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Classification of long-term disease patterns in inflammatory bowel disease and analysis of their associations with adverse health events

Fan Li[1†], Yu Chang[1†], Zhaodi Wang[1], Zhi Wang[1], Qi Zhao[1], Xiaoping Han[1], Zifeng Xu[1], Chanjiao Yu[1], Yue Liu[1], Shiyu Chang[1], Hongyan Li[1], Sileng Hu[1], Yuqin Li[1*] and Tongyu Tang[1*]

Abstract

Background With existing researches identifying an increased rate of long-term conditions (LTCs) among Inflammatory Bowel Disease (IBD) patients, yet there is a lack of exploration into the patterns of comorbidity and prognostic rates for IBD patients with multiple morbidities.

Methods The study included 8,305 participants who self-reported having IBD, comprising ulcerative colitis (UC) and Crohn's disease (CD). Latent class analysis (LCA) was utilized to create optimal categories of LTC combinations for UC and CD patients with additional long-term conditions. Using Cox proportional hazards models, we compared the all-cause mortality rates over a 16-year follow-up among UC and CD patients within different LTC categories, both without LTCs and with the addition of one LTC, the probability of major adverse cardiovascular events (MACE), and the rates of IBD-related surgeries.

Results A total of 5,617 participants reported having two or more LTCs, with the LCA method identifying three prevalence categories among CD patients, and four prevalence categories among UC patients. The highest mortality rate among CD patients was found in category 3: (HR 1.789, 95% CI (1.439–2.224)), and the highest rates of MACE were also in category 3: (HR 11.432, 95% CI (9.332–14.005)), with hypertension being the distinguishing characteristic of this category, and the highest rates of IBD-related surgeries being associated with pain in category 1: (HR 1.217, 95% CI (0.983–1.506)). Among UC patients, the highest mortality rate was in category 3: (HR 2.221, 95% CI (1.837–2.684)), with the highest MACE rates found in category 3: (HR 6.422, 95% CI (5.659–7.288)), and the highest rates of IBD-related surgeries being associated with pain, also in category 3: (HR 1.218, 95% CI (1.041–1.425)).

[†]Fan Li and Yu Chang contributed equally to this work and should be considered as co-first authors.

*Correspondence:
Yuqin Li
liyuq@jlu.edu.cn
Tongyu Tang
tangty@jlu.edu.cn

Full list of author information is available at the end of the article

Conclusion The rates of adverse health outcomes in IBD patients is closely associated with multimorbidity patterns, underscoring the need to fully consider multimorbidity patterns in the assessment, management, and treatment strategies for IBD.

Keywords Inflammatory bowel disease, Latent class analysis, Long-term conditions, Crohn disease, Ulcerative colitis

Introduction

Inflammatory Bowel Disease (IBD) is a group of diseases characterized by chronic inflammation of the gastrointestinal tract, including Ulcerative Colitis (UC) and Crohn's Disease (CD), significantly impacting the quality of life. In western countries, the increasing incidence of IBD poses a significant challenge to gastroenterologists. In the United States, the prevalence of IBD was slightly over 0.5% in 2015, with a projected increase to over 0.6% within the next decade [1]. In Asia, the incidence of IBD is 1.4 cases per 100,000 people and is showing a continuous upward trend [2]. IBD can lead to complications within the gastrointestinal tract, such as intestinal stenosis, gastrointestinal bleeding, anal fistulas, and colorectal cancer [3]. It also manifests extraintestinally, primarily affecting areas such as the eyes, skin, joints, and biliary system [4]. The systemic chronic inflammation induced by IBD increases the rate of developing other long-term conditions (LTCs), including cardiovascular diseases [5], diabetes [6], cancers [7, 8], liver diseases [9], respiratory disorders [10], and musculoskeletal diseases [11]. The systemic chronic inflammation caused by IBD disrupts the balance of neurotransmitter secretion involved in emotional regulation and cognitive function, potentially leading to the occurrence of depression and anxiety [12, 13].

IBD patients concurrently experiencing two or more LTCs may have a poorer disease prognosis, increased complications, and require higher medical expenses and healthcare needs. Previous studies have explored the increasing prevalence of IBD patients experiencing multiple LTCs concurrently over the years [5, 13]. Previous research has assessed the incidence and prevalence of patients with multiple diseases in inflammatory bowel disease [14]. However, there is currently a lack of exploration into disease combination patterns and associated prognosis rates in IBD patients with multiple conditions.

In this study, we analyzed 36 LTCs that have been demonstrated in previous studies to significantly impact mortality and major adverse cardiovascular events (MACE) [15–17]. Employing an exploratory technique, Latent Class Analysis (LCA), we effectively classified patients with multiple conditions in UC and CD, calculating associations between LTCs. Furthermore, for participants assigned to different LCA categories, we assessed overall mortality, major cardiovascular event mortality, and IBD-related surgical rates during a 16-year follow-up. The findings of this study contribute to a more precise identification of extraintestinal manifestations in IBD, laying a solid foundation for improved clinical assessment and optimized treatment of IBD.

Methods

Data source

The UK Biobank is a large-scale biobank and health database designed to facilitate research on human health and diseases. Participant information in this database was primarily obtained by collecting genetic information, blood samples, lifestyle, and environmental exposure data. Subsequently, their health and medical records were tracked and recorded for several decades. This study collected data from participants diagnosed with UC or CD and hospitalized between 2006 and 2022, aged between 40 and 70 years. The cohort included 2,926 CD patients and 5,379 UC patients. Each LTC in the database is defined as a binary variable (present/absent). We investigated combinations reported as LTCs and confined these conditions to a list of 36 LTCs (Table S1).

Study design and outcome

The basic characteristics in this study include gender, age, race (European, Asian, African, Chinese, Others), Townsend deprivation index (TDI), education level, smoking status (Never/Previous/Current smokers), alcohol drinking (Never/Previous/Current drinkers), and body mass index (BMI). As shown in Figure S1, 502,411 participants were recruited by the UK Biobank, and follow-up data for UC, CD, and total long-term conditions (TLCs) were collected over a median follow-up period of 13.1 years. We excluded 8,483 participants due to missing data on critical variables, including age, race, TDI, smoking status, drinking status, and BMI. This exclusion resulted in 493,928 participants with complete data. From this dataset, 5,262 participants had UC and 2,872 had CD. The follow-up period was assessed from baseline characteristics, and the outcomes included all-cause mortality, MACE (including stroke, myocardial infarction, etc., detailed in Table S2), and IBD-related surgeries (including colon resection, perianal surgery, etc., obtained through OPCS4 surgical record coding, detailed in Table S2).

