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Novel symptom clusters predict disease impact and healthcare utilisation in inflammatory bowel disease: Prospective longitudinal follow-up study

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Summary

Background: Predicting adverse disease outcomes and high-volume users of healthcare amongst patients with inflammatory bowel disease (IBD) is difficult.

Aims: The aim of this study is to use latent class analysis to create novel clusters of patients and to assess whether these predict outcomes during 6.5 years of longitudinal follow-up.

Methods: Baseline demographic features, disease activity indices, anxiety, depression, and somatoform symptom-reporting scores were recorded for 692 adults. Faecal calprotectin (FC) was analysed at baseline in 348 (50.3%) patients (<250 mcg/g defined biochemical remission). Using baseline gastrointestinal and psychological symptoms, latent class analysis identified specific patient clusters. Rates of glucocorticosteroid prescription or flare, escalation, hospitalisation, or intestinal resection were compared between clusters using multivariate Cox regression.

Results: A three-cluster model was the optimum solution; 132 (19.1%) patients had below-average gastrointestinal and psychological symptoms (cluster 1), 352 (50.9%) had average levels of gastrointestinal and psychological symptoms (cluster 2), and 208 (30.1%) had the highest levels of both gastrointestinal and psychological symptoms (cluster 3). Compared with cluster 1, cluster 3 had significantly increased risk of flare or glucocorticosteroid prescription (hazard ratio (HR): 2.13; 95% confidence interval (CI): 1.46–3.10), escalation (HR: 1.92; 95% CI: 1.34–2.76), a composite of escalation, hospitalisation, or intestinal resection (HR: 2.05; 95% CI: 1.45–2.88), or any of the endpoints of interest (HR: 2.06; 95% CI: 1.45–2.93). Healthcare utilisation was highest in cluster 3.

Conclusions: Novel model-based clusters identify patients with IBD at higher risk of adverse disease outcomes who are high-volume users of healthcare.

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1 | INTRODUCTION

Inflammatory bowel disease (IBD), which encompasses Crohn's disease (CD) and ulcerative colitis (UC), affects an estimated 8.6 million people worldwide.[1] Typically, IBD follows a relapsing–remitting course, with symptoms of disease activity including abdominal pain, urgency, diarrhoea, and haematochezia. Although the exact aetiology remains unclear, a complex interplay between genetic and environmental factors is believed to trigger a cascade of alterations within the gut microbiome, resulting in enteric immune system dysregulation.[2,3] IBD exerts a considerable socioeconomic burden in Western populations, with healthcare costs per person in the USA exceeding those for diabetes.[4] Healthcare expenditure is, in part, driven by the increasing use of biologics,[5] but hospitalisations and emergency department visits remain a substantial contributor.[6] In addition, the debilitating nature of symptoms generates indirect costs through restricted social interactions, impairment in work productivity, and development of functional disability.[7,8]

One of the challenges faced by physicians is that symptom burden does not always reflect underlying disease activity in IBD.[9] Up to half of patients experience persistent abdominal pain despite quiescent disease,[10] and up to one-third of patients report symptoms compatible with irritable bowel syndrome (IBS), a common disorder of gut-brain interaction influenced by psychological health.[11] In addition, the prevalence of symptoms of common mental disorders, such as anxiety or depression, in patients with IBD is twice that of the general population, affecting up to half of patients during disease flares.[12] Irrespective of disease activity, psychological symptoms are associated with worse disease outcomes and increased healthcare utilisation,[13] with some studies suggesting that the annual costs for patients with IBD with a pre-existing mental health disorder are double that of those without.[5] Despite this, screening for common mental disorders is not integrated within routine IBD care,[14] and even when such symptoms are identified, it is estimated that further action is taken in only half of cases.[15]

Incorporating psychological profiling into model-based clustering techniques in groups of patients with IBS, researchers have identified distinct and reproducible subgroups, or clusters, of patients based on the burden of gastrointestinal symptoms and psychological symptoms.[16,17] To our knowledge, only one study has used this approach in patients with IBD, and the clusters derived were similar to those seen in IBS.[18] In IBS, membership of clusters with a higher burden of psychological symptoms is associated with higher healthcare utilisation and costs, irrespective of the burden of gastrointestinal symptoms.[17,19] However, whether membership of a cluster with a high psychological or gastrointestinal symptom burden impacts disease outcomes or healthcare utilisation in patients with IBD is yet to be determined. This issue may be of relevance for healthcare organisations, where identifying patients at greatest risk of having a worse prognosis or being high-volume users of care could allow resources, such as psychological therapies, to be offered to patient groups who are likely to benefit the most.

We hypothesised that model-based clustering, applying psychological symptom profiling, in addition to gastrointestinal symptom measures, would enable the identification of distinct subgroups of patients with IBD, regardless of disease location, extent, or phenotype, and that membership of a cluster with a higher psychological symptom burden would be associated with worse disease outcomes and higher healthcare utilisation.

2 | METHODS

2.1 | Participants and setting

We recruited patients from IBD clinics based at St James's University Hospitals, Leeds, United Kingdom, between November 2012 and June 2015. Eligible patients were aged ≥16 years with an established diagnosis of CD or UC, based on endoscopic, histological, and radiological findings. Participation involved the completion of a baseline questionnaire. We, therefore, excluded patients who were unable to understand written English, as well as patients with IBD-unclassified and those with a stoma, as reliable scoring systems are not available to assess disease activity accurately in the latter two groups of individuals. We undertook a longitudinal follow-up between September 2014 and November 2021 (REC ref: 12/YH/0443/AM03), as described previously.[20] We reported study findings in accordance with the STROBE guidelines.[21]

2.2 | Data collection and synthesis

2.2.1 | Baseline data

We recorded type of IBD, current IBD-related medications, history of a prior intestinal resection for IBD, and demographic data, including age, sex, marital status, ethnicity, educational level, and tobacco and alcohol use at baseline at the point of study enrolment. In addition, we collected data regarding anxiety or depression symptoms using the hospital anxiety and depression scale (HADS), with an abnormal score defined as ≥11, as per the original validation study,[22] and somatoform symptom-reporting using the validated patient health questionnaire-15 (PHQ-15) at baseline.[23]

We assessed IBD-related gastrointestinal symptoms at baseline using the Harvey-Bradshaw index (HBI) for patients with CD,[24] and the simple clinical colitis activity index (SCCAI) for UC.[25] Patients were asked to provide a faecal calprotectin (FC) sample (Immundiagnostik, Blensheim, Germany) at the point of enrolment, which was sent for analysis. In line with local policy and international consensus,[26] biochemical remission at baseline was defined as an FC of <250 mcg/g of stool.

