Validation of claims-based indicators used to identify flare-ups in inflammatory bowel disease

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Abstract

Background & Aims: There are currently no validated claims-based indicators for identifying a worsening of disease in patients with inflammatory bowel disease (IBD). Therefore, we aimed to develop and validate indicators that identify flare-ups of IBD using data from Danish nationwide registries.

Methods: Using Danish nationwide administrative data, we identified all patients with Crohn's disease (CD) or ulcerative colitis (UC) who had at least one measurement of faecal calprotectin between 1 January 2015 and 31 June 2017. We tested several different claims-based indicators of disease flare-ups against levels of faecal (F-)calprotectin (no flare-up: <250 mg/ kg; mild flare-up: 250–1000 mg/kg; severe flare-up: ≥1000 mg/kg). A generalised estimating equation was used to evaluate whether the proposed indicators could predict disease activity.

Results: A total of 890 children and 4719 adults with CD, and 592 children and 5467 adults with UC were included in the study. During the observation period, 48–61% and 48–55% of the CD and UC patients, respectively, had no flare-up, 26–29% (CD) and 24–26% (UC) experienced a mild flare-up, and 12–23% (CD) and 21–27% (UC) experienced a severe flare-up. Combinations of indicators that could predict a flare-up in CD and UC adults included hospitalisation, surgery, initiation or switch of biological therapy, treatment with systemic steroids, locally acting steroids or topical 5-aminosalicylates, colonoscopy/sigmoidoscopy, and magnetic resonance imaging/computed tomography. In children, only the number of gastroenterology visits was significant as an indicator among UC patients, and none were seen in children with CD. Overall, the indicator combinations resulted in a predictive ability of 0.62–0.67.

Conclusion: Administrative claims data can be useful for identifying patients exhibiting (F-calprotectin defined) flare-ups of their IBD. Clinically relevant events captured in the Danish national patient registry are associated with increased levels of calprotectin and hence increased disease activity, and can be used as valid outcomes in future studies.

Keywords: claims data, Crohn's disease, flare-up, ulcerative colitis, validation

Background

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic, progressive inflammatory diseases of the gastrointestinal tract. The incidence of IBD is increasing worldwide, and in Europe alone more than 3 million people are affected.[1]

Most patients are diagnosed during adolescence and young adulthood and face a lifetime with a largely unpredictable disease course, alternating between recurrent flare-ups and periods of remission. IBD has a substantial impact on patients' quality of life, but it also places a considerable financial burden on society with its direct costs, as

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well as its indirect costs related to work disability and sick leave.[2,3]

Studies of the natural history of IBD are important for characterising its disease course and prognosis, as well as treatment patterns and outcomes. National health registries such as those in Scandinavian countries, Canada, South Korea, Taiwan and others provide large amounts of uniform, routinely collected health data from real-world practice. As they include the entire IBD population within their countries, they allow physicians to make general observations about incidence, health care resource utilisation (such as hospitalisation and surgery), treatment outcomes, and pharmacoepidemiology. However, such registries are generally not designed for research and findings based upon them might be subject to a variety of biases, including misclassification or the absence of important data such as about disease activity and severity.[4] Therefore, repeated and continuous validation of these registries is crucial. Previous studies have used events such as prescriptions of corticosteroids, hospitalisation, initiation of biological therapy or IBD-related surgery as a proxy for severe disease activity.[5,6] However, to our knowledge, no study has validated these proxies or indicators. Furthermore, mild-to-moderate flare-ups of disease not requiring hospitalisation, surgery or biological therapy are not usually included in studies of IBD disease course based on claims data. Therefore, attempts to develop indicators that capture both mild-to-moderate, as well as severe, flare-ups are needed in order to improve the quality and usefulness of claims-based registry research.

The purpose of the present study was to develop and validate indicators for identifying disease flare-ups among IBD patients using nationwide administrative registry data (i.e. 'claims data') and comparing them against levels of faecal calprotectin (F-calprotectin) as objective indicators of disease activity.