Statistical methods

Firstly, we conducted a correlation analysis of the associations between LTCs using the tetrachoric correlation method. Subsequently, LCA was employed to categorize

participants with CD and UC based on the status (presence/absence) of each LTC. LCA is a probabilistic unsupervised machine learning method applied to explore hidden structures or latent categories within sample populations, assigning individuals with similar response patterns to the categories most likely to belong to them [18].

Each individual within a latent category may not necessarily share identical conditions and attributes. In this process, we initiated with a one-category model and progressively increased categories to determine the optimal fit for the number of categories. Multiple criteria, including Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and sample size-adjusted Bayesian Information Criterion (ssBIC), were employed to assess the reference model indicators for determining the number of categories needed for the best fit. The final generated classes were characterized based on the number of LTCs or unique LTCs for the purpose of distinguishing differences between different classes.

For each category, we conducted epidemiological feature descriptions of participants, including prevalence and incidence rates. During the exploration of class features, we employed the Cox proportional hazards model to investigate the rate of all-cause mortality, MACE, and IBD-related surgeries in UC and CD patients across different LTC categories. Additionally, we examined the rates for UC and CD patients without LTCs and those with one LTC during the 16-year follow-up period. Three models were primarily established. In Model 1, adjustments were made for gender and age. In the second model, additional adjustments for smoking and deprivation were made on the foundation of Model (1) The third model involved further adjustments for alcohol consumption, physical activity, and BMI based on Model (2) All statistical analyses and plotting were performed using the R Project for Statistical Computing (version 4.3.3, The R Foundation, Vienna, Austria). All statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

Results

Baseline characteristics

Among CD patients, 55% were female, while 51% of UC patients were male. The median age for CD patients was 56.8 years, and for UC patients, it was 57.4 years. The majority of CD and UC patients were of European descent, comprising 96% and 95%, respectively. In CD, 401 participants (13.7%) reported no accompanying LTC, 474 participants (16.2%) reported only one LTC, and 2051 participants (70.0%) reported the presence of two or more LTCs. Patients reporting two or more LTCs in CD was more likely among older individuals, smokers, alcohol consumers, and those with obesity. Among UC patients, 848 participants (15.8%) reported no accompanying LTC, 965 participants (18.0%) reported only one LTC, and 3,566 participants (66.3%) reported the presence of two or more LTCs. Reporting two or more LTCs in UC was more likely among male individuals, older age groups, former smokers, alcohol consumers, and patients with obesity. More details can be seen in Table 1.

LTCs

Among CD patients, the prevalence rates of pain and hypertension were higher, at 46% and 42%, respectively. The prevalence rates of anorexia nervosa and substance abuse were both below 0.1%. Among UC patients, the prevalence rates of hypertension and pain were higher, at 44% and 37%, respectively, while the prevalence rates of anorexia nervosa and substance abuse were also below 0.1%. Figure 1 illustrates the four-line correlation of the prevalence rates of 20 LTCs with at least a 5% occurrence in CD patients and UC patients. These correlations suggest certain trends of association among specific chronic conditions. Strong associations were observed between Chronic Obstructive Pulmonary Disease (COPD) and asthma (UC: 0.466, CD: 0.475), anxiety and depression (UC: 0.675, CD: 0.727), and coronary heart disease, hypertension, heart failure, and Chronic Kidney Disease (UC: 0.409, CD: 0.405).

Table S3 shows the enrichment of these 36 LTCs among IBD patients in the the UK Biobank. Among the 474 CD patients reporting only one LTC, the three most common singular conditions were pain ($n=140$, 30%), hypertension ($n=69$, 15%), and newly diagnosed cancer within 5 years ($n=62$, 13%) (Table S3). Among 2051 CD patients reporting two or more LTCs, the three most common combinations included CD with pain, accompanied by hypertension ($n=37$, 1.8%), newly diagnosed cancer within 5 years ($n=34$, 1.7%), and CD with hypertension accompanied by newly diagnosed cancer within 5 years ($n=22$, 1.1%) (See Fig. 2 for specific details). In the 965 UC patients reporting only one LTC, the three most common singular conditions were hypertension ($n=189$, 20%), pain ($n=187$, 19%), and newly diagnosed cancer within 5 years ($n=135$, 14%) (Table S3). Among 3566 UC patients reporting two or more LTCs, the three most common combinations included UC with hypertension accompanied by pain ($n=63$, 1.8%), UC with newly diagnosed cancer within 5 years accompanied by prostate disease ($n=38$, 1.1%), and UC with hypertension accompanied by newly diagnosed cancer within 5 years ($n=38$, 1.1%) (See Fig. 3 for specific details).

Latent class analysis

In CD patients, we employed the LCA method and selected a 3-class solution (Table 2). The optimal number of classes was determined through the entropy of each

Table 1 Characteristics of IBD patients with no additional LTCs, 1 additional LTC, and ≥ 2 additional LTCs

