

ORIGINAL ARTICLE

# Inflammatory bowel disease type influences development of elevated liver enzymes

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## Key words

Crohn's disease, inflammatory bowel disease, liver disease, transaminitis, ulcerative colitis.

Accepted for publication 8 October 2022.

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**Declaration of conflict of interest:** Mandana Khalili is a recipient of research grant (to her institution) from Gilead Sciences Inc, and Intercept Pharmaceuticals and she has served as consultant for Gilead Sciences Inc.

**Author contribution:** Yao-Wen Cheng and Richard McLean contributed to the acquisition of data. Yao-Wen Cheng, Justin L. Sewell, Chiung-Yu Huang, and Mandana Khalili contributed to analysis and interpretation of data. All authors contributed to study concept, design, manuscript drafting, and manuscript revision. All authors approved the final version of the manuscript.

**Financial support:** This work was in part supported by the National Institutes of Health, Grant Number K24AA022523 (M.K.) and P30 DK026743.

**Guarantor of the article:** Mandana Khalili, M.D.

## Abstract

**Background and Aim:** Up to a third of patients with inflammatory bowel disease (IBD) have elevated liver enzymes (ELE). We evaluated the incidence, predictors, and outcomes associated with ELE in a diverse and vulnerable IBD cohort.

**Methods:** We retrospectively evaluated 336 IBD patients receiving care at the San Francisco safety net gastroenterology clinics between June 1996 and December 2019. Baseline characteristics were captured at first visit, then patients were followed until last clinic activity or death. Testing and etiology, pattern of ELE defined as transient (<1 month) or persistent (≥1 month), were assessed. Multivariate modeling evaluated predictors of ELE at baseline, new ELE at follow-up, and pattern of ELE.

**Results:** Baseline median age was 40.3 years, 62% male, 46% White (13% Black, 19% Asian, and 18% Latino), and 59% had ulcerative colitis (UC). Among those without known liver disease ( $n = 14$ ), 51.6% (166 of 322; 52 at baseline, 114 during follow-up) had ELE. In multivariate logistic regression, 5-aminosalicylic acid use (odds ratio [OR] 2.2, 95% confidence interval [CI]: 1.07–4.4,  $P = 0.03$ ) and higher body mass index (OR 1.08, 95% CI: 1.02–1.14,  $P = 0.01$ ) were associated with baseline ELE. In multivariate Cox regression, UC (vs. Crohn's disease [CD]) had a 34% lower risk of developing new ELE during follow-up (hazard ratio [HR] 0.66, 95% CI: 0.46–0.95,  $P = 0.02$ ). Mortality rate was higher for patients with ELE (0% normal vs 2.3% transient ELE vs 6.5% persistent ELE,  $P < 0.001$ ).

**Conclusion:** ELE is prevalent in IBD, and associated with higher rates of mortality. Identification and management of ELE particularly when persistent are important to IBD outcomes.

## Introduction

The prevalence of elevated liver enzymes (ELE) in patients with inflammatory bowel disease (IBD) has ranged from 18 to 36%,<sup>1–3</sup> with the most common causes reported as primary sclerosing cholangitis (PSC), drug-induced hepatotoxicity with immunosuppressants such as azathioprine or methotrexate, and non-alcoholic fatty liver disease (NAFLD).<sup>4,5</sup> Limited data suggest that among patients with ELE, up to 60% of cases are transient abnormalities that resolve spontaneously.<sup>2</sup> For persistent ELE, up to 65% have been attributed to NAFLD.<sup>2</sup>

While there have been several reports that have evaluated ELE among IBD patients, the definition for ELE has varied widely.<sup>2,6,7</sup> The American College of Gastroenterology's guideline on the evaluation of abnormal liver enzymes has defined abnormal alanine aminotransferase (ALT) levels as that above 33 U/L for males and 25 U/L for females. Aspartate aminotransferase (AST) and alkaline phosphatase levels above the local lab's normal range are considered abnormal.

Prior studies have suggested that IBD patients with ELE have an age-adjusted risk of death at 4.8 times higher than those

IBD patients with normal liver enzymes (NLE).<sup>8</sup> Patients with IBD who have limited socioeconomic status may have poor outcomes due to low follow-up rates and less access to medical care; such disparities may disproportionately impact patients, especially those from racial or ethnic minority groups.<sup>9–11</sup> However, its impact on these vulnerable populations has not been studied. The aim of our study was to (i) investigate the incidence and pattern of ELE, (ii) document the etiology of ELE, (iii) characterize risk factors associated with developing ELE, and (iv) ascertain clinical outcomes in a diverse and vulnerable cohort of patients with IBD.