2.2.2 | Longitudinal follow-up data

To enable an objective measurement of disease activity, we reviewed participant's medical records during longitudinal follow-up. This was done by a single investigator (KMF), blinded to baseline questionnaire data. We extracted the following outcomes along with the date they occurred: flare of disease activity based on either a global assessment by a physician or need for a prescription for glucocorticosteroids, escalation of medical therapy due to uncontrolled IBD activity, hospitalisation due to uncontrolled IBD activity, or intestinal resection due to uncontrolled IBD activity. We also recorded the frequency of each of these. We did not include changes to medication without evidence of uncontrolled IBD activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, as endpoints. Finally, to enable an assessment of overall healthcare utilisation, we recorded the frequency of IBD-related clinic appointments, and number of radiological and endoscopic investigations performed for IBD activity assessment.

2.3 | Statistical analysis

Due to a probable increased risk of the outcomes of interest, patients experiencing a flare at baseline were excluded from all analyses. We used LatentGOLD version 6.0 (Statistical Innovations) to perform latent class analysis (LCA).[27] LCA applies structural equation modelling to enable the identification of previously unobserved groups, referred to as latent classes, within multivariate data.[28] A statistical model is postulated for the population from which the data sample is obtained, with the assumption that a mixture of underlying probability distributions generates the data.[29] The use of LCA for this purpose is model-based clustering, which is a flexible technique, enables the inclusion of multiple variables within the same model. The analysis is iterative, evaluating multiple solutions to determine the best output for any number of clusters.[29] Finally, robust statistical criteria are used to determine the best fit of the model, and the optimum number of clusters.[30] We used the Bayesian information criterion of the log-likelihood (BIC(LL)) for this purpose, selecting the cluster solution with the lowest BIC(LL) value as the best fit for the data. We have used this methodology previously to create clusters of patients with IBS.[16] Details of the variables at baseline used in the model, along with the ordinal scales, are provided in Table S1. We included the following baseline variables in our model: HADS scores (normal, borderline abnormal, or abnormal), common components of the HBI or SCCAI (stool frequency, number of IBD-associated conditions, and general wellbeing), and responses to individual items from the PHQ-15. Using the cluster model with the lowest BIC(LL), we then calculated *z*-values for each cluster within that particular model by adjusting the cluster mean for each variable to the cohort mean and standard deviation for that variable, and then drew radar plots as a visual aid to compare the characteristics of each individual cluster.

We compared baseline characteristics of individuals in each cluster using a χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. To evaluate the influence of being in each cluster at baseline on healthcare utilisation we compared the frequency of each flare of disease activity or glucocorticosteroid prescription, escalation of medical therapy, hospitalisation, or intestinal resection from longitudinal follow-up in each of the LCA clusters, using a χ^2 test. We then performed multivariate Cox regression analysis, controlling for all baseline characteristics, to establish if being in a particular cluster was an independent predictor for the occurrence of each of the outcomes. We expressed these results as hazard ratios (HRs) with 95% CIs. Given that our a priori hypothesis was there would be statistically significant differences between the clusters, and due to multiple comparisons, a 2-tailed $p < 0.01$ was considered statistically significant for these analyses. We repeated this exercise for the subgroup of individuals who had an FC < 250 mcg/g at baseline. We also compared a number of IBD-related appointments and investigations between clusters using one-way ANOVA. We performed statistical analyses using SPSS for Windows version 26.0 (SPSS Inc.).

3 | RESULTS

A total of 760 patients were recruited, with 692 (91.1%) providing complete clinical data at baseline to allow LCA, 348 (50.3%) of whom also supplied a baseline FC. Characteristics of those providing complete data and included in the LCA model, compared with those not included, are provided in Table S2. The mean age of participants was 43.6 (SD: 16.7 years, range: 17–89 years), 382 (55.2%) were female, 647 (93.8%) were Caucasian, and 394 (56.9%) had CD. The number providing follow-up data ranged between 550 (79.5%) for need for glucocorticosteroids or flare of disease activity to 671 (97.0%) for intestinal resection.

3.1 | Cluster characteristics

The best LCA solution was obtained using a three-cluster model, as indicated by the point of convergence between the lowest BIC(LL) values for each cluster model. The three clusters each had distinct symptom profiles; cluster 1 consisted of 132 (19.1%) patients with below-average gastrointestinal and psychological symptoms, cluster 2 352 (50.9%) patients with average levels of gastrointestinal symptoms and psychological symptoms, and cluster 3 208 (30.1%) patients with the highest levels of both gastrointestinal and psychological symptoms.

The symptom profiles for each cluster are provided in Figure 1 and baseline characteristics according to cluster in Table 1. At baseline, stool frequency was between 1 and 3 times per day in almost 95% of patients in cluster 1, only one patient reported their general wellbeing as poor, no patients reported being bothered by stomach pain a lot, and extraintestinal symptom-reporting was low. In cluster 2, at baseline, almost 35% of patients had a stool frequency above 1 to 3 times per day, 8% reported general