Methods

Data sources and study population
In Denmark, individual-level cross-linkage of administrative healthcare data is made possible by the unique personal identification number assigned to all residents at birth or upon their immigration.[7] The Danish National Patient Register records hospital admissions and outpatient diagnoses according to the International Classification of Diseases ICD-10, while procedures (including surgeries and hospital-based pharmacological treatments, e.g. biological therapy) are classified as treatment procedure (SKS) codes.[8] Data such as date of dispensation, formulation and quantity are registered by all community pharmacies nationwide and according to the international Anatomical Therapeutic Chemical (ATC) classification in the Danish Registry of Medicinal Products Statistics.[9] Routinely collected F-calprotectin measurements are available in the Register of Laboratory Results for Research.

The present study includes all Danish patients with CD or UC who have at least one measurement of F-calprotectin in the Register of Laboratory Results for Research between 1 January 2015 and 31 June 2017. Patients with a diagnosis of both CD and UC were excluded in order to avoid the misclassification of patients with an unconfirmed or questionable diagnosis. Patients were divided into categories according to their age (children: <18 years *versus* adults: 18 years or older) and diagnosis (CD *versus* UC).

Use of F-calprotectin to capture flares
We used F-calprotectin to define flares in our study. This marker has a higher correlation with endoscopic disease activity than individual symptoms and serum markers such as C-reactive protein (CRP).[10] The dependent variable (F-calprotectin, mg/kg) was categorized according to three levels of severity: 'no flare-up' if a quantity smaller than 250, 'mild flare-up' if a quantity between 250 and 1000, and 'severe flare-up' if a quantity of 1000 or more. The specific cutoffs were chosen *a priori* and were based on a recent systematic review as well as from a clinical study investigating the correlation between calprotectin and disease activity.[11,12] In clinical practice and according to the European Crohn's and Colitis Organisation consensus on the use of F-calprotectin to measure disease activity, 'active disease' is considered when F-calprotectin is 250 mg/kg or greater.[13]

Defining indicators of a 'flare-up'
In the present study, we tested the following registry-based indicators of disease flare-ups in different algorithms: (a) initiation of biological therapy; (b) switch of biological therapy; (c)

number of outpatient visits; (d) treatment with systemic steroids; (e) IBD-related surgery; (f) hospitalisation due to IBD, or an IBD-related condition (e.g. bowel obstruction); (g) initiation of locally acting steroids (in the bowels) or 5-aminosalicylates; (h) a recorded code for colonoscopy/sigmoidoscopy; and (i) a recorded code for a magnetic resonance imaging/computed tomography (MRI/CT) scan.

Biological therapy included the use of infliximab, adalimumab, ustekinumab, vedolizumab or golimumab. Golimumab was prescribed only for patients with UC as it is not approved for treating CD in Denmark. 'Initiation/treatment with' meant that the drug was used in the period following the F-calprotectin measurement but not in the 3 months preceding the measurement. Hence, this indicator was available only for the 3–0 months before, and 0–3 months after, the F-calprotectin measurement was made since '6–4 months before' was used as a reference period for '3–0 months before'. A similar principle was applied to the indicators 'treatment with systemic steroids' and 'initiation of locally acting steroids (in the bowels) or 5-aminosalicylates'. The number of outpatient visits was defined as the number of visits to a gastroenterologist. A sensitivity analysis was conducted that included additional visits to general practitioners. Each of these indicators (a–i) was recorded as 0 (absent) or 1 (present), with the exception of 'c' (number of outpatient visits), which was a count variable. We obtained the frequency of the presence of each indicator (a–i) on three occasions (6–4 months before, 3–0 months before, and 0–3 months after the F-calprotectin measurement was taken) in adults and children with CD or UC.

Statistical analysis
Descriptive statistics, i.e. mean and standard deviation, were reported for F-calprotectin and age. The number and percentage were reported for each level of F-calprotectin, sex and use of non-steroidal anti-inflammatory drugs (which was evaluated 0–3 months after the F-calprotectin measurements were taken) for children and adults with CD or UC. The frequency of each indicator was recorded according to groups of patients with no flare-up, mild flare-up and severe flare-up. Before the study began it was decided that if an indicator was observed on 10 or fewer occasions

in any of the three groups it would not be included in the modelling analysis. The p values from Kruskal–Wallis tests were reported to compare whether age, sex, use of non-steroidal anti-inflammatory drugs and frequency of indicator occurrence differed among the three groups.