## Methods

**Patients.** In this retrospective cohort study, we identified adult patients (age  $\geq 18$  years) with a diagnosis of IBD and who were seen in the gastroenterology clinics at San Francisco General Hospital between June 1996 and December 2019. San Francisco General Hospital is a public safety net hospital serving the underserved and uninsured or publicly insured residents of San Francisco. Patients were excluded if they did not have liver enzyme tests recorded in their electronic medical records ( $n = 16$ ).

**Clinical and laboratory data.** From the medical record, we abstracted patient data at their initial gastroenterology clinic visit, which included baseline demographic, laboratory, and clinical data such as metabolic comorbidities (obesity, prediabetes/diabetes, hyperlipidemia, and hypertension), etiology of known liver disease, HIV status, and substance use (alcohol, intravenous drugs, and smoking). Detailed baseline IBD characteristics including type (Crohn's disease [CD] vs. ulcerative colitis [UC]), the extent and/or behavior of their IBD (based on Montreal classification<sup>12</sup>), history of IBD-related surgery, and use of IBD-related medications at their initial visit (5-aminosalicylic acids, immunomodulators, biologic therapy, and steroids within the past 6 months).

During follow-up, we recorded laboratory values at the time of ELE development and various testing performed for assessment of etiology including serologic testing (i.e. viral hepatitis A/B/C, NAFLD, autoimmune etiologies, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, and celiac disease), abdominal imaging, liver biopsy, and also referral to hepatology specialty clinic. The etiology of ELE was ultimately captured via positive testing results and/or explicit documentation in physician or provider notes. For those with ELE, we captured events occurring in the one-year preceding ELE, which included any hospitalizations, emergency department (ED) visits, use of steroids, change in IBD medication, and IBD-related surgeries. Patients were classified as having NAFLD if this diagnosis was explicitly documented in the medical record or if they fulfilled the criteria for NAFLD by the American Association for the Study of Liver Diseases guidelines.<sup>13</sup>

We also collected follow-up data, which included death, duration of follow-up, IBD-related surgery during follow-up, and use of immunomodulator and biologic therapy at the last clinic visit time point.

**Definitions.** We defined ELE as an AST or alkaline phosphatase value above the laboratory's upper limit of normal or an ALT value above 33 for males and 25 for females per the

American College of Gastroenterology guidelines.<sup>14</sup> We characterized ELE as transient if the ELE returned to normal within 1 month or persistent if it remained elevated beyond 1 month. We further characterized the pattern of ELE into cholestatic, hepatocellular, or mixed based on the R-factor equation.<sup>15,16</sup>

**Statistical analysis.** Baseline patient and IBD characteristics, and laboratory data were summarized using proportions for categorical variables, and medians, interquartile ranges (IQR), means, and SD for continuous variables, as appropriate. Comparisons between subgroups were performed using chi-squared tests for categorical variables and Kruskal–Wallis tests for continuous variables.

Multivariate logistic regressions were performed to identify risk factors associated with ELE at baseline. Candidate covariates included baseline patient and IBD characteristics with a  $P$ -value  $< 0.20$  in the univariate regressions, and variable selection was performed using a step-wise forward selection procedure. Separate multivariate logistic regression with the same variable selection procedure was applied to identify risk factors for persistent ELE (vs. transient ELE) after baseline liver function test (LFT) check and for persistent ELE at any time during follow-up, where candidate risk factors included baseline patient and IBD characteristics as well as clinical events within 1 year of ELE.

Time to new ELE from baseline among baseline NLE patients was summarized using the Kaplan–Meier method and compared between UC and CD using the log-rank test, where the censoring time for those who did not develop new ELE was set to be the date of the last clinical assessment for liver enzyme. Risk factors associated with new ELE were identified using Cox regressions. Moreover, competing risk analyses were performed to evaluate cumulative incidence and factors associated with development of transient ELE and persistent ELE among those with NLE at baseline. Cumulative incidence functions, as a function of time, were calculated and Fine–Gray models were fitted to identify risk factors associated with the two competing events. All the multivariate regression analyses adjusted for age, sex, race, IBD type, and duration of IBD, and a step-wise forward variable selection procedure was applied with an entry criterion of  $P < 0.05$  for candidate predictors. All statistical analyses were performed with SAS version 9.4. The study protocol was approved by the University of California San Francisco institutional review board.

Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

## Results

**Baseline characteristics.** Overall, 336 patients who met the inclusion criteria were identified. The median follow-up period of this cohort was 49.9 (IQR: 19.9–93.5) months. At baseline (i.e. their first gastroenterology clinic visit), 82.4% (277 of 336) had NLE and 17.6% (59 of 336) had ELE. Among those with ELE, the pattern of ELE was hepatocellular in 52.5% (31 of 59), cholestatic in 35.6% (21 of 59), and mixed in 11.9% (7 of 59). Table 1 summarizes overall patient characteristics stratified by NLE and ELE at baseline. Overall, 61.9% were male and the mean ( $\pm$ SD) age was 40.2 ( $\pm$ 13.3) years. Patient ethnicity was

**Table 1** Baseline patient characteristics stratified by normal versus elevated liver enzymes

Variable	Overall ( <i>n</i> = 336)	Normal liver enzymes ( <i>n</i> = 277)	Elevated liver enzymes ( <i>n</i> = 59)	<i>P</i> -value*
Age, mean (SD)	40.2 (13.3)	40.3 (13.6)	39.3 (11.4)	0.80
Sex: Male, <i>n</i> (%)	208 (61.9%)	163 (58.8%)	45 (76.3%)	<b>0.01</b>
Race, <i>n</i> (%)				0.41
White	154 (45.8%)	121 (43.7%)	33 (55.9%)	
Black	43 (12.8%)	35 (12.6%)	8 (13.6%)	
Latinx	63 (18.8%)	54 (19.5%)	9 (15.3%)	
Asian	63 (18.8%)	56 (20.2%)	7 (11.9%)	
Other	13 (3.9%)	11 (4.0%)	2 (3.4%)	
Medical comorbidities				
BMI, mean (SD)	25.4 (5.5)	25.1 (5.4)	26.7 (6.1)	0.06
Hypertension, <i>n</i> (%)	42 (12.5%)	32 (11.6%)	10 (17.0%)	0.26
Glucose status, <i>n</i> (%)				0.41
Prediabetes	28 (8.3%)	24 (8.7%)	4 (6.8%)	
Diabetes	9 (2.7%)	6 (2.2%)	3 (5.1%)	
None	299 (89.0%)	247 (89.2%)	52 (88.1%)	
Hyperlipidemia, <i>n</i> (%)	50 (14.9%)	37 (13.4%)	13 (22.0%)	0.09
HIV, <i>n</i> (%)	14 (4.2%)	8 (2.9%)	6 (10.2%)	<b>0.01</b>
Known liver disease, <i>n</i> (%)	14 (4.2%)	7 (2.5%)	7 (11.9%)	<b>0.001</b>
Substance use				
Current alcohol abuse, <i>n</i> (%)	129 (38.4%)	103 (37.2%)	26 (44.1%)	0.32
Current smoking, <i>n</i> (%)	78 (23.2%)	60 (21.7%)	18 (30.5%)	0.14
Current IV drug use, <i>n</i> (%)	26 (7.7%)	17 (6.1%)	9 (15.25%)	<b>0.02</b>
Liver enzymes				
ALT, median (IQR)	21 (15–30)	19 (15–24)	43 (33–70)	<b>&lt;0.0001</b>
AST, median (IQR)	22 (19–28)	21 (18–25)	35 (27–46)	<b>&lt;0.0001</b>
Alkaline phosphatase, median (IQR)	75 (62–92)	73 (61–89)	80 (69–116)	<b>&lt;0.001</b>

\*Bold represents *P*<0.05.

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; HIV, human immunodeficiency virus; IV, intravenous.

54.2% White, 12.8% Black, 18.7% Latinx, 18.7% Asian, and 3.9% identified as other. The mean body mass index (BMI) was 25.4 kg/m<sup>2</sup>, 12.5% had hypertension, 2.7% had diabetes, 14.9% had hyperlipidemia; 25.3% (85 of 336) had risk factors for NAFLD, and 6.9% (23 of 336) had confirmed NAFLD. Finally, 4.2% of patients had HIV infection.

With respect to IBD characteristics at baseline visit (Table 2), 58.6% of the eligible patients had UC. Among patients with UC, 41.1% had extensive colitis, 27.4% had left-sided colitis, and 26.4% had proctitis at baseline. The majority of patients with CD had colonic disease (40.3%) or ileocolonic disease (44.6%), and the majority had no penetrating or stricturing disease (54.7%). At the baseline initial gastroenterology clinic visit, 42% used 5-aminosalicylic acid (ASA), 6.3% used immunomodulators, and 4.5% used biologic agents. At last follow-up, use of immunomodulators was 20.3% and biologic agents was 31.8%.

