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Influence of nonalcoholic fatty liver disease on inflammatory bowel disease hospitalizations in the United States

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Abstract

Background The reported prevalence of nonalcoholic fatty liver disease (NAFLD) in patients with inflammatory bowel disease (IBD) is 32%. We assessed the influence of NAFLD on IBD hospitalizations in the United States (US).

Methods We utilized the National Inpatient Sample database, from 2016-2019, to identify the total IBD hospitalizations in the US and we further subdivided them according to the presence or absence of NAFLD. Hospitalization characteristics, comorbidities and outcomes were compared. Statistical significance was set at P<0.05.

Results There were 1,272,260 IBD hospitalizations in the US, of which 5.04% involved NAFLD. For IBD hospitalizations with NAFLD, the mean age was 50-64 years, and the proportion of males was 46.97%. IBD hospitalizations with NAFLD had a lower proportion of African Americans (8.7% vs. 11.38%, P<0.001). Comorbidities such as hypertension (50.34% vs. 44.04%, P<0.001) and obesity (18.77% vs. 11.81%, P<0.001) were significantly higher in the NAFLD cohort. Overall, based on the Charlson Comorbidity Index, patients with NAFLD had a higher number of comorbidities (52.77% vs. 20.66%, P<0.001). Mortality was higher in the NAFLD compared to the non-NAFLD cohort (3.14% vs. 1.44%, P<0.001). Patients with NAFLD also incurred significantly higher hospital charges ($69,536 vs. $55,467, p<0.001) and had a longer mean length of stay (6.10 vs. 5.27 days, P<0.001) compared to the cohort without NAFLD. Complications and inpatient procedure requirements were also higher in the NAFLD cohort.

Conclusion Our study revealed greater mortality, morbidity, and healthcare resource utilization in patients with IBD who were hospitalized with a concomitant diagnosis of NAFLD.

Keywords Nonalcoholic fatty liver disease. inflammatory bowel disease, outcomes, mortality, costs

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Introduction

The spectrum of nonalcoholic fatty liver disease (NAFLD) encompasses a wide range of liver diseases, ranging from milder early hepatic steatosis to late-stage steatohepatitis [1]. Worldwide, NAFLD is believed to be the most common form of chronic liver disease, with a prevalence of 25% [2]. In the United States (US), about 33% of the adult American population have some degree of NAFLD [3]. Common risk factors implicated in developing NAFLD include obesity, metabolic syndrome, and insulin resistance [4]. The pathogenesis of NAFLD stems from insulin resistance and hyperinsulinemia. Hyperinsulinemia also promotes a proinflammatory environment with elevated cytokines, tumor necrosis factor-α, and endocrine disruption with higher leptin and lower adiponectin levels. This complex multifactorial process leads to steatotic deposits in the liver and promotes fibrosis of the hepatocytes and the surrounding extracellular matrix [5]. The diagnosis and grading of NAFLD are based on the absence of significant alcohol consumption, coexisting causes of chronic liver disease, and the extent of steatosis and

Conflict of Interest: None

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fibrotic changes within the liver [6]. NAFLD places a significant burden on the US healthcare system. The annual cost of care for a NAFLD patient with private insurance was estimated to be $7804 on average for a new diagnosis. In contrast, the total annual cost for a matched control with similar comorbidities but without NAFLD was $2298 [7].

Inflammatory bowel disease (IBD) results from an immune dysregulation of the gastrointestinal mucosa in response to intestinal microbes in genetically susceptible hosts [8,9]. It consists of two clinically distinct entities, Crohn's disease (CD) and ulcerative colitis (UC). The current literature reports that NAFLD may be seen in about one third of IBD patients [10]. Alterations in the gut microbiota, immunosuppressive therapy, colonic surgeries and total disease duration are considered possible predictors of NAFLD development in IBD patients [11,12]. However, there is a significant paucity of data on NAFLD and its influence on IBD hospitalizations. Hence, we utilized the National Inpatient Sample (NIS) to highlight and compare hospitalization characteristics and clinical outcomes of IBD hospitalizations with NAFLD and without NAFLD in the US.