Single indicators
A generalised estimating equation (GEE) was used to evaluate whether the indicators proposed could predict disease activity by correlating them with observations made within individuals. The dependent variable was constructed as a binary variable with 0 representing no flare-up (F-calprotectin <250 mg/kg) and 1 representing a flare-up (a F-calprotectin of ≥250 mg/kg).[13] Each indicator (present or not) was used as an explanatory variable one at a time to identify and predict flare-ups, while age and sex served as confounders. Use of non-steroidal anti-inflammatory drugs was not significantly different among the three groups and hence was not included as a confounder in the GEE models. Odds ratio, p value and AUC [area under the receiver operating characteristic (ROC) curve], a measurement of predictive ability, were obtained for each indicator 6–4 months before, 3–0 months before, and 0–3 months after the F-calprotectin was measured. The analyses were performed for all children and adults with either CD or UC.

Multiple indicators/multicollinearity
As there were many potential indicators, data reduction techniques, including factor analysis, were considered to help identify those that might be able to predict flare-ups. Correlations among all instances of all of the indicators were examined to determine whether factor analysis could be used. However, the correlations were found to be weak, indicating few commonalities, and so factor analysis was not necessary. As each indicator had been evaluated, from there on, we focussed instead only on significant single indicators and investigated which combination of these indicators could predict disease activity. GEE models were applied with the same settings as were used for single indicators, but this time the explanatory variables included all relevant significant indicators based on their evaluations among all patients. Odds ratio, p value and AUC were reported for each GEE model.

Table 1. Distribution of F-calprotectin and population characteristics.

	CD (*N* = 5609)		UC (*N* = 6059)	
	Children (*n* = 890)	Adults (*n* = 4719)	Children (*n* = 592)	Adults (*n* = 5467)
F-calprotectin, mg/kg mean (SD)	629.78 (823.38)	409.08 (619.86)	754.26 (997.96)	598.23 (891.07)
No flare-up, <250, *n* (%)	425 (47.75)	2893 (61.31)	281 (47.47)	3031 (55.44)
Mild, 250–1000, *n* (%)	259 (29.10)	1237 (26.21)	152 (25.68)	1306 (23.89)
Severe, ≥1000, *n* (%)	206 (23.15)	589 (12.48)	159 (26.86)	1130 (20.67)
Age, mean (SD)	14.00 (2.66); $p = 0.3098$	40.49 (15.95); $p < 0.0001$	14.03 (3.37); $p = 0.0224$	45.48 (16.84); $p < 0.0001$
Gender	$p = 0.5858$	$p = 0.0571$	$p = 0.8382$	$p < 0.0001$
Female, *n* (%)	386 (43.37)	2643 (56.01)	347 (58.61)	2906 (53.16)
Male, *n* (%)	504 (56.63)	2076 (43.99)	245 (41.39)	2561 (46.84)
Use of non-steroidal anti-inflammatory drugs, *n* (%)	16 (1.80); $p = 0.4422$	244 (5.17); $p = 0.3670$	3 (0.51); $p = 0.5905$	246 (4.50); $p = 0.6803$

p values from Kruskal–Wallis tests are reported to compare whether the population characteristics differ among the three groups according to flare-ups (no, mild and severe).
CD, Crohn's disease; F-calprotectin, faecal calprotectin; SD, standard deviation; UC, ulcerative colitis.

All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

Descriptive statistics

There were 890 children and 4719 adults with CD, and 592 children and 5467 adults with UC. The average age of child participants was 14 in both CD and UC, while the average age of adult participants was 40 for CD and 45 for UC (Table 1). The mean value of F-calprotectin was higher in children than in adults, and it was lower in individuals with CD than with UC. The mean value of F-calprotectin in children and adults with CD was 630 and 409 mg/kg, respectively; in UC it was 754 and 598 mg/kg, respectively (Table 1). During the observation period, 48–61% of the patients had no flare-ups, 24–29% experienced mild flare-ups, while 12–27% experienced severe flare-ups (Table 1). The age of children with UC, age of adults with UC, and gender of adults with UC differed among the three groups (no, mild and severe flare-ups). The use of non-steroidal anti-inflammatory drugs was 0.5–5.2%; this potential confounder did not differ between the groups (Table 1). Hence, only age and gender were used as confounders in the modelling analysis. The mean value of the first measurement of F-calprotectin was significantly higher than that of subsequent measurements, other than among children with UC, for which the 95% confidence interval (CI) overlapped (Supplemental Table A1).