	Overall *N* = 493,928	**UC** *N* = 5,262	**Number of LTCs in CD patients**				**CD** *N* = 2,872	**Number of LTCs in CD patients**			
			=0 *N* = 840	**=1** *N* = 951	**>=2** *N* = 3,471	***p*-value**		**=0** *N* = 397	**=1** *N* = 471	**>=2** *N* = 2,004	***p*-value**
Sex, n (%)						**0.001**					> 0.9
Female	269,202 (55%)	2,560 (49%)	435 (52%)	499 (52%)	1,626 (47%)		1,588 (55%)	219 (55%)	263 (56%)	1,106 (55%)	
Male	224,726 (45%)	2,702 (51%)	405 (48%)	452 (48%)	1,845 (53%)		1,284 (45%)	178 (45%)	208 (44%)	898 (45%)	
Age (years), Mean (SD)	56.527 (8.091)	57.433 (7.925)	53.705 (7.813)	55.431 (8.059)	58.883 (7.491)	**< 0.001**	56.750 (8.149)	52.698 (7.848)	54.641 (8.159)	58.048 (7.836)	**< 0.001**
Ethnicity, n (%)						0.49					0.5
European	467,879 (95%)	4,999 (95%)	797 (95%)	894 (94%)	3,308 (95%)		2,757 (96%)	386 (97%)	458 (97%)	1,913 (95%)	
Mixed-race	2,909 (0.6%)	29 (0.6%)	5 (0.6%)	7 (0.7%)	17 (0.5%)		5 (0.2%)	0 (0%)	0 (0%)	5 (0.2%)	
Asian	9,419 (1.9%)	130 (2.5%)	15 (1.8%)	31 (3.3%)	84 (2.4%)		59 (2.1%)	6 (1.5%)	8 (1.7%)	45 (2.2%)	
African	7,793 (1.6%)	50 (1.0%)	8 (1.0%)	9 (0.9%)	33 (1.0%)		28 (1.0%)	3 (0.8%)	2 (0.4%)	23 (1.1%)	
Chinese	1,541 (0.3%)	6 (0.1%)	2 (0.2%)	2 (0.2%)	2 (< 0.1%)		4 (0.1%)	0 (0%)	2 (0.4%)	2 (< 0.1%)	
Others	4,387 (0.9%)	48 (0.9%)	13 (1.5%)	8 (0.8%)	27 (0.8%)		19 (0.7%)	2 (0.5%)	1 (0.2%)	16 (0.8%)	
Townsend deprivation index, Mean (SD)	-1.317 (3.081)	-1.119 (3.158)	-1.486 (2.968)	-1.414 (3.052)	-0.949 (3.218)	**< 0.001**	-0.951 (3.194)	-1.302 (3.027)	-1.287 (2.894)	-0.802 (3.282)	**0.005**
Smoking status, n (%)						**< 0.001**					**< 0.001**
Never	270,562 (55%)	2,395 (46%)	442 (53%)	467 (49%)	1,486 (43%)		1,263 (44%)	213 (54%)	230 (49%)	820 (41%)	
Previous	171,322 (35%)	2,373 (45%)	339 (40%)	408 (43%)	1,626 (47%)		1,145 (40%)	138 (35%)	171 (36%)	836 (42%)	
Current	52,044 (11%)	494 (9.4%)	59 (7.0%)	76 (8.0%)	359 (10%)		464 (16%)	46 (12%)	70 (15%)	348 (17%)	
Alcohol drinking, n (%)						**< 0.001**					**0.003**
Never	21,714 (4.4%)	274 (5.2%)	30 (3.6%)	40 (4.2%)	204 (5.9%)		179 (6.2%)	16 (4.0%)	26 (5.5%)	137 (6.8%)	
Previous	17,641 (3.6%)	267 (5.1%)	24 (2.9%)	37 (3.9%)	206 (5.9%)		174 (6.1%)	11 (2.8%)	26 (5.5%)	137 (6.8%)	
Current	454,573 (92%)	4,721 (90%)	786 (94%)	874 (92%)	3,061 (88%)		2,519 (88%)	370 (93%)	419 (89%)	1,730 (86%)	
BMI (kg/m^2), Mean (SD),	27.425 (4.798)	27.583 (4.747)	26.357 (4.037)	26.883 (4.282)	28.071 (4.947)	**< 0.001**	27.340 (4.991)	25.650 (3.982)	26.410 (4.572)	27.893 (5.156)	**< 0.001**

Note The p-values for the tests of differences were determined based on the type of variable: analysis of variance was used for continuous variables, and the chi-square test was used for categorical variables. Abbreviation: LTC: long-term conditions; UC: ulcerative colitis; CD: crohn's disease, SD, Standard Deviation, BMI, Body mass index

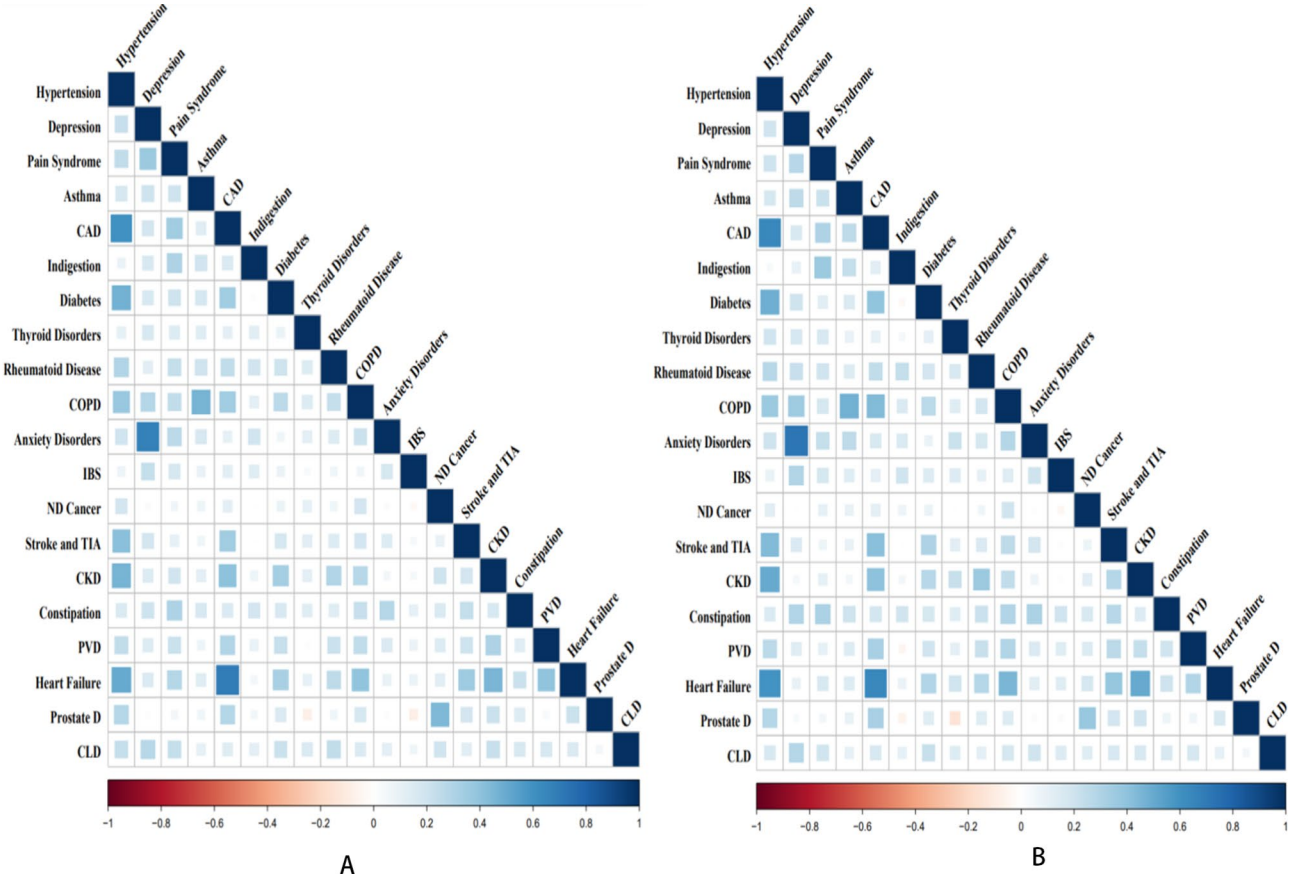

Fig. 1 Associations among Long-Term Conditions in IBD patients. Legends: The heat map represents the tetrachoric correlation between LTCs, displaying data for the 20 LTCs with prevalence rates ≥ 5% in the study sample. The color represents the value of the correlation coefficient (r). **A**): UC, **B**): CD