Materials and methods

Design and data source

This retrospective cohort study used the NIS database to derive the study population for 2016-2019. The NIS database is a publicly available database of inpatient hospital stays derived from the billing data submitted by hospitals to statewide data organizations across the US, covering more than 97% of the US population [13,14]. The databases were entirely coded using the International Classification of Diseases, Tenth Revision, and Clinical Modification/Procedure Coding System (ICD-10-CM/PCS). The primary diagnosis was the main ICD-10 code for hospitalization.

Study population

The NIS database was searched for all adult (≥18 years) hospitalizations with a primary/principal discharge diagnosis of IBD in the US between 2016 and 2019. As the NIS database does not have any identifiers, it is safe to assume that the total IBD hospitalizations may include patients who were hospitalized either once or multiple times with the diagnosis of IBD. The study population was further subdivided based on the presence or absence of NAFLD. Patients with other causes leading to liver damage as mentioned in Supplementary Table 1 were excluded.

Outcome measures

A analysis was performed to compare IBD hospitalizations with and without NAFLD. We compared hospitalization characteristics, clinical outcomes, complications and healthcare burden. The Charlson Comorbidity Index (CCI) was used to control for the prognostic influence of multiple comorbidities on the outcomes. The CCI is a clinimetric index comprising the sum of 19 different medical conditions and their associated weights. It helps predict long-term mortality amongst hospitalized patients. Predictors of inpatient mortality for IBD hospitalizations with NAFLD were also analyzed.

Statistical analysis

Stata® version 16 software (StataCorp, Texas, USA) was used for the statistical analysis. All analyses were conducted using weighted samples for national estimates, in compliance with Healthcare Cost and Utilization Project (HCUP) regulations for using the NIS database. Descriptive statistics were provided, including mean (standard error of the mean) for continuous variables and count (percentage) for categorical variables. The Rao-Scott test was used to examine the association between categorical variables and the diagnosis of NAFLD for IBD. F-statistics from the weighted regression model tested the difference between the mean length of stay and total charge. Multivariable logistic regressions were used to examine the risk factors of death for IBD patients. All P-values were 2-sided, with 0.05 considered as the threshold for statistical significance.

Ethical considerations

The NIS database lacks patient and hospital-specific identifiers. In 2012, NIS also removed state-level and hospital identifiers. This has enhanced patient privacy, protection, and anonymity. Hence, this study was exempt from Institutional Review Board (IRB) approval.

Results

Hospitalization characteristics

Between 2016 and 2019, there were 1,272,260 IBD hospitalizations in the US. Of these hospitalizations, 64,090 IBD hospitalizations with NAFLD were compared to 1,208,170

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Table 1 Comparison of hospital characteristics, comorbidities, outcomes, and hospitalization characteristics in cohorts of patients with IBD, with or without NAFLD