**Etiology of ELE.** After excluding 14 patients with known liver disease at baseline, 51.6% (166 of 322) had ELE either at baseline (*n* = 52) or developed ELE during follow-up (*n* = 114). On evaluation, 54.2% (90 of 166) of these patients underwent a workup for ELE, which was transient in 45.6% (41 of 90), persistent in 46.7% (42 of 90), and unknown in 7.8% (7 of 90). Of the 76 patients who did not undergo workup, 43 (56.6%) had transient ELE, whereas 25 (32.9%) had persistent ELE, and in 7 (9.2%) status was unknown. The most commonly ordered tests

were liver imaging (68.9%; 62 of 90) and viral hepatitis serologies (94.4%; 85 of 90); other less common tests included assessment for celiac disease (42.2%; 38 of 90), autoimmune hepatitis (AIH, 38.9%; 35 of 90), and genetic liver diseases (30.0%; 27 of 90) such as Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency.

The etiology of ELE was identified with a documentation within physician/provider note or a positive serology for viral hepatitis. Ten percent (9 of 90) of these patients were referred to liver specialty clinic and 4.4% (4 of 90) underwent diagnostic liver biopsy. The documented etiology of ELE was primarily related to chronic liver disease (28.9%; 26 of 90), followed by medications (8.9%; 8 of 90), sepsis (2.2%; 2 of 90), and IBD flare (1.1%; 1 of 90). Among the eight patients with ELE attributed to medications, the offending medications were 6-MP in five patients and in one patient each they were infliximab, isoniazid, and sulfasalazine. In the 26 patients with diagnosis of chronic liver disease, 50% (13 of 26) had NAFLD, 15.4% (4 of 26) had hepatitis C, 7.7% (2 of 26) each had AIH, PSC, or alcohol-related, and 3.8% (1 of 26) each had celiac disease, chronic hepatitis B, or acute hepatitis A.

There was no documented etiology for ELE in 58.9% (53 of 90) patients of which 29 had transient ELE, 18 had persistent ELE, and 6 had only a single liver enzyme value documentation. Among those without documented ELE etiology, 26 were noted to have a history of heavy alcohol use.

**Table 2** Baseline inflammatory bowel disease characteristics stratified by normal and elevated liver enzymes

Variable	Overall (n = 336)	Normal liver enzymes (n = 277)	Elevated liver enzymes (n = 59)	P-value
Type of IBD, n (%)				0.68
Crohn's disease	139 (41.4%)	116 (41.9%)	23 (39.0%)	
UC	197 (58.6%)	161 (58.1%)	36 (61.0%)	
UC montreal classification, n (%)				0.47
Proctitis	52 (26.4%)	43 (26.7%)	9 (25.0%)	
Left-sided colitis	54 (27.4%)	47 (29.2%)	7 (19.4%)	
Extensive colitis	81 (41.1%)	64 (39.8%)	17 (47.2%)	
Unknown	10 (5.1%)	7 (4.4%)	3 (8.3%)	
Crohn's Location, n (%)				0.98
L1—Terminal ileum	12 (8.6%)	10 (8.6%)	2 (8.7%)	
L2—Colon	56 (40.3%)	46 (39.7%)	10 (43.5%)	
L3—Ileocolonic	62 (44.6%)	52 (44.8%)	10 (43.5%)	
Other	1 (0.7%)	1 (0.9%)	0	
Unknown	8 (5.8%)	7 (6.0%)	1 (4.6%)	
Crohn's behavior, n (%)				0.63
B1—No complications	76 (54.7%)	62 (53.5%)	14 (60.9%)	
B2—Stricturing	25 (18.0%)	23 (19.8%)	2 (8.7%)	
B3—Penetrating/perianal	21 (15.1%)	16 (13.8%)	5 (21.7%)	
Stricturing and penetrating	9 (6.5%)	8 (6.9%)	1 (4.3%)	
Unknown	8 (5.8%)	7 (6.0%)	1 (4.3%)	
Prior IBD-related surgery, n (%)	32 (9.5%)	27 (9.7%)	5 (8.5%)	0.76
5-Aminosalicylic acid use, n (%)	141 (42.0%)	114 (41.2%)	27 (45.8%)	0.51
Topical therapy, n (%)	59 (17.6%)	49 (17.7%)	10 (16.9%)	0.89
Immunomodulator use, n (%)	21 (6.3%)	17 (6.1%)	4 (6.8%)	0.85
Biologic use, n (%)	15 (4.5%)	14 (5.1%)	1 (1.7%)	0.26
Steroid use within the past 6 months, n (%)	55 (16.4%)	42 (15.2%)	13 (22.0%)	0.20