model in the analysis of 20 LTCs (Figure S2). Hypertension and pain predominated in each class, with most LTCs present in each class. Table S4 summarizes the baseline characteristics of each class in CD patients, and Table S3 summarizes the number of cases and prevalence rates for each class. The most distinctive conditions among participants in the first class were pain (77% prevalence within the class), depression (71%), and anxiety (41%). This class included individuals with a median of 5 additional LTCs, comprising 110 participants aged 60 or above (3.8% of the class) and 117 participants with a BMI above 30 (4.0%). The two most common combinations in the first class were CD with depression accompanied by anxiety (n=6, 1.7%) and pain, depression accompanied by irritable bowel syndrome (n=4, 1.1%). The most distinctive conditions among participants in the second class were pain (34% prevalence within the class), hypertension (24%), and newly diagnosed cancer within 5 years (21%). We observed that 1379 participants (72.7%) had two or fewer diseases, and 1712 participants (90.3%) had three or fewer diseases in this classification. The two most common combinations in the second class were CD with pain (n=140, 74%) and CD with hypertension (n=69, 3.6%). The most distinctive conditions among participants in the third class were hypertension (94% prevalence within the class), pain (62%), and coronary heart disease (58%). The class was primarily characterized by a median of 6 additional LTCs, with no other distinctive features identified. The two most common combinations in the third class were CD with hypertension, pain, coronary heart disease (n=11, 1.6%) and CD with hypertension, pain, coronary heart disease, heart failure (n=4, 0.6%) (Figures S3-S5).

In UC patients, we conducted an analysis of 20 LTCs using BIC and selected a 4-class solution (Table 2). The optimal number of classes, obtained through BIC analysis of 20 LTCs (Figure S1B), encompasses the majority of LTCs within the four identified classes. The primary diseases in UC patients for Classes 1 to 4 are as follows: hypertension (Class 1=1,138, 73%; Class 2=601, 94%), pain (Class 3=516, 68%; Class 4=467, 19%). Participants in the first class were uniquely characterized by hypertension (73% prevalence within the class), newly diagnosed cancer within 5 years (43%), and pain (35%). This class includes individuals with a median of 4 additional LTCs and a BMI above 30, with no other identifiable

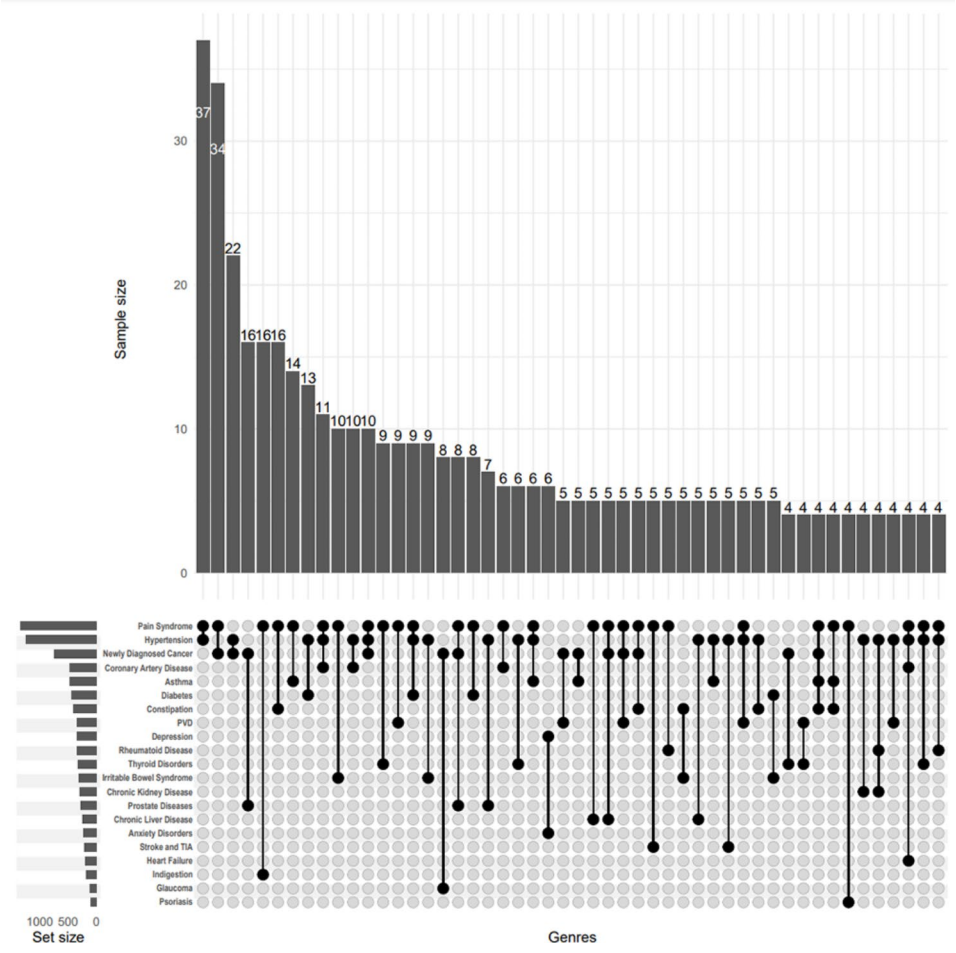

Fig. 2 The 50 most common combinations of LTCs in CD and patients with ≥ 2 LTCs. Legends: These combinations are ranked by prevalence. Black dots and lines represent specific combinations of LTCs. The top bar chart depicts the number of participants reporting each LTC combination. The side bar chart illustrates the number of participants reporting each individual LTC. LTCs: Long-Term Conditions