The frequency of each indicator in children and adults with CD or UC is provided in Supplemental Tables A2a–d, along with the *p* value from the Kruskal–Wallis tests to show whether these frequencies differed among the three flare-up groups. In general, the presence of these indicators was lower among children than adults and lower in cases of CD than in UC. During the 3-month study courses (e.g. 6–4 months before, or 3–0 months before, or 0–3 months after the F-calprotectin measurement) children with CD had collectively 10–30 visits to a gastroenterologist and had 150–400 visits in total to either a gastroenterologist or a general practitioner; adults with CD had 150–850 visits to a gastroenterologist and 900–4900 visits in total; children with UC had only 5–20 visits to a gastroenterologist and 100–200 visits in total; adults with UC had 300–1100 visits to a gastroenterologist and

1500–5000 visits in total to a gastroenterologist or a general practitioner.

Single indicator

Only the indicators with a frequency greater than 10 instances in each category of the dependent variable (no flare-up *versus* flare-up) based on Supplemental Tables A2a–d were evaluated in the GEE models. The odds ratio, *p* value and predictive ability measured by AUC are shown in Supplemental Tables A3a–c. In general, there were more significant indicators for adults than for children, although the predictive ability was no higher than 0.6 for any of them. Comparing the three time points, there were more significant indicators in the 3–0 months before and 0–3 months after the original F-calprotectin measurements than in 6–4 months before. None of the indicators could predict flare-ups in a significant way among children with CD, with a AUC of 0.52–0.59 (Supplemental Tables A3a–c). Single indicators that could predict flare-ups to a significant degree among children with UC were the number of gastroenterologist visits (6–4 months before and 0–3 months after), treatment with systemic steroids (0–3 months after), hospitalisation (0–3 months after) and colonoscopy/sigmoidoscopy (0–3 months after), with an AUC range between 0.55–0.63 (Tables A3a–c).

For adults with CD, indicators with a significant predictive ability that were evaluated 6–4 months before the original F-calprotectin measurement were a switch of biological therapy (AUC of 0.53) and colonoscopy/sigmoidoscopy (AUC of 0.54). Half of the indicators recorded 3–0 months before the measurement proved significant in their predictive ability, including treatment with systemic steroids, hospitalisation, initiation of locally acting steroids, colonoscopy/sigmoidoscopy and MRI/CT scan, with an AUC between 0.54 and 0.55. Nearly all indicators evaluated 0–3 months the F-calprotectin measurement were associated significantly with the probability of a flare-up, other than initiation of biological therapy and the number of total visits to a doctor, with an AUC between 0.53 and 0.55 (Supplemental Table A3a–c).

For adults with UC, significant indicators recorded 6–4 months before the F-calprotectin measurement were the number of gastroenterologist visits, hospitalisation, colonoscopy/sigmoidoscopy and

MRI/CT scan, with an AUC between 0.57 and 0.58 (Supplemental Table A3a–c). All indicators assessed in the 3–0 months before the F-calprotectin measurement were significant predictors for a flare-up – other than IBD-related surgery, which had a low frequency – and the AUC was between 0.57 and 0.59 (Supplemental Tables A3a–c). Similarly, all indicators apart from the switching of biological therapy (due to low frequency) were associated significantly with the likelihood of a flare-up in adults with UC, with a AUC between 0.57 and 0.60 (Supplemental Tables A3a–c).

Multiple indicators

Confounders. Next, all significant indicators were included in the GEE model simultaneously to identify the combination of indicators that could best predict the likelihood of a flare-up. Age was found to play a role in children and adults with UC, as older individuals tended to have a slightly lower probability of experiencing flare-ups (Table 2). Adult males had more flare-ups than adult females, while male and female children did not differ in their probability of experiencing a flare-up. More specifically, the odds of experiencing a flare-up among males with CD was 1.2 times higher than that of females with CD, while the odds of experiencing a flare-up among males with UC was 1.4 times higher than that of females with UC (Table 2).