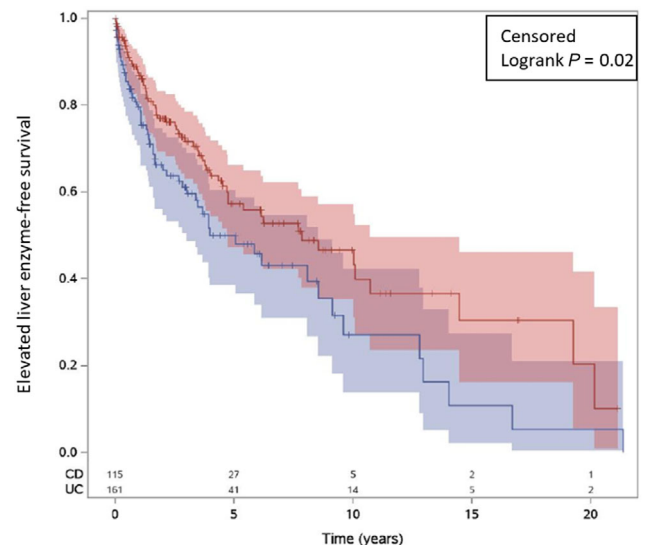
ASA, aminosalicylic acid; CD, Crohn's disease; CRP, C-reactive protein; IBD, inflammatory bowel disease; IQR, interquartile ratio; UC, ulcerative colitis.

**Factors associated with ELE at baseline.** Compared with patients with baseline NLE, patients with ELE were more likely to be male (76.3% vs 58.8%,  $P = 0.01$ ) and a higher proportion had HIV infection (10.2% vs 2.9%,  $P = 0.02$ ), IV drug use (15.2% vs 6.1%,  $P = 0.03$ ), and known chronic liver disease (11.9% vs 2.5%,  $P = 0.01$ ) (Table 1).

When excluding patients with known chronic liver disease, the factors that remained significantly associated with ELE at baseline in the multivariate logistic regression model were use of 5-ASA (odds ratio [OR] 2.2, 95% confidence interval [CI]: 1.1–4.4,  $P = 0.03$ ) and higher BMI (OR 1.1, 95% CI: 1.02–1.1,  $P = 0.01$ ) after adjusting for age, sex, race, IBD type, and duration of IBD (Table S1, Supporting information).

**Incidence of new ELE during follow-up among those with NLE at baseline and its associated risk factors.** Figure 1 shows the Kaplan–Meier curves for time to development of new ELE during follow-up stratified by UC versus CD. Patients with CD developed new ELE at a faster rate than those with UC ( $P = 0.02$ ). Among those with CD, 25% had developed ELE at 1.3 years (95% CI: 0.7–1.7) compared with 2.6 years (95% CI: 1.3–3.7) in those with UC, and 50% had developed ELE at 4 years (95% CI: 3.0–8.5) compared with 7.8 years (95% CI: 4.7–10.7) in those with UC. The risk of developing new ELE was also higher among those who were overweight/obese compared with those with normal weight. The median time to developing new ELE in patients with overweight/obesity was 4.5 years

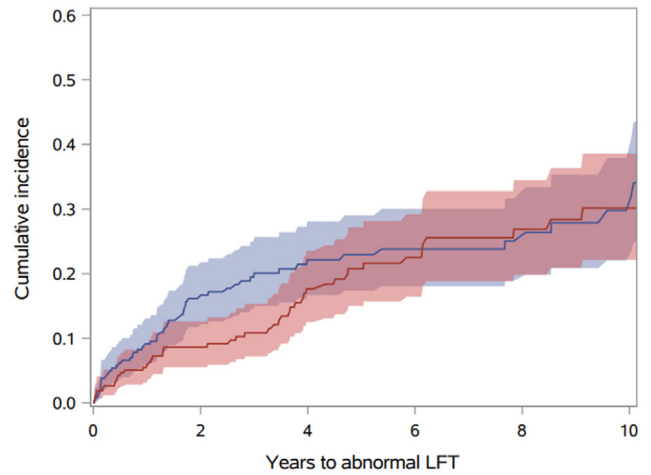
(95% CI: 2.6–9.1), compared with 7.7 (95% CI: 4.0–16.7) years in those with normal weight, but this did not reach statistical significance ( $P = 0.06$ ).