features. The two most common combinations in the first class were UC with pain accompanied by depression (n=11, 1.2%) and UC with depression accompanied by anxiety (n=9, 0.7%). Participants in the second class were uniquely characterized by hypertension (94% prevalence within the class), coronary heart disease (76%), and pain (74%). This class includes individuals with a median of 4 additional LTCs, with no other identifiable features. The two most common combinations in the second class were UC with newly diagnosed cancer accompanied by prostate disease (n=38, 2.4%) and UC with hypertension accompanied by newly diagnosed cancer within 5 years (n=38, 2.4%). Participants in the third class were uniquely characterized by pain (68% prevalence within the class), depression (45%), and hypertension (38%). We observed that participants in this class, with four or more LTCs, numbered 527 (69.9%). The two most common combinations in the third class were UC with hypertension, coronary heart disease, pain, and heart failure (n=4, 0.6%), and UC with hypertension, coronary heart disease, diabetes, and depression (n=4, 0.6%). Participants in the fourth class were uniquely characterized by pain (19% prevalence within the class), hypertension (13%), and newly diagnosed cancer within 5 years (12%). We observed that participants in the fourth class with two or fewer LTCs numbered 2347 (96.4%), and those with one or fewer LTCs numbered 1809 (74.3%). The two most common combinations in the fourth class were UC with hypertension (n=189, 7.8%) and UC with pain (n=187, 7.7%) (Figures S6-S9).

Exploration of class features

All-cause mortality

A total of 369 (12.6%) CD patients died during a median follow-up of 13.4 years. After adjusting for gender, age, smoking, drinking, deprivation, and BMI factors, the first class (pain) and third class (hypertension) exhibited the highest mortality rates compared to CD in other classes, with an increased rate of all-cause mortality by 78.9% (HR 1.789, 95% CI 1.439–2.224) and 45.4% (HR 1.454,

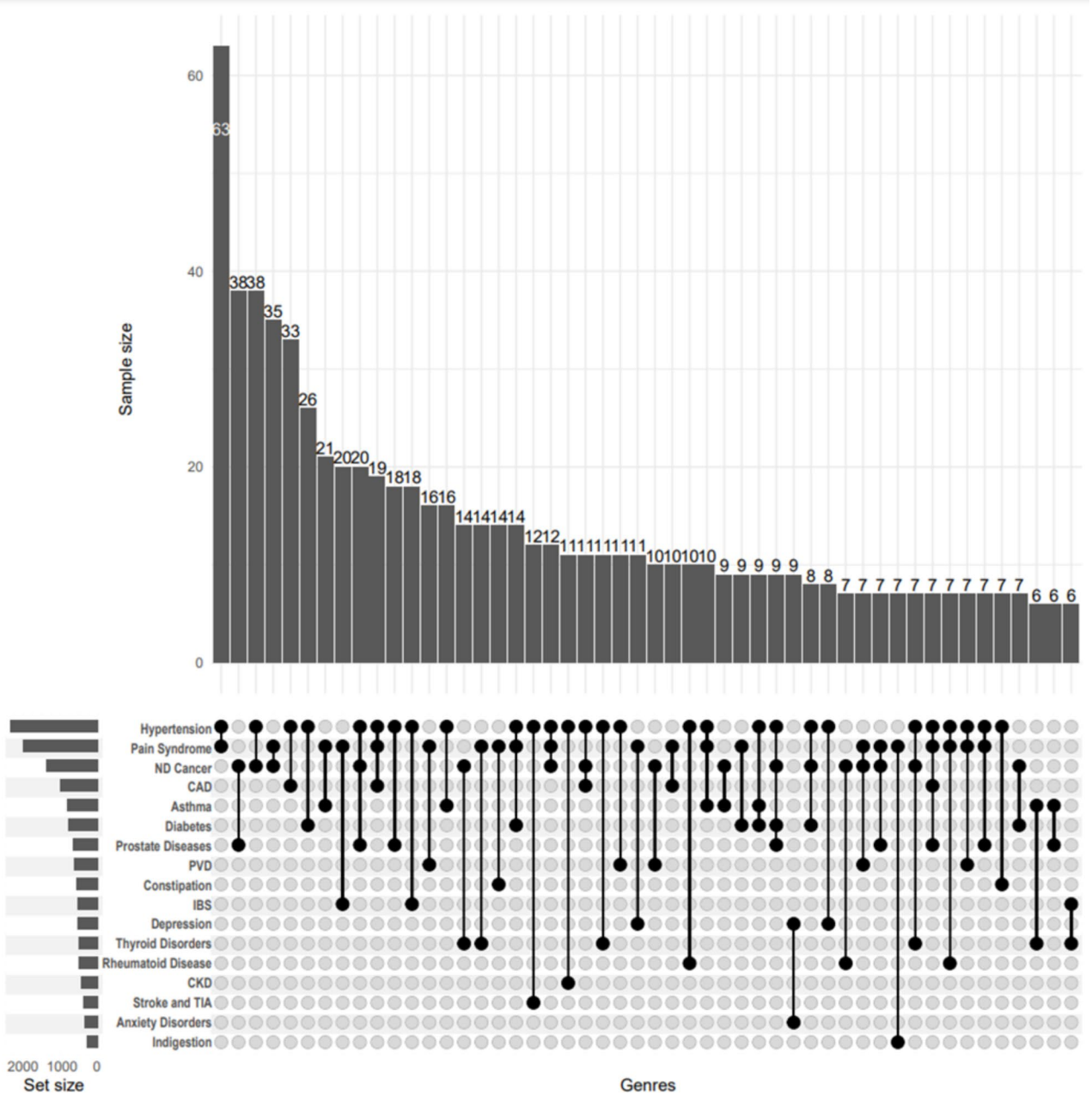

Fig. 3 The 50 most common combinations of LTCs in UC and patients with ≥ 2 LTCs. Legends: These combinations are ranked by prevalence. Black dots and lines represent specific combinations of LTCs. The top bar chart depicts the number of participants reporting each LTC combination. The side bar chart illustrates the number of participants reporting each individual LTC. LTCs: Long-Term Conditions

95% CI 1.090–1.939), respectively (Table 3). A total of 596 (11.1%) UC patients died during a median follow-up of 13.3 years. In the adjusted Model 3, compared to UC in other classes, the second class (hypertension) and third class (pain) exhibited the highest mortality rates, with an increased rate of all-cause mortality by 122.1% (HR 2.221, 95% CI 1.837–2.684) and 20.5% (HR 1.205, 95% CI 1.016–1.431), respectively (Table 4).

Major adverse cardiovascular events (MACE)

A total of 588 (20.1%) CD patients experienced MACE during a median follow-up of 13.4 years, with the highest rate observed in the second class (pain) and third class (hypertension). Among them, 531 patients (20.7%) encountered MACE events during the follow-up period. Compared to CD patients and those with no other LTCs, the fully adjusted hazard ratios (HR) for the second and third classes were (HR 0.098, 95% CI 0.078–0.123) and (HR 11.432, 95% CI 9.332–14.005), respectively (Table 3).