Demographics	IBD with NAFLD	IBD without NAFLD	P-value
Baseline demographics (%)	64,090 (5.04%)	1,208,170 (94.96%)	<0.001
Type of IBD			
Crohn's disease	38,860 (60.63%)	770,745 (63.79%)	<0.001
Ulcerative colitis	25,720 (40.13%)	443,310 (36.69%)	<0.001
Mean age (years)			<0.001
18-34	7535 (11.76%)	252,760 (20.92%)	
34-49	14,945 (23.32%)	256,895 (21.26%)	
50-64	22,320 (34.83%)	294,925 (24.41%)	
65-79	16,075 (25.08%)	287,060 (23.76%)	
≥80	3215 (5.02%)	116,530 (9.65%)	
Sex (%)			<0.001
Men	30,095 (46.97%)	526,435 (43.59%)	
Women	33,980 (53.03%)	681,385 (56.41%)	
Race (%)			<0.001
White	49,620 (79.91%)	922,765 (78.81%)	
Black	5405 (8.70%)	133,235 (11.38%)	
Hispanic	4790 (7.71%)	69,960 (5.97%)	
Other	2280 (3.67%)	44,945 (3.84%)	
Expected primary payer (%)			0.0298
Medicare	27,980 (43.73%)	510,760 (42.33%)	
Medicaid	9345 (14.61%)	178,535 (14.80%)	
Private	22,435 (35.06%)	438,895 (36.37%)	
Uninsured	2230 (3.49%)	42,545 (3.53%)	
Other	1995 (3.12%)	35,855 (2.97%)	
Co-morbidities (%)			
Hypertension	32,260 (50.34%)	532,085 (44.04%)	<0.001
Diabetes	18,005 (28.09%)	207,500 (17.17%)	<0.001
Obesity	12,030 (18.77%)	142,720 (11.81%)	<0.001
Dyslipidemia	16,090 (25.11%)	288,810 (23.90%)	<0.001
Smoking	15,990 (24.95%)	304,795 (25.23%)	0.5012
Heart failure	7440 (11.61%)	135,485 (11.21%)	0.1813
Chronic kidney disease	6245 (9.74%)	97,860 (8.10%)	<0.001
Chronic pulmonary disease	13,920 (21.72%)	256,395 (21.22%)	0.2024
Atrial fibrillation	6355 (9.92%)	129,605 (10.73%)	7.8192
Peripheral vascular disease	3890 (6.07%)	66,740 (5.52%)	0.0120
Previous myocardial infarction	2455 (3.83%)	48,630 (4.03%)	0.2925
Colorectal cancer	420 (0.66%)	7,410 (0.61%)	0.5530
Charlson comorbidity index			<0.001
0	1545 (2.41%)	564,870 (46.75%)	
1	18,210 (28.41%)	242,640 (20.08%)	
2	10,515 (16.41%)	151,005 (12.50%)	
≥3	33,820 (52.77%)	249,655 (20.66%)	
Hospital characteristics			
Hospital location (%)			<0.001
Rural	3840 (5.99%)	88,685 (7.34%)	
Urban, non-teaching	11,905 (18.58%)	242,395 (20.06%)	
Urban, teaching	48,345 (75.43%)	877,090 (72.60%)	
Hospital size (%)			<0.001
Small	11,830 (18.46%)	237,585 (19.66%)	
Medium	17,060 (26.62%)	337,615 (27.94%)	
Large	35,200 (54.92%)	632,970 (52.39%)	
Hospital region (%)			<0.001
Northeast	11,880 (18.54%)	262,475 (21.73%)	
Midwest	15,630 (24.39%)	300,300 (24.86%)	
South	24,595 (38.38%)	439,885 (36.41%)	
West	11,985 (18.70%)	205,510 (17.01%)	

IBD, inflammatory bowel disease; NAFLD, nonalcoholic fatty liver disease

IBD hospitalizations without NAFLD. IBD hospitalizations with NAFLD had a higher proportion of patients with UC than the non-NAFLD cohort (40.1% vs. 36.7%, P<0.001). In contrast, the IBD hospitalizations without NAFLD had a higher proportion of patients with CD than the NAFLD cohort (63.8% vs. 60.6%, P<0.001).

We observed that IBD patients with NAFLD had more hospitalizations at a younger age (58.15% vs 45.67%, p<0.001 for ages 34-64 years) and a higher proportion of males (46.97% vs. 43.59%, P<0.001) compared to the non-NAFLD cohort. From a race perspective, IBD hospitalizations with NAFLD had a higher proportion of Whites (79.9% vs. 78.8%, P<0.001) and Hispanics (7.7% vs. 6%, P<0.001) compared to the non-NAFLD cohort, which had a higher proportion of African Americans (8.7% vs. 11.38%, P<0.001) (Table 1).

We also noted a higher proportion of patients with CCI score ≥3 (52.8% vs. 20.7%, P<0.001) for IBD hospitalizations with NAFLD compared to IBD hospitalizations without NAFLD. The IBD hospitalizations with NAFLD also had a higher proportion of comorbidities, such as hypertension (50.34% vs. 44.04%, P<0.001), type 2 diabetes mellitus (T2DM) (28.09% vs. 17.17%, P<0.001), dyslipidemia (25.11% vs. 23.09%, P<0.001), obesity (18.77% vs. 11.81, P<0.001), and chronic kidney disease (9.74% vs. 8.10%, P<0.001) compared to the IBD hospitalizations without NAFLD (Table 1).