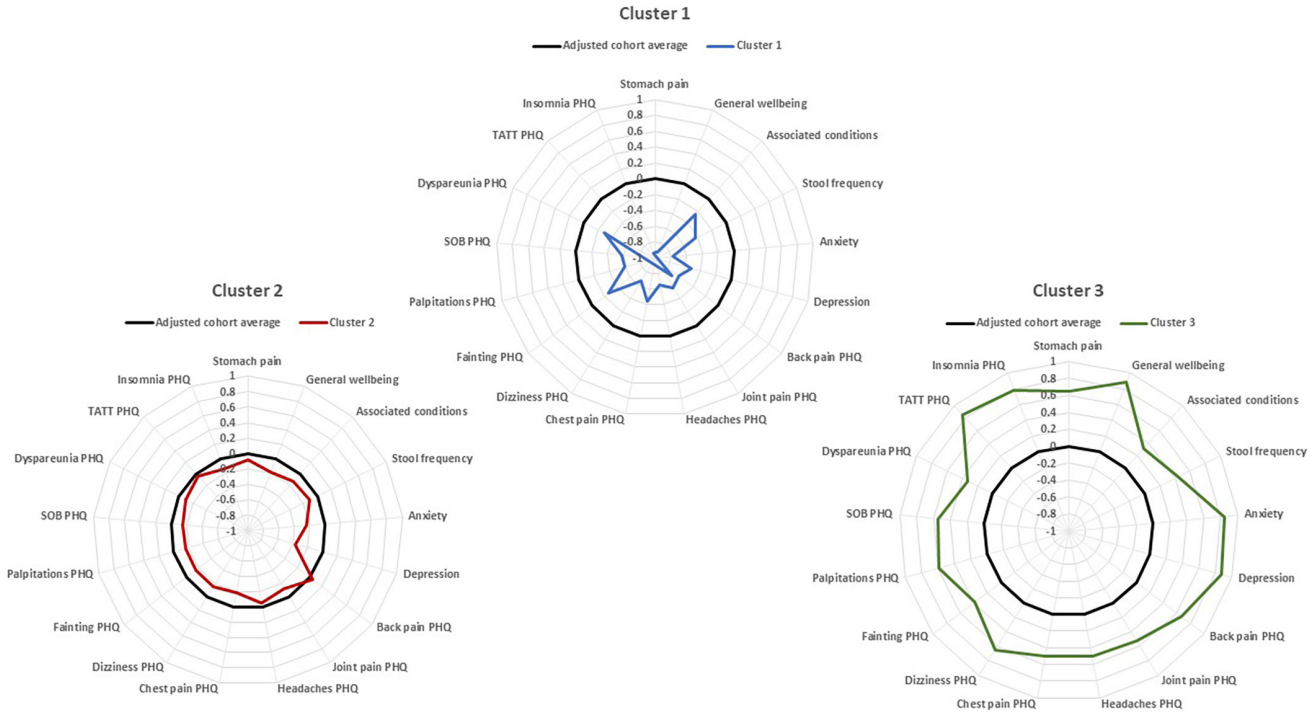

FIGURE 1 Profiles of the three latent class clusters identified in 692 patients with IBD.

wellbeing as poor or worse, 21% reported being bothered by stomach pain a lot, and extraintestinal symptom-reporting was average other than for back pain, which was above average. In cluster 3, at baseline, almost 45% had a stool frequency above 1 to 3 times per day, more than 50% reported general wellbeing as poor or worse, over 60% reported being bothered by stomach pain a lot, and rates of extraintestinal symptom-reporting were extremely high for all symptoms.

Cluster 1 contained the lowest proportion of females, smokers, and individuals reporting glucocorticosteroid use at baseline, and with a history of previous intestinal resection, and the highest proportion of alcohol users. There was also a trend towards cluster 1 having the lowest proportion of patients with CD. There were no significant differences between location, extent, or behaviour of IBD, or other IBD-related medication use at baseline. Mean FC at baseline was similar across all three clusters.

3.2 | Glucocorticosteroid prescription or flare of disease activity

A total of 294 (53.5%) of 550 patients across all three clusters required a prescription for glucocorticosteroids or had a flare of disease activity during a mean follow-up of 4.0 years (range: 7 days to 8.7 years). The likelihood was lowest in cluster 1 with below average levels of both gastrointestinal and psychological symptoms (40.0%) and was significantly higher in both clusters 2 (52.8%) and 3 (66.0%) than cluster 1, and in cluster 3 versus cluster 2 (Table 2). More than 80% of patients requiring a prescription for glucocorticosteroids or experiencing a flare were in clusters 2 and 3. The mean number of prescriptions for glucocorticosteroids or flares during follow-up was significantly higher in clusters 2 and 3.

Following multivariate Cox regression, controlling for all baseline data and using cluster 1 as the reference cluster, the increase in the likelihood of prescription for glucocorticosteroids or flare remained significant in cluster 3 (HR = 2.13; 95% CI: 1.46–3.10, $p < 0.001$) (Table 2 and Figure 2). Younger age was also independently associated with a reduced likelihood of flare or need for glucocorticosteroids (HR per year = 0.98; 95% CI: 0.97–0.99, $p < 0.001$) and UC with a higher likelihood (HR = 1.60; 95% CI: 1.15–2.21, $p = 0.005$). Results were similar when only individuals with an FC < 250 mcg/g were considered in the analysis (HR for cluster 3 versus cluster 1 = 3.63; 95% CI: 1.83–7.22, $p < 0.001$ (Table S3) and were also similar for those with CD and UC (Tables S4 and S5).

3.3 | Escalation of medical therapy due to uncontrolled IBD activity

Of the 607 patients providing complete data, 329 (54.2%) required escalation of medical therapy during a mean follow-up of 3.8 years (range: 4 days to 8.7 years). Likelihood was lowest in cluster 1 with below average levels of both gastrointestinal and psychological symptoms (40.8%) and was significantly higher in both clusters 2 (55.8%) and 3 (60.9%) than cluster 1 (Table 2). Again, more than 80% of patients requiring escalation were in clusters 2 and 3. The mean number of escalations during follow-up was significantly higher in clusters 2 and 3 versus cluster 1.