Table 2 Characteristics of participants in each latent class

LTC Class	Description	Participants *n* (%)	Median number of conditions (IQR)	Number of distinct combinations of LTCs	Female (%)	Age > 60 years (%)	BMI > 30 (%)	Current or previous smoker (%)	Reside in most deprived quintile (%)
CD1	Pain, Depression and Anxiety Dominant	360 (12.3%)	5 (4–7)	334	262 (9.0%)	110 (3.8%)	117 (4.0%)	213 (7.3%)	302 (10.3%)
CD2	(Few LTC) Pain, Hypertension and Cancer Dominant	1896 (64.8%)	2 (1–3)	526	1068 (36.5%)	625 (21.4%)	359 (12.3%)	982 (33.6%)	1442 (49.3%)
CD3	Hypertension, Pain, and Coronary Artery Disease Dominant	670 (22.9%)	6 (5–8)	632	290 (9.9%)	427 (14.6%)	226 (7.7%)	432 (14.8%)	537 (18.4%)
UC1	Hypertension, Cancer and Pain Dominant	754 (14.0%)	4 (3–5)	634	516 (9.6%)	270 (5.0%)	179 (3.3%)	411 (7.6%)	598 (11.1%)
UC2	Hypertension, Coronary Artery Disease and Pain Dominant	1554 (28.9%)	4 (3–5)	929	546 (10.2%)	929 (17.3%)	467 (8.7%)	886 (16.5%)	1192 (22.2%)
UC3	(More LTC) Pain, Depression and Hypertension Dominant	636 (11.8%)	8 (6–9)	618	237 (4.4%)	430 (8.0%)	263 (4.9%)	423 (7.9%)	524 (9.7%)
UC4	(Few LTC) Pain, Hypertension and Cancer Dominant	2435 (45.3%)	1 (0–2)	183	1321 (24.6%)	751 (14.0%)	439 (8.2%)	1184 (22.0%)	1828 (34.0%)

Note The "Description" column provides a subjective description of potential categories by the authors. Abbreviation: BMI, Body mass index; CD, crohn's disease, UC, ulcerative colitis, IQR, Interquartile Range, LTCs, long-term conditions

Table 3 Adverse health outcomes for CD participants. Hazard ratios for all-cause mortality, MACE, and IBD-related surgeries

CD	LTC(class)	Number of events	Events per 100 person years	model 1		model 3		model 2	
				HR 95%CI	*P*	HR 95%CI	HR 95%CI	*P*	HR 95%CI
All-cause mortality	None	3	0.056	0.064(0.020 ~ 0.198)	< 0.001	0.069(0.022 ~ 0.216)	< 0.001	0.072(0.023 ~ 0.223)	< 0.001
	one LTC	30	0.472	0.498(0.343 ~ 0.724)	< 0.001	0.535(0.368 ~ 0.777)	0.001	0.531(0.365 ~ 0.774)	0.001
	class 1	59	1.223	1.619(1.221 ~ 2.147)	0.001	1.489(1.118 ~ 1.983)	0.006	1.454(1.090 ~ 1.939)	0.011
	class 2	159	0.626	0.451(0.367 ~ 0.554)	< 0.001	0.486(0.394 ~ 0.599)	< 0.001	0.491(0.396 ~ 0.608)	< 0.001
	class 3	178	1.983	1.928(1.561 ~ 2.382)	< 0.001	1.813(1.466 ~ 2.242)	< 0.001	1.789(1.439 ~ 2.224)	< 0.001
	All	369	0.941						
Major adverse cardiovascular events (MACE)	None	2	0.037	0.025(0.006 ~ 0.101)	< 0.001	0.026(0.007 ~ 0.105)	< 0.001	0.029(0.007 ~ 0.115)	< 0.001
	one LTC	10	0.157	0.089(0.048 ~ 0.167)	< 0.001	0.093(0.050 ~ 0.174)	< 0.001	0.098(0.052 ~ 0.183)	< 0.001
	class 1	57	1.182	0.946(0.717 ~ 1.248)	0.695	0.898(0.680 ~ 1.186)	0.448	0.875(0.661 ~ 1.157)	0.350
	class 2	99	0.390	0.095(0.076 ~ 0.118)	< 0.001	0.097(0.078 ~ 0.121)	< 0.001	0.098(0.078 ~ 0.123)	< 0.001
	class 3	432	4.812	12.087(9.927 ~ 14.717)	< 0.001	11.643(9.550 ~ 14.194)	< 0.001	11.432(9.332 ~ 14.005)	< 0.001
	All	588	1.500						
IBD-related Operation	None	82	1.526	0.705(0.558 ~ 0.889)	0.003	0.722(0.570 ~ 0.913)	0.007	0.697(0.549 ~ 0.883)	0.003
	one LTC	128	2.015	1.041(0.860 ~ 1.261)	0.681	1.055(0.870 ~ 1.279)	0.586	1.035(0.853 ~ 1.256)	0.727
	class 1	107	2.218	1.209(0.982 ~ 1.487)	0.073	1.205(0.978 ~ 1.485)	0.080	1.217(0.983 ~ 1.506)	0.071
	class 2	498	1.960	1.030(0.883 ~ 1.201)	0.706	1.044(0.894 ~ 1.221)	0.588	1.014(0.863 ~ 1.191)	0.866
	class 3	154	1.715	0.835(0.692 ~ 1.006)	0.059	0.822(0.681 ~ 0.992)	0.041	0.851(0.702 ~ 1.030)	0.099
	All	759	1.936						

Note Model 1 was adjusted for gender and age. Model 2 was further adjusted for smoking and deprivation index based on Model 1 adjustments. Model 3 was further adjusted for alcohol consumption, physical activity, and BMI based on Model 2 adjustments. CD participants are classified into 3 latent classes using latent class analysis. The prevalence of all LTCs varies across each class. Abbreviation: IBD, inflammatory bowel disease; LTC, long-term condition, MACE, major adverse cardiovascular events, CI, confidence interval, HR, hazard ratio

Table 4 Adverse health outcomes for UC participants. Hazard ratios for all-cause mortality, MACE, and IBD-related surgeries