Clinical outcomes

IBD hospitalizations with NAFLD had significantly higher all-cause inpatient mortality than IBD hospitalizations without NAFLD (3.1% vs. 1.4%, P<0.001). They also had higher race-specific mortality for Whites (3.12% vs. 1.49%, P<0.001), Blacks (2.59% vs. 1.13%, P<0.001), and Hispanics (3.44% vs. 1.27%, P<0.001). The cohort with NAFLD also had higher mortality for both males (3.36% vs. 1.55%, P<0.001) and females (2.94% vs. 1.36%, P<0.001). For all age groups, mortality was higher in the IBD hospitalizations with NAFLD than in those without NAFLD (Table 2).

Healthcare burden

The IBD hospitalizations with NAFLD had a longer mean length of stay (6.1 vs. 5.27 days, P<0.001) and mean total healthcare cost ($69,536 vs. $55,467, P<0.001) compared to the non-NAFLD cohort.

Complications

The NAFLD cohort had a higher proportion of complications, such as acute kidney injury (22.69% vs. 15.63%, P<0.001), acute respiratory failure (6.65% vs. 4.62%, P<0.001), shock (2.02% vs. 1.07%, P<0.001), acute liver failure (1.37% vs. 0.655, P<0.001), peritonitis (3.07% vs. 2.04%, P<0.001), *Clostridioides difficile* (*C. difficile*) infection (5.14% vs. 4.35%, P<0.001) and malnutrition (4.22% vs. 3.55%, P<0.001) (Table 2). The cohort of IBD hospitalizations with NAFLD did not have a higher chance of undergoing surgery like colectomy and ileectomy or having surgical complications (Table 2).

Predictors of inpatient mortality

Increasing age (adjusted odds ratio [aOR] 1.041, 95% confidence interval [CI] 1.038-1.045, P<0.001) and higher CCI (for CCI=2, aOR 3.742, 95%CI 3.186-4.394, P<0.001; and for CCI>3, aOR 6.587, 95%CI 5.613-7.730, P<0.001) were identified to be independent predictors of all-cause inpatient mortality for IBD hospitalizations with NAFLD (Table 3).

Discussion

To our knowledge, this is the first national study to examine the influence of NAFLD on inpatient outcomes in IBD patients. We compared 1,208,170 IBD hospitalizations without NAFLD to 64,090 IBD hospitalizations with NAFLD. We noted a higher mean age, male predominance, and a greater proportion of Whites and Hispanics in the IBD hospitalizations with NAFLD. We noted higher values for all-cause mortality (3.14% vs. 1.44%, P<0.001), length of stay by 0.83 days, healthcare burden by $14,069, and complications such as acute kidney injury, acute respiratory failure, and shock for IBD hospitalizations with NAFLD. Those patients also had higher age-specific, race-specific, and sex-specific mortality. Increasing age and a higher comorbidity burden were independent predictors of mortality in hospitalized IBD patients with NAFLD.

NAFLD is a global pandemic in the modern world. Numerous studies have confirmed the epidemiological burden of NAFLD in IBD [16,17]. Nevertheless, there are no screening guidelines for NAFLD in the general population or those with IBD [15]. Our study provides gastroenterologists with real-world information about the influence of NAFLD on IBD hospitalizations and identifies individuals at higher risk of adverse clinical outcomes.

The risk of combined NAFLD and IBD has been associated with inflammation, a prolonged disease course and immunosuppressive therapy [18]. Advancing age, male sex, higher body mass index and prior surgery have also been associated with developing NAFLD in IBD patients [18,19]. The peak prevalence of NAFLD is reported in individuals between the ages of 50 and 65 years, mostly attributed to the increased risk of metabolic syndromes with aging [20,21]. Our study also shows a higher mean age for IBD hospitalizations with NAFLD, correlating to increased risk with prolonged inflammation and a longer disease course. Numerous studies have also shown an increased prevalence of NAFLD in males [22]. One of the most widely accepted explanations is the lower risk from gynoid

Table 2 Comparison of clinical outcomes in IBD with NAFLD and IBD without NAFLD cohorts