TABLE 1 Baseline characteristics of patients according to cluster at baseline.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms ($n = 132$)	Cluster 2: Average levels of gastrointestinal and psychological symptoms ($n = 352$)	Cluster 3: Highest levels of gastrointestinal and psychological symptoms ($n = 208$)	p value[a]
Mean age in years at baseline (SD)	45.2 (19.1)	43.5 (16.7)	42.6 (14.9)	0.38
Female sex (%)	57 (43.2)	180 (51.1)	145 (69.7)	<0.001
Married or co-habiting (%)	73 (55.3)	229 (65.6)	122 (58.9)	0.074
University graduate/professional (%)	42 (31.8)	105 (30.1)	50 (24.4)	0.25
Tobacco user (%)	14 (10.6)	52 (14.8)	50 (24.4)	0.002
Alcohol user (%)	96 (72.7)	253 (72.1)	102 (49.5)	<0.001
CD (%)	66 (50.0)	193 (54.8)	135 (64.9)	0.013
CD location (%)				
Ileal	16 (24.2)	35 (18.1)	35 (25.9)	
Colonic	19 (28.8)	59 (30.6)	34 (25.2)	
Ileocolonic	31 (47.0)	99 (51.3)	66 (48.9)	0.49
Non-stricturing, non-penetrating CD (%)	54 (81.8)	163 (84.5)	107 (79.3)	0.11
Perianal CD (%)	8 (12.1)	24 (12.4)	5 (3.7)	0.020
UC extent (%)				
Proctitis	14 (21.2)	34 (21.5)	23 (31.1)	
Left-sided	29 (43.9)	79 (50.0)	29 (39.2)	
Extensive	23 (34.8)	45 (28.5)	22 (29.7)	0.38
5-ASA use (%)	64 (48.5)	170 (48.3)	92 (44.2)	0.61
Immunomodulator use (%)	44 (33.3)	136 (38.6)	69 (33.2)	0.33
Anti-TNFα use (%)	31 (23.5)	69 (19.6)	28 (13.5)	0.051
Glucocorticosteroid use (%)	7 (5.3)	35 (9.9)	34 (16.3)	0.004
Previous intestinal resection (%)	18 (13.6)	65 (18.5)	58 (27.9)	0.003
FC < 250 mcg/g at baseline (%)	45 (64.3)	104 (58.4)	62 (62.0)	0.66
General wellbeing at baseline (%)				
Very good	113 (85.6)	108 (30.7)	5 (2.4)	
Slightly below par	18 (13.6)	216 (61.4)	93 (44.7)	
Poor	1 (0.8)	27 (7.7)	79 (38.0)	
Very poor	0 (0.0)	1 (0.3)	21 (10.1)	
Terrible	0 (0.0)	0 (0.0)	10 (4.8)	<0.001
Stool frequency at baseline (%)				
1–3 times per day	124 (93.9)	268 (76.1)	118 (56.7)	
4–6 times per day	7 (5.3)	68 (19.3)	54 (26.0)	
7–9 times per day	1 (0.8)	12 (3.4)	16 (7.7)	
≥10 times per day	0 (0.0)	4 (1.1)	20 (9.6)	<0.001
Number of IBD-associated conditions at baseline (%)				
0	122 (92.4)	311 (88.4)	148 (71.2)	
1	9 (6.8)	34 (9.7)	50 (24.0)	
2	1 (0.8)	7 (2.0)	7 (3.4)	
3	0 (0.0)	0 (0.0)	3 (1.4)	<0.001
Stomach pain in the last 4 weeks (%)				
None	86 (65.2)	69 (19.6)	8 (3.8)	
A little	46 (34.8)	209 (59.4)	71 (34.1)	
A lot	0 (0.0)	74 (21.0)	129 (62.0)	<0.001

[a]One-way ANOVA for comparison of normally distributed continuous data; χ^2 for comparison of categorical data across all three groups.

TABLE 2 Clinical outcomes of patients according to cluster at baseline.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms ($n = 132$)	Cluster 2: Average levels of gastrointestinal and psychological symptoms ($n = 352$)	p value[a]	Cluster 3: Highest levels of gastrointestinal and psychological symptoms ($n = 208$)	p value[a]	p value[b]	p value[c]
Glucocorticosteroids/flare (%) (% of all glucocorticoids/flares)	48/120 (40.0) (16.3)	151/286 (52.8) (51.4)	0.019	95/144 (66.0) (32.3)	<0.001	0.009	<0.001
Multivariate HR for glucocorticosteroids/flare (95% CI)	1.00 (reference)	1.50 (1.07–2.09)	0.019	2.13 (1.46–3.10)	<0.001	N/A	<0.001
Mean number of glucocorticosteroids/flares (SD)	0.98 (1.52)	1.50 (1.80)	0.002	1.81 (1.72)	<0.001	0.048	<0.001
Escalation (%) (% of all escalations)	51/125 (40.8) (15.5)	172/308 (55.8) (52.3)	0.005	106/174 (60.9) (32.2)	0.001	0.28	0.002
Multivariate HR for escalation (95% CI)	1.00 (reference)	1.61 (1.17–2.22)	0.003	1.92 (1.34–2.76)	<0.001	N/A	0.001
Mean number of escalations (SD)	0.74 (1.10)	1.17 (1.29)	<0.001	1.19 (1.20)	0.001	0.80	0.002
Hospitalisation (%) (% of all hospitalisations)	23/129 (17.8) (13.9)	71/339 (20.9) (43.0)	0.45	71/199 (35.7) (43.0)	<0.001	<0.001	<0.001
Multivariate HR for hospitalisation (95% CI)	1.00 (reference)	1.07 (0.66–1.72)	0.79	1.61 (0.97–2.68)	0.064	N/A	0.048
Mean number of hospitalisations (SD)	0.26 (0.72)	0.29 (0.70)	0.67	0.54 (0.90)	0.002	0.001	<0.001
Intestinal resection (%) (% of all intestinal resections)	11/129 (8.5) (13.4)	33/339 (9.7) (40.2)	0.69	38/203 (18.7) (46.3)	0.011	0.003	0.003
Multivariate HR for intestinal resection (95% CI)	1.00 (reference)	0.98 (0.49–1.98)	0.96	1.70 (0.82–3.56)	0.16	N/A	0.10
Mean number of intestinal resections (SD)	0.11 (0.38)	0.10 (0.31)	0.83	0.19 (0.41)	0.056	0.006	0.011
Escalation, hospitalisation, or intestinal resection (%) (% of all escalations, hospitalisations, or intestinal resections)	56/125 (44.8) (15.9)	179/308 (58.1) (50.7)	0.012	118/173 (68.2) (33.4)	<0.001	0.029	<0.001
Multivariate HR for escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	1.51 (1.11–2.05)	0.009	2.05 (1.45–2.88)	<0.001	N/A	<0.001
Glucocorticosteroids/flare, escalation, hospitalisation, or intestinal resection (%) (% of all glucocorticosteroids/flares, escalations, hospitalisations, or intestinal resections)	57/120 (47.5) (17.1)	174/286 (60.8) (52.1)	0.013	103/143 (72.0) (30.8)	<0.001	0.022	<0.001
Multivariate HR for glucocorticosteroids/flare, escalation, hospitalisation, or intestinal resection (95% CI)	1.00 (reference)	1.48 (1.09–2.01)	0.012	2.06 (1.45–2.93)	<0.001	N/A	<0.001

Abbreviation: N/A, not applicable.