**Figure 1** Kaplan–Meier curve of time to development of elevated liver enzymes during follow-up for ulcerative colitis (UC) versus Crohn's disease (CD) patients. IBD type: (—), CD, Crohn's disease; (---), UC, ulcerative colitis.

In univariate Cox analysis, the only factor associated with development of new ELE was IBD type (UC compared with CD, hazard ratio [HR] 0.66, 95% CI: 0.46–0.94,  $P = 0.02$ ). When further adjusting for age, sex, race, and duration of IBD in a multivariate Cox model, UC was associated with a 34% lower risk of developing new ELE when compared with CD (HR 0.66, 95% CI: 0.46–0.95  $P = 0.02$ ). When evaluating the influence of disease severity on development of new ELE in UC patients with baseline NLE, univariate Cox regression found that those with extensive disease had a higher risk of developing new ELE compared with those with either left-sided UC or ulcerative proctitis (HR 1.88, 95% CI: 1.10–3.20,  $P = 0.02$ ). Similarly, among those with CD, patients with penetrating disease had higher risk of new ELE compared with those without penetrating and/or stricturing disease (HR 2.0, 95% CI: 1.03–4.0,  $P = 0.04$ ). However, these associations did not reach statistical significance in multivariate models that adjusted for age, sex, race, and duration of IBD (Table 3).

**Pattern of new ELE during follow-up among those with NLE at baseline and its associated risk factors.** Of the 277 patients with baseline NLE, 61 developed transient ELE and 51 persistent ELE during follow-up. The overall cumulative incidence of transient ELE and persistent ELE among those with NLE at baseline are shown in Figure 2. In the first 2 years of follow-up, the cumulative incidence of transient ELE was nearly twice that of persistent ELE (16.2% vs 8.6%), but by



**Figure 2** Cumulative incidence of development of transient and persistent elevated liver enzymes (ELE) at follow-up among those with normal baseline liver enzymes. LFT, liver function test. (■), Transient ELE; (■), persistent ELE.

5 years of follow-up, the cumulative incidence was similar at 23.0 and 20.8%, respectively.

No baseline patient and IBD characteristics as well as clinical events within 1 year of ELE were significantly associated with presence of persistent ELE *versus* transient ELE after baseline LFT check and at any time during follow-up when adjusting

**Table 3** Cox proportional hazards model of time to elevated liver enzymes during follow-up when excluding those with baseline elevated liver enzymes ( $n = 277$ )

Variables	Univariate Cox regression			Multivariate Cox regression		
	Hazard ratio	95% confidence interval	$P$ -value	Hazard ratio	95% confidence interval	$P$ -value
Age (decades)	0.96	0.84–1.11	0.60	0.97	0.84–1.11	0.66
Male (vs female)	1.21	0.83–1.76	0.31	1.22	0.84–1.78	0.30
White race (vs non-White)	1.04	0.71–1.51	0.85	0.96	0.66–1.41	0.85
IBD type (vs Crohn’s disease)	0.66	0.46–0.94	0.02	0.66	0.46–0.95	0.02
Duration of IBD (years)	0.99	0.97–1.01	0.44	0.99	0.97–1.02	0.47
HIV	1.91	0.78–4.70	0.16			
Hypertension	1.23	0.74–2.00	0.43			
Diabetes	1.58	0.50–5.00	0.44			
Hyperlipidemia	0.85	0.49–1.49	0.57			
Current alcohol abuse	0.88	0.60–1.29	0.51			
Current smoker	1.44	0.95–2.20	0.09			
History of IBD-related surgery	1.28	0.75–2.20	0.37			
Baseline 5-ASA	0.90	0.62–1.31	0.58			
Baseline topical medication	0.57	0.32–1.01	0.05			
Baseline immunomodulator	0.33	0.08–1.33	0.12			
Baseline biologic	0.63	0.20–1.99	0.43			
Baseline steroid	0.77	0.44–1.32	0.34			
Extensive UC (vs left-sided colitis or ulcerative proctitis)	1.88	1.10–3.20	0.02			
Ileocolonic CD (vs other distributions of CD)	1.04	0.61–1.77	0.88			
Penetrating CD (vs no complications of CD)	2.00	1.03–4.00	0.04			
Body mass index	1.01	0.98–1.50	0.45			

ASA, aminosalicylic acid; CD, Crohn’s disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.