Predictive indicators for adults with CD. Combinations of indicators that could predict flare-ups in adults with CD included switching biological therapy 6–4 months before or 0–3 months after the F-calprotectin measurement, treatment with systemic steroids 3–0 months before and 0–3 months after, hospitalisation 3–0 months before, initiation of locally acting steroids or 5-aminosalicylates 0–3 months after measurement, and colonoscopy/sigmoidoscopy at all three time points (Table 2). Predictive ability of the combination of indicators, represented by AUC, increased to 0.618 (Table 2). The odds of experiencing a flare-up among adults with CD who had switched biological therapy in the 6–4 months before and 0–3 months after the F-calprotectin measurement were 2.7 and 2.6 times higher than for those who had no switch during the corresponding periods, respectively (Table 2). Similarly, the odds of experiencing a flare-up among adults with CD who had been treated with systemic steroids 3–0 months before and 0–3 months

Table 2. Results from GEE models in terms of odds ratios and *p*-values with multiple indicators involved.

Covariates	Timing	Adults with CD (AUC = 0.618)		Children with UC (AUC = 0.669)		Adults with UC (AUC = 0.674)	
		Odds ratio	*p* value	Odds ratio	*p* value	Odds ratio	*p* value
Age		0.9979	0.4374	0.9127	0.0151	0.9943	0.0090
Sex (male)		1.2397	0.0144	1.2516	0.4034	1.4263	<0.0001
Initiation of biologic therapy	6–4m b						
	3–0m b					1.5307	0.0310
	0–3m a					1.3371	0.0803
Switch of biologic therapy	6–4m b	2.7020	0.0444				
	3–0m b					1.8309	0.0815
	0–3m a	2.6031	0.0485				
Number of gastroenterologist visits	6–4m b					1.0662	0.3958
	3–0m b					1.1193	0.0827
	0–3m a	1.0920	0.3289	2.5873	0.0366	1.0385	0.6297
Number of gastroenterologist and general practitioner visits	6–4m b			1.2357	0.0345		
	3–0m b					1.0186	0.4203
	0–3m a					1.0077	0.7525
Treatment with systemic steroids	6–4m b						
	3–0m b	1.9113	0.0001			1.7305	<0.0001
	0–3m a	1.6815	0.0009	1.5671	0.1764	1.7045	<0.0001
IBD-related surgery	6–4m b						
	3–0m b						
	0–3m a	1.0240	0.9343			2.7045	0.0192
Hospitalisation due to IBD or an IBD-related condition	6–4m b					1.2003	0.3500
	3–0m b	1.4805	0.0127			1.0870	0.5757
	0–3m a	1.4789	0.0651	1.1929	0.0712	1.5103	0.0294
Initiation of locally acting steroids (in the bowels) or 5aminosalicylate	6–4m b						
	3–0m b	1.5638	0.0744			1.5076	<0.0001
	0–3m a	1.4789	<0.0001			2.0432	<0.0001
Colonoscopy/sigmoidoscopy	6–4m b	1.4064	0.0023				
	3–0m b	1.3782	0.0034			1.3588	0.0003
	0–3m a	1.3608	0.0034	1.2204	0.5754	1.4236	<0.0001
MRI/CT scan	6–4m b					1.1679	0.4332
	3–0m b	1.1848	0.2691			1.3868	0.0436
	0–3m a	1.3090	0.1510			1.1909	0.3364

Empty cells represent no inclusion of the corresponding indicators.
a, after; AUC, area under the ROC curve; b, before; CD, Crohn's disease; GEE, generalised estimating equation; IBD, inflammatory bowel disease; MRI/CT, magnetic resonance imaging/computed tomography; ROC, receiver operating characteristic; UC, ulcerative colitis.

after were 1.9 and 1.7 times higher than for those who were not treated with systemic steroids during the corresponding periods, respectively (Table 2). The odds of having a flare-up among adults with CD who were hospitalised 3–0 months before the F-calprotectin measurement were 1.5 times higher than for those who were not hospitalised (Table 2). The odds of having a flare-up among adults with CD who had treatment initiated with locally acting steroids 0–3 months after the F-calprotectin measurement were 1.5 times higher than for those who did not (Table 2). The odds of having a flare-up among adults with CD who had a colonoscopy/sigmoidoscopy at any time were around 1.4 times higher than for those who did not (Table 2).

Predictive indicators for children with CD. None of the indicators were significant to predict flare probability in children with CD, and AUC was between 0.52 and 0.59. Thus, no more exploration was appropriate among these children.