UC	LTC(class)	Number of events	Events per 100 person years	model 1		model 2		model 3	
				HR 95%CI	*P*	HR 95%CI	*P*	HR 95%CI	*P*
All-cause mortality	None	13	0.114	0.157(0.090 ~ 0.272)	< 0.001	0.164(0.095 ~ 0.286)	< 0.001	0.173(0.100 ~ 0.301)	< 0.001
	one LTC	33	0.255	0.314(0.221 ~ 0.446)	< 0.001	0.328(0.230 ~ 0.466)	< 0.001	0.340(0.239 ~ 0.485)	< 0.001
	class 1	238	1.143	1.180(0.924 ~ 1.506)	0.184	1.131(0.884 ~ 1.447)	0.327	1.140(0.889 ~ 1.461)	0.301
	class 2	179	2.100	1.191(1.006 ~ 1.411)	0.043	1.188(1.002 ~ 1.408)	0.047	1.205(1.016 ~ 1.431)	0.033
	class 3	77	0.762	2.467(2.059 ~ 2.955)	< 0.001	2.342(1.951 ~ 2.811)	< 0.001	2.221(1.837 ~ 2.684)	< 0.001
	class 4	102	0.313	0.322(0.259 ~ 0.401)	< 0.001	0.340(0.273 ~ 0.423)	< 0.001	0.345(0.276 ~ 0.432)	< 0.001
	All	596	0.827						
Major adverse cardiovascular events (MACE)	None	5	0.044	0.025(0.011 ~ 0.061)	< 0.001	0.026(0.011 ~ 0.063)	< 0.001	0.028(0.012 ~ 0.067)	< 0.001
	one LTC	38	0.294	0.154(0.111 ~ 0.213)	< 0.001	0.158(0.115 ~ 0.219)	< 0.001	0.165(0.119 ~ 0.228)	< 0.001
	class 1	546	2.622	0.546(0.436 ~ 0.683)	< 0.001	0.516(0.411 ~ 0.649)	< 0.001	0.518(0.412 ~ 0.652)	< 0.001
	class 2	506	5.937	1.588(1.411 ~ 1.787)	< 0.001	1.595(1.417 ~ 1.796)	< 0.001	1.575(1.398 ~ 1.775)	< 0.001
	class 3	84	0.831	6.832(6.053 ~ 7.711)	< 0.001	6.687(5.912 ~ 7.564)	< 0.001	6.422(5.659 ~ 7.288)	< 0.001
	class 4	65	0.199	0.070(0.054 ~ 0.090)	< 0.001	0.071(0.056 ~ 0.092)	< 0.001	0.073(0.057 ~ 0.094)	< 0.001
	All	1201	1.666						
IBD-related Operation	None	69	0.607	0.494(0.384 ~ 0.634)	< 0.001	0.497(0.387 ~ 0.639)	< 0.001	0.495(0.384 ~ 0.638)	< 0.001
	one LTC	119	0.920	0.822(0.675 ~ 1.001)	0.051	0.824(0.676 ~ 1.004)	0.055	0.835(0.685 ~ 1.018)	0.074
	class 1	271	1.301	1.263(1.083 ~ 1.474)	0.003	1.249(1.070 ~ 1.459)	0.005	1.218(1.041 ~ 1.425)	0.014
	class 2	106	1.244	1.119(0.907 ~ 1.380)	0.294	1.111(0.900 ~ 1.373)	0.329	1.122(0.905 ~ 1.390)	0.293
	class 3	142	1.405	1.525(1.266 ~ 1.836)	< 0.001	1.531(1.270 ~ 1.845)	< 0.001	1.538(1.274 ~ 1.858)	< 0.001
	class 4	267	0.818	0.596(0.510 ~ 0.696)	< 0.001	0.599(0.512 ~ 0.701)	< 0.001	0.602(0.513 ~ 0.706)	< 0.001
	All	786	1.090						

Note Model 1 was adjusted for gender and age. Model 2 was further adjusted for smoking and deprivation index based on Model 1 adjustments. Model 3 was further adjusted for alcohol consumption, physical activity, and BMI based on Model 2 adjustments. UC participants are classified into 4 latent classes using latent class analysis. The prevalence of all LTCs varies across each class. Abbreviation: IBD, inflammatory bowel disease; LTC, long-term condition, MACE, major adverse cardiovascular events, CI, confidence interval, HR, hazard ratio

A total of 1201 (22.3%) UC patients experienced MACE events during a median follow-up of 13.3 years, with the highest rate observed in the third class (pain and depression) and second class (hypertension and coronary heart disease). Compared to UC patients and those with no other LTCs, the fully adjusted HR for the third and second classes were (HR 6.422, 95% CI 5.659–7.288) and (HR 1.575, 95% CI 1.398–1.775), respectively (Table 4).

IBD-related operation

A total of 759 (25.9%) CD patients underwent IBD-related surgeries during a follow-up period of 13.4 years. In the fully adjusted Model 3, the highest rate for IBD-related surgery was observed in the first class (Pain, Depression, and Anxiety), with a fully adjusted HR of 1.217 (95% CI 0.983–1.506). The lowest rate for IBD-related surgery was observed in the third class (Hypertension, Pain, and Cancer), with a fully adjusted HR of 0.851 (95% CI 0.702–1.030) (Table 3). A total of 786 (14.6%) UC patients underwent IBD-related surgeries during a follow-up period of 13.3 years. In the fully adjusted Model 3, the highest rate for IBD-related surgery was observed in the third class (Many LTCs), with a fully adjusted hazard ratio (HR) of 1.538 (95% CI 1.274–1.858). The lowest rate for IBD-related surgery was observed in the fourth class (Few LTCs), with a fully adjusted HR of 0.602 (95% CI 0.513–0.706) (Table 4).

Upon applying the LCA models established for UC and CD patients to the entire population, we found that these models still demonstrated good generalizability, as detailed in Table S5. Besides, Table S6 presents the adverse health outcomes for IBD participants, specifically analyzing the hazard for all-cause mortality and MACE. The data show that the rate of all-cause mortality and MACE varies significantly across different latent classes. participants with no LTC had the lowest rate, while those in class 1 had the highest rate for both outcomes. These findings highlight the varying degrees of health rates among IBD patients based on their LCA.

Discussion

This study employed LCA to categorize CD and UC patients into three and four classes, respectively, based on a multitude of LTCs. Participants in different classes exhibited significant variations in distribution characteristics. Among CD patients, the first class (Pain and Depression) had a higher proportion of females, the second class primarily involved pain and hypertension, with

a majority of female participants. The third class predominantly featured hypertension and pain, with a higher proportion of male participants. Moreover, the third-class patients faced a significantly higher rate of mortality compared to CD participants without other LTCs, with a hazard ratio as high as 1.789. Among UC patients, the first class was characterized by hypertension and cancer, with a higher proportion of male participants. The second class predominantly involved cardiovascular diseases such as hypertension and coronary heart disease, with male participants as the majority. This class of patients exhibited a higher rate of all-cause mortality and MACE events compared to UC participants without other LTCs. The third class primarily featured pain and depression, with a predominant female presence. This class of patients faced significantly higher rates of mortality, MACE events, and IBD-related surgeries compared to UC participants without other LTCs. The fourth class is characterized by a predominance of pain and hypertension, with a higher proportion of female participants.