Outcomes	IBD with NAFLD	IBD without NAFLD	P-value
Disposition			<0.001
Routine (home)	42,425 (66.24%)	837,335 (69.35%)	
Transfer to short-term hospital	1920 (3.00%)	24,250 (2.01%)	
Transfer to another facility: skilled nursing facility or intermediate care facility	7035 (10.98%)	135,255 (11.20%)	
Home healthcare	9630 (15.04%)	172,160 (14.26%)	
Discharge against medical advice	1010 (1.58%)	21,005 (1.74%)	
Inpatient mortality (%)	2010 (3.14%)	17,420 (1.44%)	<0.001
Sex-specific inpatient mortality (%)			
Male	1010 (3.36%)	8,180 (1.55%)	<0.001
Female	1000 (2.94%)	9,235 (1.36%)	<0.001
Race-specific inpatient mortality (%)			
White	1545 (3.12%)	13,760 (1.49%)	<0.001
African American	140 (2.59%)	1510 (1.13%)	<0.001
Hispanic	165 (3.44%)	890 (1.27%)	<0.001
Others	105 (4.61%)	745 (1.66%)	<0.001
Age-group specific inpatient mortality			
18-34	100 (1.33%)	550 (0.22%)	<0.001
34-49	235 (1.57%)	1105 (0.43%)	<0.001
50-64	715 (3.20%)	3875 (1.31%)	<0.001
65-79	780 (4.85%)	7015 (2.45%)	<0.001
≥80	180 (5.60%)	4875 (4.18%)	0.0863
Mean length of stay (days)	6.10 (0.07)	5.27 (0.02)	<0.001
Mean total healthcare cost (in US Dollars)	69,536 (1227)	55,467 (483)	<0.001
Complications			
Acute kidney injury	14,540 (22.69%)	188,810 (15.63%)	<0.001
Acute respiratory failure	4265 (6.65%)	55,820 (4.62%)	<0.001
Shock	1295 (2.02%)	12,880 (1.07%)	<0.001
Acute liver failure	1,745 (2.72%)	4,555 (0.38%)	<0.001
Need for pressors	875 (1.37%)	7,820 (0.65%)	<0.001
Need for dialysis	710 (1.11%)	9,185 (0.76%)	<0.001
Need for mechanical ventilation	1,805 (2.82%)	18,580 (1.54%)	<0.001
Intestinal perforation	445 (0.69%)	10,385 (0.86%)	0.0452
Intestinal strictures	2,900 (4.52%)	58,920 (4.88%)	0.0722
Megacolon	45 (0.07%)	870 (0.07%)	0.9411
Clostridioides difficile colitis	3,295 (5.14%)	52,615 (4.35%)	<0.001
Malnutrition	2,705 (4.22%)	42,875 (3.55%)	<0.001
Colectomy	1,275 (1.99%)	46,185 (3.83%)	0.8923
Ileostomy/Ilectomy	3,405 (5.32%)	89,175 (7.38%)	0.0781

IBD, inflammatory bowel disease; NAFLD, nonalcoholic fatty liver disease

gluteal-femoral subcutaneous fat distribution compared to the higher risk seen with android visceral adiposity. This is because upper body subcutaneous and visceral fat deposition, especially the abdominal, is associated with a higher risk for type 2 diabetes and cardiovascular disease. Lower body fat deposits, such as gluteal or femoral, are related to metabolic health and a lower risk for abnormalities of glucose and lipid homeostasis [23]. However, with increasing age, females also have an equally high risk of developing NAFLD, mostly due to changes in adiposity patterns [23]. Similarly, in our study there was a higher proportion of males in the IBD hospitalizations with NAFLD compared to females.