Predictive indicators for children with UC. Indicators that could predict flare-ups in children with UC were the number of gastroenterologist visits 0–3 months after, and total number of doctor visits 6–4 months before, the F-calprotectin measurement (Table 2). Based on the number of medical visits, the predictive ability increased to 0.669 (Table 2). For an increase of 1 in the number of gastroenterologist visits and total number of doctor visits, the odds of having a flare-up increased by a factor of 2.6 and 1.2, respectively (Table 2).

Predictive indicators for adults with UC. Combinations of indicators that could predict flare-ups in adults with UC were the initiation of biological therapy 3–0 months before the F-calprotectin measurement, treatment with systemic steroids both 3–0 months before and 0–3 months after, IBD-related surgery 0–3 months after, hospitalisation 0–3 months after, initiation of locally acting steroids or 5-aminosalicylates 3–0 months before and 0–3 months after, colonoscopy/sigmoidoscopy 3–0 months before and 0–3 months after, and MRI/CT scan 3–0 months before the measurement. Based on this information, the predictive ability increased to 0.674. The odds of experiencing a flare-up among adults with UC who initiated biological therapy in the 3–0 months before the F-calprotectin measurement were 1.5 times higher than those who did not initiate biological therapy.

Similarly, the odds of experiencing a flare-up among adults with UC who were treated with systemic steroids in the 3–0 months before or 0–3 months after the measurement were 1.7 times higher than for those who did not during the corresponding periods. The odds of having a flare-up among adults with UC who had undergone IBD-related surgery 0–3 months after the F-calprotectin measurement were 2.7 times higher than for those who did not undergo surgery. The odds of having a flare-up among adults with CD who were hospitalised 0–3 months after the F-calprotectin measurement were 1.5 times higher than for those who were not. The odds of having a flare-up among adults with UC who had treatment initiated with locally acting steroids 3–0 m before and 0–3 m after the F-calprotectin measure were 1.5 and 2.0 times higher, respectively, than for those who did not initiate similar treatment during the same periods. The odds of having a flare-up among adults with UC who had undergone a colonoscopy/sigmoidoscopy in the 3–0 months before or 0–3 months after measurement were 1.4 times higher than for those who did not undergo these procedures. The odds ratio of having a flare-up among adults with UC that had undergone a MRC/CT scan in the 3–0 months before the F-calprotectin measurement were also 1.4 times higher than for those who did not. All these data are presented in Table 2.

The Supplemental tables present further details for each of the indicators tested.

Discussion

In this study, we investigated different indicators that could potentially be useful to identify disease flare-ups in patients with IBD using data from the Danish nationwide administrative (claims-based) registries. By using increased levels of F-calprotectin obtained from routinely collected administrative data as an objective marker of active disease, we found that indicators such as treatment with biological therapy, systemic steroids, locally acting steroids or 5-aminosalicylates, IBD-related surgery, hospitalisation, endoscopy and imaging procedures were significantly related to disease flare-ups in adult patients with CD or UC. For paediatric patients, we did not identify any reliable predictors among those with CD, and determined that only the number of outpatient visits could predict a disease flare-up in children with UC. Overall, the combination of indicators

resulted in a predictive ability AUC of between 0.62 and 0.67.

Administrative healthcare databases are important tools for investigating the epidemiology of IBD, and provide the opportunity to conduct high-quality, population-based disease surveillance. However, despite their many advantages, such databases pose challenges that can bias the interpretation of findings inferred from them. This includes misclassification and inaccuracies in data coding, and therefore the development and validation of indicators for case definitions, as well as disease-related outcomes, is a necessary step towards the reproducibility and credibility of administrative database research. While several studies on the reliable diagnosis of IBD within different administrative healthcare databases exist,[14–16] to date no claims-based registry indicators have been validated for the identification of disease flare-ups in patients with CD and UC.