[a] χ^2 for comparison of categorical data or independent samples t-test for comparison of continuous data or hazard ratios vs. cluster 1.

[b] χ^2 for comparison of categorical data or independent samples t-test for comparison of continuous data vs. cluster 2.

[c] χ^2 for comparison of categorical data or one-way ANOVA for comparison of continuous data or hazard ratios across all three groups.

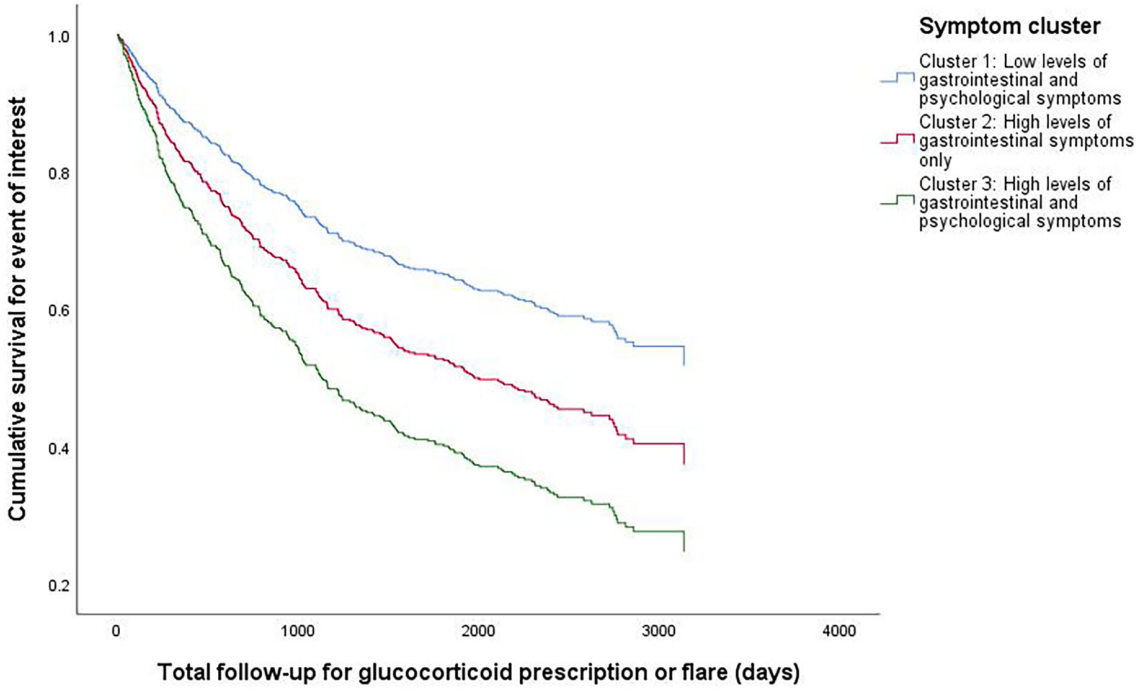

FIGURE 2 Survival analysis for occurrence of glucocorticosteroid prescription or flare of disease activity according to baseline cluster.

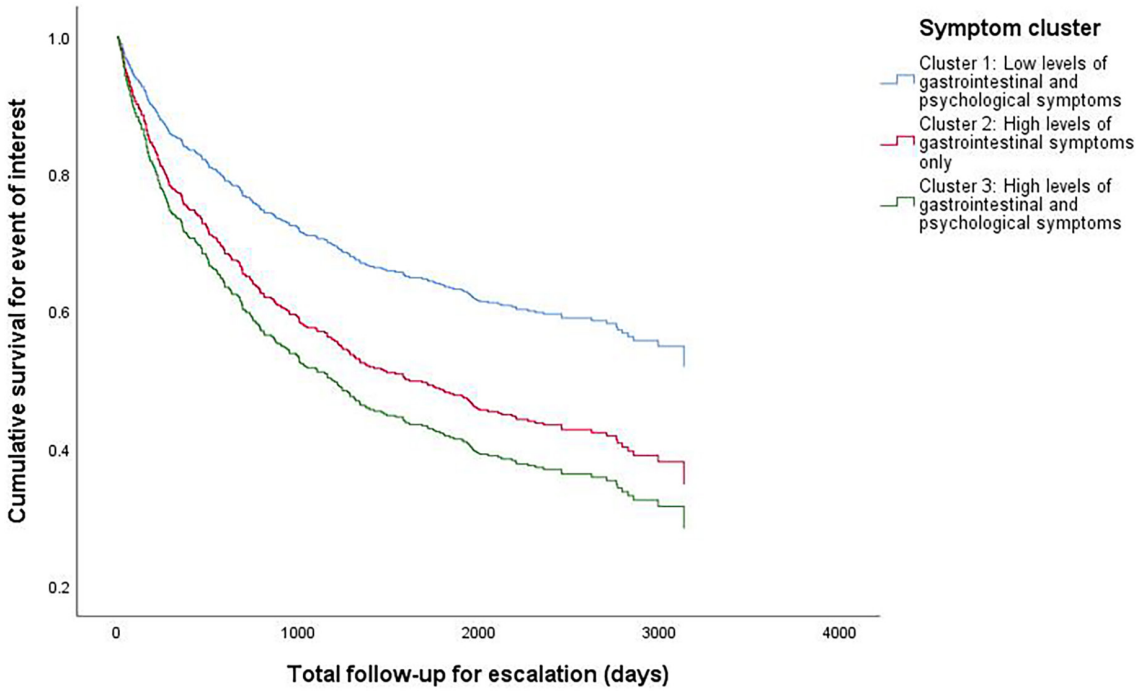

FIGURE 3 Survival analysis for occurrence of escalation of medical therapy due to uncontrolled IBD activity according to baseline cluster.