A recent study by Kubiliun *et al* assessed the impact of known genetic variants. It revealed that African American individuals generally carried fewer risk-increasing alleles for the development of NAFLD, compared to Whites and Hispanics [24]. Although most studies agree that the prevalence of NAFLD is lowest in African-Americans and highest in Hispanics, few demonstrate variability in the prevalence of NAFLD when comparing Whites with Hispanics. It has been theorized that this variation is due to differences in geography and diagnostic modalities [25]. Studies by Lazo *et al* and Trico *et al* showed a higher prevalence of NAFLD in Hispanics, followed by whites [26,27]. Kasarala *et al* noted similar racial patterns, with White (odds ratio [OR] 1.13, 95%CI 1.04-1.22; P<0.001) and Hispanic (OR 1.52, 95%CI 1.34-1.73; P<0.001) populations showing a higher percentage of NAFLD, whereas the African American population (OR 0.592, 95%CI 0.518-0.678; P<0.001) had a lower proportion of NAFLD [28]. We also noted racial disparities in our study, with the NAFLD cohort having a greater proportion of Hispanics and Whites, while the non-NAFLD cohort had

Table 3 Multivariable logistic regression of IBD patients with NAFLD that died

Predictors of mortality	aOR	95%CI	P-value
Age	1.041	1.038-1.045	<0.001
Sex			
Male, N (%)	Reference	0.950-1.113	0.493
Female, N (%)	1.028		
Charlson comorbidity index	Reference	2.229-3.053	<0.001
0	2.609	3.186-4.394	<0.001
1	3.742	5.613-7.730	<0.001
2	6.587		
≥3			
Complications			
Acute liver failure	3.893	3.157-4.799	<0.001
Need for pressors	2.968	2.435-3.618	<0.001
Need for dialysis	1.850	1.483-2.308	<0.001
Need for mechanical ventilation	7.200	6.337-8.180	<0.001
Intestinal perforation	3.301	2.432-4.480	<0.001
Intestinal strictures	1.159	0.952-1.410	0.141
Megacolon	1.941	0.676-5.573	0.218
Clostridioides difficile colitis	1.730	1.510-1.983	<0.001

IBD, inflammatory bowel disease; NAFLD, nonalcoholic fatty liver disease

a higher percentage of African Americans (Table 1). This disparity has been mainly attributed to variables such as lifestyle, dietary habits, genetic differences and socioeconomic factors [29]. The Western diet has more processed foods and includes more red meat, and high amounts of saturated fats and high-sugars [24].

Studies have demonstrated that T2DM, hypertension, dyslipidemia, and prior surgery were associated with a greater risk of NAFLD in IBD patients [17]. Emerging evidence shows that patients with chronic kidney disease, with or without dialysis, are more likely to develop hepatic steatosis due to inflammation, oxidative stress, insulin resistance, atherogenic dyslipidemia and various metabolic defects [30]. In a retrospective study of 80,000 patients, IBD was also associated with a greater risk of chronic kidney disease, especially in the younger patient population (hazard ratio 7.88, 95%CI 2.56-24.19; P<0.05). However, the pathophysiology is not completely understood [31]. Hypertension and cardiovascular disease are strongly linked with the aging of the liver via various molecular and cellular processes, which can enhance the development of NAFLD [32]. IBD is also independently associated with a greater risk of atherosclerotic cardiovascular disease, heart failure and atrial fibrillation. This is linked to shared risk factors, such as obesity, T2DM, gut microbiome dysfunction, and IBD disease progression or its treatment [33]. Similarly, in our study, there was a higher proportion of patients with hypertension, obesity, T2DM and chronic kidney disease in the NAFLD cohort compared to the non-NAFLD cohort (Table 1).

Prior bowel resection has been associated with a higher incidence of NAFLD and IBD concurrently. This association has been noted in multiple studies [10,34]. The pathophysiology was theorized to be small intestinal bacterial overgrowth, activation of toll-like receptor-4 leading to increased intestinal inflammation [35,36]. In our study, ileostomy as a complication in the IBD hospitalizations with NAFLD was statistically significant (OR 0.68, 95%CI 0.56-0.83; P=0.001). This is a unique finding that warrants further investigation.