The ability to accurately identify flare-ups in patients with IBD is critical in assessing the effectiveness of treatment. However, administrative databases do not usually capture data for clinical or objective signs of active disease and hence require researchers to use proxies for severe disease flare-ups, including hospitalisation, surgery or the use of steroids. One strength of this study is that population-based levels of F-calprotectin were available. F-calprotectin provides a quantifiable, noninvasive and relatively inexpensive measure of mucosal inflammation.[17] Several studies have established that calprotectin has a higher correlation with endoscopic disease activity than with clinical disease activity indices focussing on symptoms and serum markers of inflammation, including C-reactive protein (CRP).[10] Furthermore, F-calprotectin can discriminate groups of patients with inactive endoscopic activity from those with mild activity, mild from moderate activity, and moderate from high activity.[18,19] In this way we were able to assess, for the first time, the correlation between registry-based indicators for increased disease activity and an objective marker of inflammation. We could hereby confirm that the proxies of corticosteroids, biological therapy, topical 5-aminosalicylates and surgery can, in fact, be used to identify increased levels of calprotectin and hence flare-ups of IBD. Our findings are reassuring, as these are treatments indicated for active or refractory disease, including both mild,

moderate and severe cases.[20,21] Furthermore, most indicators were shown to be reliable up to 3 months before and after the F-calprotectin measurement was made.

Interestingly, despite the fact that we identified well-known markers of disease activity, the predictive value of these indicators for flare-ups was found to be modest. While F-calprotectin can be used to predict a relapse of quiescent IBD,[22] physicians sometimes choose to use it instead to monitor treatment response following a flare-up and after diagnostic assessment with endoscopy or imaging. More, the use of F-calprotectin in the care of paediatric IBD patients is limited by compliance requirements, especially for adolescent patients that may not always remember to bring a stool sample for visits.[23] The combination of the indicators evaluated increased the predictive accuracy only slightly, which again could be explained by the use of F-calprotectin and that many of these indicators are typically used together in a clinical setting.

Another strength of this study, in addition to the availability of F-calprotectin measurements, is the use of a large cohort of IBD patients based on a nationwide registry that included information about diagnostic investigations and laboratory results. The validity of the Danish national patient registry is generally high and registration of IBD diagnoses has been found to be nearly complete for both UC and CD.[8,24]

However, this study has some limitations that should be considered. First, information about disease classifications were not available. Second, and as already mentioned, our results were potentially biased by differences in the use of F-calprotectin testing in clinical practice. Third, while the Danish health care system provides unfettered access to general practitioners and specialist gastroenterologists for all residents, the findings of the current study may not necessarily apply to other health care systems. Fourth, we did not analyse whether patients potentially had infections that overlapped or mimicked flares of IBD and could lead to increased levels of calprotectin. Fifth, while F-calprotectin is a sensitive marker for mucosal inflammation it also shows large variability, which limits its value in determining grades of disease activity. Finally, and related to the preceding point, studies have

suggested that the reliability of F-calprotectin for disease monitoring and assessment of ileal CD differs from that of UC and colonic CD.[25]

In conclusion, we have used nationwide registry claims data to demonstrate that indicators already used for initiating treatments and evaluating disease course can also be used to help identify patients exhibiting flare-ups of their IBD. While combinations of indicators were not much better than single indicators, we confirmed that clinically relevant events captured in the Danish national patient registry are associated with increased levels of F-calprotectin and hence increased disease activity, and can be used as valid outcomes in future studies.

Author contributions

HZ had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the data analysis. Study concept and design: All authors. Acquisition, analysis and interpretation of data: All authors. Drafting of the manuscript: JB and AE. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: HZ. Obtained funding: AE. Administrative, technical or material support: AE. Study supervision: AE.

Conflict of interest

JB has received research funding from Takeda, Tillots Pharma, Merck Sharp & Dohme, Bristol-Myers Squibb and the Novo Nordisk Foundation, and honoraria as consultant and/or speaker from Samsung Bioepis, Pfizer, Tillots, AbbVie, Takeda, Pharmacosmos, Bristol-Myers Squibb and Janssen Pharmaceuticals. HZ has no conflicts to declare. K-CC, DN, AN, TG and IG are currently employed by Eli Lilly and Company. AE has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, Bristol-Myers Squibb and Janssen Pharmaceuticals.

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Involvement of study sponsor

Design and conduct of the study   Yes X No __

Collection, management, analysis and interpretation of data Yes X No __

Preparation, review, or approval of the manuscript Yes X No __

Decision to submit the manuscript for publication   Yes X No __

Ethics approval and consent to participate

Not required for register studies according to Danish law

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to national security requirements but are available from the corresponding author following approval from the Danish Data Agency and Statistics Denmark.

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Supplemental material

Supplemental material for this article is available online.

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