After multivariate Cox regression, the likelihood of escalation was significantly higher in cluster 2 than cluster 1 (HR = 1.61; 95% CI: 1.17–2.22, $p = 0.003$) and again highest in cluster 3 (HR = 1.92; 95% CI: 1.34–2.76, $p < 0.001$) (Table 2 and Figure 3). Younger age (HR per year = 0.98; 95% CI: 0.97–0.99, $p < 0.001$) was associated with a reduced likelihood of escalation (HR = 0.98; 95% CI: 0.97–0.99, $p < 0.001$) and glucocorticosteroid use at baseline an increased likelihood (HR = 1.66; 95% CI: 1.17–2.35, $p = 0.005$). Again, results were similar when only those with an FC < 250 mcg/g were included in the analysis (HR for cluster 3 versus cluster 1 = 3.48;

95% CI: 1.69–7.19, $p = 0.001$) (Table S3). There was no significant difference in the likelihood of escalation according to cluster in patients with CD, but in those with UC cluster 3 had a significantly higher likelihood of escalation (Tables S4 and S5).

3.4 | Hospitalisation due to uncontrolled IBD activity

A total of 165 (24.7%) of 667 patients were hospitalised due to uncontrolled IBD activity during a mean follow-up of 5.4 years (range: 2 days to 8.7 years). The likelihood of hospitalisation was significantly higher in both cluster 2 (20.9%) and cluster 3 (35.7%) compared with cluster 1 (17.8%), and in cluster 3 versus cluster 2 (Table 2). Again, over 80% of individuals hospitalised were in clusters 2 or 3. The mean number of hospitalisations during follow-up was significantly higher in clusters 2 and 3 versus cluster 1, and significantly higher in cluster 3 versus cluster 2.

Following multivariate Cox regression, there was no significant difference in likelihood of hospitalisation between clusters (Table 2). Results were similar when only individuals with an FC < 250 mcg/g, CD, or UC were considered in the analysis (Tables S3–S5).

3.5 | Intestinal resection due to uncontrolled IBD activity

Overall, 82 (12.2%) of 671 patients underwent intestinal resection due to uncontrolled IBD activity during a mean follow-up of 6.0 years (range: 4 days to 8.7 years). The likelihood of intestinal resection was higher in cluster 3 (18.7%) than both cluster 1 (8.5%) and cluster 2 (9.7%) but was only significantly higher than cluster 2 (Table 2). Again, over 80% of individuals undergoing intestinal resection were in cluster 2 or 3. The mean number of intestinal resections was significantly higher in cluster 3 than cluster 1.

After multivariate Cox regression, the differences in likelihood of intestinal resection between the three clusters failed to reach statistical significance (Table 2). There were also no statistical differences between the clusters for the likelihood of intestinal resection when limiting the analysis to patients with an FC < 250 mcg/g, those with CD, or those with UC (Tables S3–S5).

3.6 | Escalation, hospitalisation, or intestinal resection due to uncontrolled IBD activity

In total, 353 (58.3%) of 606 patients experienced one or more of these endpoints during longitudinal follow-up (Table 2). Cluster 1 had the lowest proportion of events (44.8%), followed by cluster 2 (58.1%), and then cluster 3 (68.2%). Likelihood was only significantly higher in cluster 3 than cluster 1 (Table 2). Following multivariate Cox regression, those in both cluster 2 (HR = 1.51; 95% CI: 1.11–2.05, $p = 0.009$) and cluster 3 (HR = 2.05; 95% CI: 1.45–2.88, $p < 0.001$) were more likely to experience one or more of escalation, hospitalisation, or intestinal resection than cluster 1 (Figure 4). Results were similar for those with an FC < 250 mcg/g (Table S3), but amongst those with CD or UC only cluster 3 had a significantly higher likelihood of escalation, hospitalisation, or intestinal resection (Tables S4 and S5).

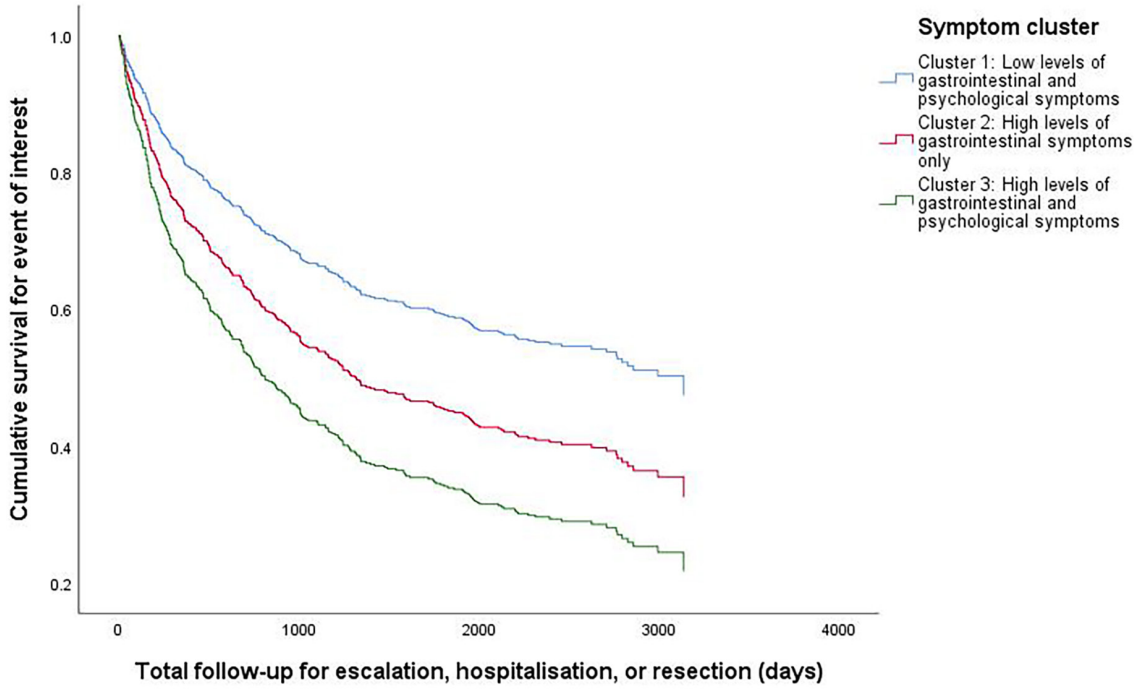

FIGURE 4 Survival analysis for occurrence of escalation of medical therapy, hospitalisation, or intestinal resection due to uncontrolled IBD activity according to baseline cluster.