Multimorbidity is defined as the coexistence of two or more chronic diseases within an individual, a concept recently introduced into the population of IBD patients. Compared to non-IBD patients, individuals with IBD exhibit a higher prevalence of comorbidities [19]. Some studies have described the prevalence of diseases associated with IBD and explored the connections among various comorbidities. These studies posit a close association between comorbidities in IBD and higher rates of mortality, hospitalization, and unfavorable disease outcomes [20, 21]. Additionally, comorbidities accompanying IBD significantly impact the quality of life for patients, exacerbating economic burdens and treatment costs. Therefore, early identification and close monitoring of comorbidities are advantageous for enhancing treatment outcomes, improving the quality of life for IBD patients, and reducing treatment costs.

In our study, hypertension, pain, depression, and cancer are considered the four most common chronic comorbidities among IBD patients. Multiple studies indicate a close correlation between IBD and an increased likelihood of mental health disorders such as anxiety and depression [22–24]. In our study, depression predominates among comorbidities in the first class of CD patients and the third class of UC patients. A study in Switzerland suggests that cardiovascular diseases are considered the most common comorbidities in IBD [21], and a study in Finland includes hypertension among the comorbidities associated with IBD [19]. Consistent with our study findings, in CD, hypertension significantly dominates in comorbidity within the second and third classes, while in UC, the second class is primarily characterized by cardiovascular diseases such as hypertension and coronary heart disease. In each category, the rate of adverse health events (death, cardiovascular events, relevant surgeries) generally increases with the number of LTCs.

IBD progressively evolves into systemic chronic inflammation, where aberrant activation of inflammatory cells and abnormal release of inflammatory mediators (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6)) lead to endothelial dysfunction, reduced vascular dilation capacity, and inadequate tissue perfusion. This phenomenon may be closely associated with poor or non-healing of intestinal mucosal ulcers and the ineffectiveness of drug treatments [25]. Chronic inflammation can alter the composition and overall function of the intestinal microbiota, leading to the accumulation of harmful metabolic by-products [26]; long-term use of immunosuppressants to control inflammation can increase the rate of tumor development. Furthermore, IBD commonly induces malnutrition and anemia; long-term malnutrition is likely to result in electrolyte imbalances such as potassium and sodium disturbances, and prolonged use of IBD therapeutic drugs (glucocorticoids, immunosuppressants) can exacerbate the rate of hypertension [27]. IBD patients often experience prolonged discomfort and pain, coupled with the burden of disease progression, side effects of medication, and the psychological stress of repeated examinations, increasing the rate of depression and anxiety [28].

This study represents the first large prospective cohort investigation employing the LCA method and an extensive array of additional LTCs to classify patients with CD and UC. This approach assigns each participant to a specific class, revealing the significance of underlying patterns in an exploratory manner. Previous analyses of IBD were confined to exploring the intrinsic correlations among its various phenotypes, comorbidity prevalence and incidence, and relationships with multiple comorbidities [14]. Our study considered a comprehensive and extensive range of LTCs in UC and CD patients, incorporating a substantial amount of robust and high-quality long-term follow-up data on hospitalization and mortality rates. We extensively leveraged the analytical advantages of LCA, exploring the composite distribution characteristics of different patient classes and assessing their associated rates with death, cardiovascular events, and IBD-related surgeries. However, our study has several notable limitations. Firstly, our data are derived from self-reported UC, CD, and LTCs in the UK Biobank, which may introduce reporting errors or omissions. Additionally, participants in this database are typically voluntary UK residents and, therefore, cannot be considered a fully representative national sample. Furthermore, the operational complexity of using LCA to classify UC and CD patients with a broad spectrum of LTCs may impose limitations on its clinical applicability.

Conclusion

In this study, we investigated the characteristics of patients with CD and UC who possess LTCs, and conducted latent class analysis on UC and CD patients respectively using unsupervised machine learning, exploring the attributes of patients across different categories. In CD, Categories 1 and 3 exhibited higher rates of mortality and MACE compared to participants with no other LTCs or with only one LTC. In UC, Categories 2 and 3 demonstrated higher rates of death and MACE compared with participants without other LTCs or with only one LTC, with Categories 1 and 3 also having heightened rates of undergoing surgery related to IBD. In most categories, the rate of adverse outcome events increased with the number of LTCs. These findings are beneficial in elucidating the relationship between the type of IBD, the multimorbidity status, and the adverse outcomes associated with IBD, laying a solid foundation for future comprehensive consideration of multimorbidity patterns in the assessment, management, and treatment strategies of IBD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20638-y.

Supplementary Material 1

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Author contributions

Conceptualization: Yuqin Li, Tongyu Tang. Data curation: Fan Li, Yu Chang. Formal analysis: Fan Li, Yu Chang. Investigation: Zhaodi Wang, Zhi Wang, Qi Zhao, Xiaoping Han, Zifeng Xu, Chanjiao Yu, Yue Liu, Shiyu Chang, Hongyan Li, Sileng Hu. Methodology: Fan Li, Yu Chang. Project administration: Fan Li. Resources: Yuqin Li, Tongyu Tang. Software: Fan Li, Yu Chang. Supervision: Yuqin Li, Tongyu Tang. Validation: Zhaodi Wang, Zhi Wang, Qi Zhao. Xiaoping Han, Zifeng Xu. Visualization: Fan Li, Yu Chang. Writing -original draft: Fan Li, Yu Chang, Zhaodi Wang, Zhi Wang, Qi Zhao, Xiaoping Han, Zifeng Xu, Chanjiao Yu, Yue Liu, Shiyu Chang, Hongyan Li, Sileng Hu. Writing-review & editing: Yuqin Li, Tongyu Tang.

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Data availability

Sequence data that support the findings of this study can be downloaded here: https://www.ukbiobank.ac.uk/.

Declarations

Ethics approval and consent to participate

The UK Biobank received ethical approval from the North West Multi-center Research Ethics Committee, Manchester, U.K. (REC reference for UK Biobank 11/NW/0382), and all participants provided written informed consent.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]The First Hospital of Jilin University, No.1 Xinmin Street, Changchun 130012, China

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