With the recent advances in clinical practice and the evolution of biological and non-biological IBD treatments, the previously noted higher mortality risk in the IBD population has seen an overall improvement in the last decade [37]. In IBD populations, studies suggest a higher mortality rate in patients with UC compared to CD [38]. A study by Abomhya *et al* compared CD and NAFLD patients to NAFLD alone and found that patients with CD and concomitant NAFLD did not have higher mortality [39]. According to a study by Nooriyan *et al*, patients with CD and NAFLD were at a higher risk of death compared to those with CD alone (adjusted hazard ratio [aHR] 2.72, 95%CI 1.68-4.42; P<0.001) however the same was not true for patients with UC and NAFLD (aHR 1.35, 95%CI 0.79-2.32; P=0.27) [40]. In our study, we noted greater inpatient mortality among IBD hospitalizations with NAFLD compared to the non-NAFLD cohort (3.1% vs. 1.4%, P<0.001). Age-specific, sex-specific and race-specific mortality was also higher in patients with NAFLD.

A multivariate logistic regression analysis of risk factors in IBD hospitalizations with and without NAFLD showed that increasing age and comorbidities are major contributors to inpatient mortality. Although cardiovascular disease is reported to be most the common cause of death overall, our study interestingly did not show this association with inpatient mortality [41-43]. Our study also showed a higher risk of acute kidney injury including need for hemodialysis, lung injury with associated acute liver failure, and poor respiratory outcomes needing mechanical ventilator support, in patients with NAFLD. The underlying pathogenesis of NAFLD with increased hepatic factors, hepatokines (angiopoietin-like protein 4, fetal globulins and fibroblast growth factor), along with impaired reticuloendothelial system activity and inflammatory mediators contribute to the subsequent kidney, liver and lung injury patterns [44,45].

Based on a study by Peery *et al*, the annual health care expenditure estimated for gastrointestinal disease was $135.9 billion, with IBD accounting for $7.2 billion [46]. It is clear that IBD makes a substantial contribution to the increased healthcare burden in terms of total healthcare cost and increased use of healthcare services. NAFLD further amplifies this cost. In a study conducted by Allen *et al*, using a large national administrative claims database, it was found that the annual healthcare costs for NAFLD were almost double beyond the initial peri-diagnosis period ($3789 vs. $2298 per subject) [7]. Our study noted a higher mean total healthcare cost ($69,536 vs. $55,467, P<0.001) and a longer mean length of stay in the NAFLD cohort as compared to the non-NAFLD cohort. This is most likely due to more complications of disease courses resulting from different comorbidities, medical and surgical management, and other acute care needs. Higher

admissions were noted in urban teaching hospitals (75.43%), constituting two-thirds of total inpatient admissions for NAFLD patients, followed by urban non-teaching (18.58 %) and rural hospitals (5.99%). Additionally, larger hospitals were found to have more than half of the admissions for NAFLD with IBD, with the rest going to medium and small hospitals. This may be mostly because large academic centers are usually tertiary care referral centers and accept complex and advanced patients. They also have highly trained and specialized physicians, along with the resources necessary for the management of complications, when compared to non-teaching urban and rural centers.

Our study had several strengths. The data for this study were gathered from the NIS, the largest multi-ethnic national database encompassing IBD hospitalizations. Additionally, our study was designed to analyze many items of outcome-oriented and biodemographic information and provides a comprehensive detailing of the magnitude of this disease. It will also help physicians understand the magnitude and burden of this disease. This positive association of hospital outcomes in patients of IBD with NAFLD warrants the benefits of a prospective study that can help physicians with resource allocation, predicting hospitalization courses and in turn improving prognostication.

However, our study is not without its limitations. There were inherent limitations due to its retrospective nature. The usage of ICD codes means that coding errors and misclassification cannot be excluded. The data analyzed were not from individual patients, but rather hospitalizations of IBD patients. Another limitation of the NIS data is an appropriate ICD-10-based billing of the disease and risk factors by providers. This might have introduced record bias by underreporting and potential misclassification of NAFLD patients into the non-NAFLD group. However, given the nature of the study and the database that was used, it is not possible to estimate the patient population that had NAFLD but were not tested or previously diagnosed. Hence, a more prospective study with both test and control arms will give a better understanding of these patterns and eliminate this record bias altogether.

Nevertheless, our sample size and analysis provide more information and a unique perspective on the impact of NAFLD in IBD patients. Large, multicenter prospective studies are needed to further investigate these associations and the associated risk of morbidity and mortality.

