1053/j.gastro.2020.12.031>
31. Tabibian A, Tabibian JH, Beckman LJ, Raffals LL, Papadakis KA, Kane SV. Predictors of health-related quality of life and adherence in Crohn's disease and ulcerative colitis: implications for clinical management. *Dig Dis Sci.* 2015;60(5):1366–74. <https://doi.org/10.1007/s10620-014-3471-1>
32. Mikocka-Walus A, Pittet V, Rossel JB, von Känel R, Anderegg C, Bauerfeind P, et al. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2016;14(6):829–835.e1. <https://doi.org/10.1016/j.cgh.2015.12.045>
33. Mules TC, Swaminathan A, Hirschfeld E, Borichevsky G, Frampton C, Day AS, et al. The impact of disease activity on psychological symptoms and quality of life in patients with inflammatory bowel disease—results from the stress, anxiety and depression with disease activity (SADD) study. *Aliment Pharmacol Ther.* 2022;55(2):201–11. <https://doi.org/10.1111/apt.16616>
34. Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *The Lancet.* 2017;390(10114):2779–89. [https://doi.org/10.1016/S0140-6736\(17\)32641-7](https://doi.org/10.1016/S0140-6736(17)32641-7)
35. Lores T, Goess C, Mikocka-Walus A, Collins KL, Burke ALJ, Chur-Hansen A, et al. Integrated psychological care reduces

- health care costs at a hospital-based inflammatory bowel disease service. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc.* 2021;19(1):96–103.e3. <https://doi.org/10.1016/j.cgh.2020.01.030>
36. Click B, Ramos Rivers C, Koutroubakis IE, Babichenko D, Anderson AM, Hashash JG, et al. Demographic and clinical predictors of high healthcare use in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2016;22(6):1442–9. <https://doi.org/10.1097/MIB.0000000000000763>
  37. Hingorani AD, Windt DA, van der Riley RD, et al. Prognosis research strategy (PROGRESS) 4: stratified medicine research. *BMJ.* 2013;346:e5793. <https://doi.org/10.1136/bmj.e5793>
  38. Solberg IC, Cvanarova M, Vatn MH, Moum B, IBSEN Study Group. Risk matrix for prediction of advanced disease in a population-based study of patients with Crohn's disease (the IBSEN study). *Inflamm Bowel Dis.* 2014;20(1):60–8. <https://doi.org/10.1097/O1.MIB.0000436956.78220.67>
  39. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. *Clin Gastroenterol Hepatol.* 2018;16(3):343–356.e3. <https://doi.org/10.1016/j.cgh.2017.06.016>
  40. Burisch J, Kiudelis G, Kupcinskas L, Kievit HAL, Andersen KW, Andersen V, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an EPI-IBD study. *Gut.* 2019;68(3):423–33. <https://doi.org/10.1136/gutjnl-2017-315568>
  41. Cosnes J, Bourrier A, Nion-Larmurier I, Sokol H, Beaugerie L, Seksik P. Factors affecting outcomes in crohn's disease over 15 years. *Gut.* 2012;61(8):1140–5. <https://doi.org/10.1136/gutjnl-2011-301971>
  42. Biasci D, Lee JC, Noor NM, Pombal DR, Hou M, Lewis N, et al. A blood-based prognostic biomarker in IBD. *Gut.* 2019;68(8):1386–95. <https://doi.org/10.1136/gutjnl-2019-318343>
  43. Lee JC, Lyons PA, McKinney EF, et al. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. *J Clin Invest.* 2011;121(10):4170–9. <https://doi.org/10.1172/JCI59255>
  44. Edwards SJ, Barton S, Bacelar M, Karner C, Cain P, Wakefield V, et al. Prognostic tools for identification of high risk in people with Crohn's disease: systematic review and cost-effectiveness study. *Health Technol Assess.* 2021;25(23):1–138. <https://doi.org/10.3310/hta25230>

## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

**How to cite this article:** Swaminathan A, Fan D, Borichevsky GM, Mules TC, Hirschfeld E, Frampton CM, et al. The disease severity index for inflammatory bowel disease is associated with psychological symptoms and quality of life, and predicts a more complicated disease course. *Aliment Pharmacol Ther.* 2022;56:664–674. <https://doi.org/10.1111/apt.17058>