**Table 4** Patient outcomes at last follow-up stratified by normal liver enzymes, acute, and persistent elevated liver enzymes

Variable	Overall	Normal liver enzymes (n = 157)	Transient elevated liver enzymes (n = 87)	Persistent elevated liver enzymes (n = 77)	P-value*
Duration of follow-up (month), median (IQR)	53.2 (21.2–97.8)	33.7 (13.2–66.8)	72.6 (31.5–117.6)	87.3 (53.2–123.7)	0.49
Patient disposition, n (%)					<b>&lt;0.001</b>
Death	7 (2.2%)	0 (0%)	2 (2.3%)	5 (6.5%)	
No longer followed in clinic	192 (59.8%)	111 (70.7%)	44 (50.6%)	37 (48.1%)	
Currently followed in clinic	122 (38.0%)	46 (29.3%)	41 (47.1%)	35 (45.5%)	
IBD-related surgery, n (%)	47 (14.6%)	13 (8.28%)	20 (23.0%)	14 (18.2%)	<b>0.004</b>
Immunomodulator exposure, n (%)	65 (20.3%)	23 (14.7%)	25 (28.7%)	17 (22.1%)	<b>0.03</b>
Biologic use, n (%)	102 (31.8%)	36 (22.9%)	45 (51.7%)	21 (27.3%)	<b>&lt;0.001</b>

\*Bold represents  $P < 0.05$ .

IBD, inflammatory bowel disease; IQR, interquartile range.

for age, sex, IBD type, and duration of IBD. When excluding ELE patients at baseline, in competing risk analysis of persistent ELE and transient ELE using Fine–Gray models, no significant associations with developing new persistent ELE were identified. However, presence of extensive UC at baseline (*vs.* non-extensive, subdistribution HR [sHR] 3.1, 95% CI: 1.5–6.3,  $P = 0.002$ ) and penetrating CD at baseline (*vs.* non-penetrating and/or stricturing, sHR 2.9, 95% CI: 1.3–6.9,  $P = 0.01$ ) were associated with development of new transient ELE in univariate Fine–Gray model. Moreover, the risk of developing transient ELE remained statistically significant for patients with extensive UC at baseline (*vs.* non-extensive, sHR 3.1, 95% CI: 1.4–7.1,  $P = 0.005$ ) after adjusting for age, sex, race, and duration of IBD (Table S2). On further evaluation, we noted that a greater proportion of those with extensive UC had hospitalizations (28.7% *vs.* 5.6%,  $P < 0.0001$ ) and steroid use (35.9% *vs.* 11.1%,  $P = 0.0002$ ) in the 1 year prior to transient ELE development compared with those with more limited disease distribution that may account for the observed relationship between the extent of disease and transient ELE.

**Patient disposition at end of follow-up.** At the end of follow-up, 36.9% continued to be followed in the gastroenterology clinics and 2.1% had died. Table 4 summarizes patient disposition in those with NLE, transient ELE, and persistent ELE. There were higher rates of mortality among patients with persistent ELE and higher rates of loss to follow-up among patients with NLE. A higher proportion of patients with either transient or persistent ELE had an IBD-related surgery during follow-up compared with those who had NLE (23.0% and 18.2% compared with 8.3%, respectively). Moreover, a higher proportion of patients with transient ELE had exposure to biologics, whereas a lower proportion of patients with NLE had exposure to immunomodulators.

## Discussion

Our study revealed that the incidence of ELE in this racially and ethnically diverse cohort of IBD patients was 53%, which is significantly higher than the 18–36% incidence rates found in prior studies of ELE in IBD patients of the general population.<sup>1–3</sup> Patients with ELE (especially persistent ELE) had higher mortality rates compared with those with NLE. While both medication

use and obesity were associated with ELE at baseline visit, IBD type was the only independent predictor of development of ELE during follow-up among those with NLE at baseline. Specifically, patients with CD were more likely to develop new ELE compared with those with UC on follow-up. Our data expand understanding of contributors to, and impact of, ELE among racially and ethnically diverse patients with IBD.