3.7 | Any endpoint

Overall, 334 (60.8%) of 549 patients experienced one or more of the four endpoints during longitudinal follow-up (Table 2). Again, cluster 1 had the lowest likelihood (47.5%), followed by cluster 2 (60.8%), and cluster 3 (72.0%). Only cluster 3 had a significantly higher likelihood of one or more of these endpoints than cluster 1. Following multivariate Cox regression analysis, again only individuals in cluster 3 had a significantly higher likelihood of experiencing one or more of these endpoints (HR = 2.06; 95% CI: 1.45–2.93, $p < 0.001$) than cluster 1. When only those with an FC < 250 mcg/g were considered in the analysis both cluster 2 and 3 had a significantly higher likelihood of any event than cluster 1 (Table S3), but when IBD type was considered only cluster 3 had a significantly higher likelihood of experiencing any event in CD or UC (Tables S4 and S5).

3.8 | Healthcare utilisation during longitudinal follow-up

Mean number of IBD helpline calls and clinic appointments with a gastroenterologist were significantly higher in both clusters 2 and 3 than cluster 1, and were highest in cluster 3, although not significantly higher than in cluster 2 (Table 3). There was also a significant increase in mean number of radiological investigations for IBD in cluster 3 compared with both clusters 1 and 2, but no statistically significant difference between clusters 1 and 2. Finally, mean number of endoscopic investigations was significantly higher in clusters 2 and 3, when compared with cluster 1, but there was no statistical difference between clusters 2 and 3.

4 | DISCUSSION

We have established the feasibility of subgrouping beyond conventional measures of disease location, phenotype, and disease activity in a large, well-characterised, cohort of patients with IBD. Furthermore, we examined the effects of cluster membership on disease outcomes and healthcare utilisation. To the best of our knowledge, this is the first study to do so in IBD. We identified three unique clusters, each with distinct characteristics, derived from a combination of gastrointestinal symptoms and psychological symptoms at baseline, including anxiety, depression, and somatoform symptom-reporting. Cluster 1 was characterised by below average gastrointestinal and psychological symptoms at baseline, cluster 2 by average levels of gastrointestinal symptoms and psychological symptoms at baseline, and cluster 3 by the highest levels of both gastrointestinal and psychological symptoms at baseline. Amongst these, members of cluster 3 were most likely to report increased stool frequency and stomach pain and to have undergone previous intestinal resection. However, there were no other significant differences in disease characteristics or activity between the clusters at baseline, including FC levels in a subset of patients. Disease outcomes and healthcare utilisation were significantly impacted by cluster membership; over 80% of all disease endpoints occurring amongst members of clusters 2 and 3, both with a higher gastrointestinal symptom burden. However, cluster 3, the cluster with the highest psychological symptom burden, had both the greatest proportion of patients with each of the disease endpoints and the highest levels of healthcare utilisation. After controlling for all baseline data, membership of cluster 3 was associated with a significantly higher risk of disease flare or glucocorticosteroid prescription, treatment escalation, a composite of

TABLE 3 Healthcare utilisation of patients according to cluster at baseline.

	Cluster 1: Below average levels of gastrointestinal and psychological symptoms ($n = 132$)	Cluster 2: Average levels of gastrointestinal and psychological symptoms ($n = 352$)	p value[a]	Cluster 3: Highest levels of gastrointestinal and psychological symptoms ($n = 208$)	p value[a]	p value[b]	p value[c]
Mean number of clinic appointments with a gastroenterologist (SD)	6.57 (5.36)	9.59 (6.49)	<0.001	10.76 (6.37)	<0.001	0.041	<0.001
Mean number of IBD helpline calls (SD)	3.12 (4.82)	5.07 (6.72)	0.001	5.85 (7.18)	<0.001	0.21	0.001
Mean number of radiological investigations related to IBD activity (SD)	0.60 (1.20)	0.83 (1.39)	0.080	1.34 (1.72)	<0.001	<0.001	<0.001
Mean number of endoscopic investigations related to IBD activity (SD)	0.57 (0.83)	0.96 (1.12)	<0.001	1.02 (1.18)	<0.001	0.56	<0.001

[a]Independent samples t test for comparison of continuous data vs. cluster 1.
[b]Independent samples t test for comparison of continuous data vs. cluster 2.
[c]One-way ANOVA for comparison of continuous data across all three groups.

escalation, hospitalisation, or resection, and of reaching any of the adverse disease outcomes of interest, compared with cluster 1. The strength of these associations increased further when only patients in biochemical remission at baseline were considered in the analysis.

Being the sole provider of care to these patients, together with the use of electronic records, means the likelihood that the endpoints of interest have been captured accurately during the study period is maximised. These patients were seen in secondary care and are, therefore, likely to be generalisable to many other patients with IBD in the UK healthcare system. Our inclusion of multiple measures of IBD activity at baseline, some of which are less likely to be subject to over-reporting by participants, and blinding the assessor to baseline data, enabled an objective assessment of adverse disease outcomes and markers of healthcare utilisation during longitudinal follow up. Use of multivariate Cox regression, controlling for other baseline data, ensured that any associations observed relating to these outcomes are likely to be independent. It has been suggested that disease activity indices based on symptoms, such as the HBI and SCCAI, are subject to over-reporting in patients with somatoform behaviour.[9] Therefore, in addition to our primary analyses, we used FC as a marker of activity in a subset of patients, to compare the effects of cluster membership amongst only patients in biochemical remission at baseline, which further strengthens our findings.