In our study, 5-ASA use and a higher BMI were associated with ELE at baseline. Elevated BMI may predispose patients to NAFLD, which in turn can cause ELE. In this health system, mesalamine is the most common (>95%) prescribed 5-ASA with a minority taking balsalazide or sulfasalazine. While sulfasalazine is more often associated with abnormal liver enzymes, mesalamine can also result in asymptomatic mild elevations of AST and ALT.<sup>17</sup>

We found that patients with CD had a 34% higher risk of developing new ELE during follow-up compared with those with UC. These data are consistent with the only other study that has investigated ELE by IBD type.<sup>6</sup> The design of our study does not permit us to determine the reasons for these differences, and this requires further investigation. However, considering recent data suggesting that the majority of IBD patients with NAFLD have CD rather than UC,<sup>18</sup> and that CD in the setting of NAFLD is associated with advanced fibrosis,<sup>19</sup> it is possible that the higher risk of ELE in CD may represent undiagnosed NAFLD. Practically, it may be advisable to follow liver tests more frequently for patients with CD to address modifiable factors, particularly given the increased risk for mortality among IBD patients with ELE.

Considering IBD phenotype, those with extensive UC were three times more likely to develop transient ELE during follow-up; there was no difference for persistent ELE. A possible explanation is that patients with extensive UC were more likely to be hospitalized and receive steroids in the 1 year prior to the acute ELE occurring. Conversely, there was no difference in ELE rates for different CD phenotypes. This likely reflects that CD phenotyping does not directly reflect the extent of bowel involvement and by extension degree of systemic inflammation.

Previous estimates of liver disease in patients with underlying IBD were between 2.3 and 5.8%.<sup>6,8,20</sup> In our population, 11.9% (40 of 336) of patients were identified as having chronic liver disease, the majority of which consisted of NAFLD (40%; 16 of 40), HCV (32.5%; 13 of 40), and alcohol use (10%; 4 of 40). Relatively high rates of substance use disorders in our

service population likely account for the observed HCV and alcohol-related liver disease rates.<sup>21,22</sup> Regarding NAFLD, Bessisow and colleagues have previously demonstrated that development of NAFLD was predicted by disease activity, disease duration, and prior surgery for IBD.<sup>23</sup> Our cohort had a relatively low percentage of patients who were overweight or obese compared with national estimates (36% vs 74%),<sup>24</sup> as well as low rates of hypertension, hyperlipidemia, and diabetes at baseline. Furthermore, 42.6% (11 of 26) of newly diagnosed instances of chronic liver disease were attributed to NAFLD in our study, suggesting that NAFLD may be under-recognized in those with IBD and may be present without traditional NAFLD risk factors.

Our study demonstrated a significant association difference in mortality between the type of ELE. Mortality was 0% among those with always normal LFTs, while it was 2.3% in transient ELE and 6.5% in persistent ELE. The only other study to evaluate links between ELE and mortality in IBD patients demonstrated similar findings (90.4% survival at 16 months for those with ELE vs. 98.5% for those with NLE).<sup>8</sup> The authors concluded that the age-adjusted risk of death was 4.8 times higher among patients with ELE. A total of seven deaths occurred in our study cohort, one related to liver disease and none directly related to IBD. It is most likely that ELE in patients who died reflected overall systemic illness, which may or may not be related to IBD.

Our study had several limitations. This was a retrospective study with baseline clinic visits occurring over a 23-year period, during which time substantial changes in treatment for IBD occurred. Namely, biologic therapies were introduced in the mid-1990s, recommended as salvage therapy in the early 2000s, and subsequently viewed as first-line therapies for severe disease in the top-down therapy paradigm.<sup>25–27</sup> Of patients with ELE, 45% did not undergo testing to identify the etiology of ELE (though only one-third of these had persistent ELE); it is unclear how this would systematically impact our analyses. Due to the inherent complexity of capturing multiple complex variables over an extended time period retrospectively, characteristics for IBD and patient comorbidities were only captured from baseline visit. Likewise, the study did not extensively evaluate the severity of IBD and instead measured IBD-related surgery and use of biologic agents as surrogates for disease severity.

In summary, we found that rates of ELE and chronic liver disease among patients in our diverse population with IBD were higher than rates previously reported among more general IBD populations,<sup>1–3</sup> and we confirmed associations between ELE and mortality. Clinicians should thoroughly investigate ELE, particularly when persistent, to promote optimal outcomes for patients with IBD.

**Data availability statement.** Datasets are restricted and not publicly available.

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

**Table S1.** Multivariable analysis of factors associated with elevated liver enzymes at baseline when excluding those with known chronic liver disease ( $n = 281$ ).

**Table S2.** Fine-Gray model of time to transient elevated liver enzymes follow-up when excluding those with baseline elevated liver enzymes.