We did not validate the LCA model externally on another dataset and the three-cluster solution may, therefore, not perform as well when applied to other cohorts. As the study ran alongside routine clinical care, study participants were treated by several physicians with potentially different interpretations of patient-reported symptoms and, thus, some of the more subjective endpoints may be subject to inter-observer variation. For similar reasons, we could not mandate endoscopic assessment at baseline in all patients, hence our attempt to collect a baseline FC sample from patients. Only half of patients provided this, which may impact the reliability of analyses in this group, particularly for less frequent outcomes. Although we used an FC < 250 mcg/g to define biochemical remission, in line with international consensus, we accept that this cut off has a lower sensitivity for active disease than lower thresholds and may, therefore, overestimate the proportion of patients in remission.[26,31] Additionally, despite all electronic patient records being reviewed by a single assessor, blinded to baseline data, health records could contain documentation relating to a previous common mental disorder or co-existing functional disorder. We were unable to remove this potential element of bias when assessing endpoints. We hypothesised that membership of a cluster with a higher psychological symptom burden would be associated with worse disease outcomes, but the rate of hospitalisation or intestinal resection, although numerically higher in cluster 3, was not significantly different from cluster 1. This could relate to a lack of power to detect these rarer endpoints. Finally, the study was not an inception cohort, so we cannot exclude the possibility that those in cluster 3 already had experienced a worse disease course and, therefore, had higher levels of psychological symptoms as a result. This may mean that the association between higher levels of psychological symptoms and adverse disease outcomes is due to confounding and, in truth, relates to a more aggressive disease course to the point of study enrolment.

Psychological co-morbidity is highly prevalent alongside other chronic diseases, and distinct subgroups of patients, including one or more characterised by an increased psychological symptom burden, have been identified in cohorts of patients with multiple sclerosis,[32] breast cancer,[33] and heart failure.[34] However, to our knowledge, only one other group have attempted to incorporate measures of psychological health to establish the presence of such clusters in patients with IBD.[18] In this study, three of the clusters mirrored the symptom profiles we observed. However, Conley et al. identified the presence of a fourth cluster characterised by low levels of gastrointestinal symptoms and high levels of psychological symptoms. These variations in the number and specific characteristics of the clusters are, of course, inevitable when different variables are used to generate the model and underscore the importance of scrutinising which are used. It is important to point out that stool frequency, which is regarded as a fundamental symptom of IBD, was not one of the variables used in the study by Conley et al. Despite the differences in the number and specific characteristics of the clusters, baseline characteristics of the clusters in our study were comparable with those of the corresponding clusters, with females and tobacco users being more likely to belong to a cluster with the highest psychological symptom burden. This is perhaps not surprising, given that female sex is consistently associated with higher levels of psychological co-morbidity in IBD,[12] and tobacco use is linked with worsening disease outcomes in CD,[35] which in our study had the highest association with membership to cluster 3.

With a mean follow up duration of 6.5 years, we have been able to capture several measures of healthcare utilisation and demonstrate that model-based clustering can be used to identify subgroups of patients with IBD who are likely to be higher utilisers of healthcare, in addition to being more likely to experience adverse disease outcomes. Furthermore, membership of cluster 3, with the highest gastrointestinal and psychological symptom burden, was associated with the greatest healthcare utilisation, and increased frequency of adverse disease outcomes, despite an FC at baseline similar to that of individuals in clusters 1 and 2. This work, therefore, adds to an expanding body of evidence that psychological co-morbidity is a fundamental influence on disease activity in IBD,[36,37] and a major contributor to healthcare utilisation.[13,37–39]

Previous research has suggested that the presence of symptoms of anxiety or depression in patients with IBD may be more detrimental to the natural history of the disease than mucosal inflammation.[38] In the present study, those in cluster 3, who had the highest gastrointestinal and psychological symptom burden, including extraintestinal symptom-reporting, had higher rates of all the endpoints of interest, and a significantly higher rate of composites of these endpoints, as well as higher healthcare utilisation. The magnitude of these associations increased when only those with an FC < 250 mcg/g were included in the analyses. Despite this, psychological health is not considered a treatment target in IBD,[40] and access to psychological

services for many patients with IBD remains limited.[41,42] Some studies have demonstrated that addressing psychological health in routine care reduces emergency department visits, hospitalisations, and glucocorticosteroids prescriptions in patients with IBD.[36,37,39] A previous meta-analysis of randomised controlled trials found that psychological therapies produced short-term improvements in anxiety, depression, and quality of life scores in IBD.[43] However, any benefit during subsequent follow-up was observed only for depression scores. In a meta-analysis of observational studies, including over 30,000 patients with IBD, the prevalence of mood disorders was highest during times of disease activity,[12] yet most trials examining the effect of psychological therapies in IBD have been conducted in unselected patients with quiescent disease and no psychological co-morbidity.[43]

With finite funding and resources available, effective integration of psychological care in routine IBD practice is not possible without clear guidance to direct physicians as to how to screen for psychological co-morbidities, and which patients to select for psychological therapies. The clusters we observed may serve to detect patients with a high gastrointestinal and psychological symptom burden, who are more likely to experience a poor prognosis and who are high-volume users of medical care. Application of the clusters in clinical practice could, therefore, serve to identify not only patients more likely to experience an aggressive disease course in whom early intervention with immunosuppressants or biologics may be warranted but also patients whose natural history is more likely to be indolent, and who could have therapy de-escalated or be followed up less frequently in outpatient clinic. However, as this was not an inception cohort, this is somewhat speculative. The former group of individuals could represent a population in whom psychological therapies may be effective. Future research should first look to establish the external validity of the clusters we describe in different cohorts of patients with IBD and, if replicated, prospective trials could then compare psychological therapies with usual care to assess if cluster membership can be used to predict response.

AUTHOR CONTRIBUTIONS

Christy Riggott: Conceptualization (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal). **Keeley Maria Fairbrass:** Data curation (equal); writing – review and editing (equal). **Christopher Black:** Conceptualization (equal); formal analysis (equal); software (equal); writing – review and editing (equal). **David J Gracie:** Conceptualization (equal); data curation (equal); writing – review and editing (equal). **Alexander Ford:** Conceptualization (equal); data curation (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal).

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AUTHORSHIP

Guarantor: ACF is guarantor. He accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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SUPPORTING INFORMATION

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

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