In conclusion, NAFLD is an important consequence of IBD. Our study found that IBD hospitalizations with NAFLD had higher all-cause inpatient mortality than non-NAFLD IBD patients (3.1% vs. 1.4%, P<0.001). NAFLD-IBD cohort patients also had a longer mean length of stay and greater total healthcare costs. This cohort of patients was also predisposed to a greater extent to severe complications, such as acute kidney injury, acute respiratory failure, acute liver failure and *C. difficile* infection, among others. More research into the association between the duration of IBD, IBD medication history and the development of NAFLD may provide a more thorough understanding of the correlation between NAFLD and IBD.

Summary Box

What is already known:

- Nonalcoholic fatty livery disease (NAFLD) is more prevalent in patients with inflammatory bowel disease (IBD) as compared to the general population
- Patients with concomitant Crohn's disease and NAFLD have higher mortality
- The annual cost of care for a NAFLD patient with private insurance was estimated to be higher than the total annual costs for a matched control with similar comorbidities but without NAFLD

What the new findings are:

- IBD hospitalizations with NAFLD had a longer length of stay and higher healthcare costs
- They were also associated with a higher risk of complications such as acute kidney injury, respiratory failure, and a need for inpatient procedures
- Greater age and number of comorbidities are predictors of in-patient mortality in patients with IBD and NAFLD

References

1. Soni A, Yekula A, Singh Y, et al. Influence of non-alcoholic fatty liver disease on non-variceal upper gastrointestinal bleeding: a nationwide analysis. *World J Hepatol* 2023;**15**:79-88.
2. Cotter TG, Rinella M. Nonalcoholic fatty liver disease 2020: the state of the disease. *Gastroenterology* 2020;**158**:1851-1864.
3. AlShaalan R, Aljiffry M, Al-Busafi S, Metrakos P, Hassanain M. Nonalcoholic fatty liver disease: noninvasive methods of diagnosing hepatic steatosis. *Saudi J Gastroenterol* 2015;**21**:64-70.
4. Paschos P, Paletas K. Non alcoholic fatty liver disease and metabolic syndrome. *Hippokratia* 2009;**13**:9-19.
5. Golbidi S, Laher I. Exercise induced adipokine changes and the metabolic syndrome. *J Diabetes Res* 2014;**2014**:726861.
6. Ando Y, Jou JH. Nonalcoholic fatty liver disease and recent guideline updates. *Clin Liver Dis (Hoboken)* 2021;**17**:23-28.
7. Allen AM, Van Houten HK, Sangaralingham LR, Talwalkar JA, McCoy RG. Healthcare cost and utilization in nonalcoholic fatty liver disease: real-world data from a large U.S. claims database. *Hepatology* 2018;**68**:2230-2238.
8. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009;**361**:2066-2078.
9. Neuman MG. Immune dysfunction in inflammatory bowel disease. *Transl Res* 2007;**149**:173-186.
10. Lin A, Roth H, Anyane-Yeboa A, Rubin DT, Paul S. Prevalence of nonalcoholic fatty liver disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2021;**27**:947-955.
11. Bringiotti R, Ierardi E, Lovero R, Losurdo G, Di Leo A, Principi M. Intestinal microbiota: the explosive mixture at the origin of inflammatory bowel disease? *World J Gastrointest Pathophysiol* 2014;**5**:550-559.
12. Miele L, Valenza V, La Torre G, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty

liver disease. *Hepatology* 2009;**49**:1877-1887.
13. Healthcare Cost and Utilization Project. Introduction to the HCUP National Inpatient Sample (NIS). The national (nationwide) inpatient sample database documentation. Rockville, MD: Agency for Healthcare Research and Quality. Available from: https://hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp [Accessed 8 August 2023].
14. Healthcare Cost and Utilization Project (HCUP). December 2022. Agency for Healthcare Research and Quality, Rockville, MD. Available from: https://hcup-us.ahrq.gov/reports/methods/methods.jsp [Accessed 8 August 2023].
15. Noureddin M, Ntanios F, Malhotra D, et al. Predicting NAFLD prevalence in the United States using National Health and Nutrition Examination Survey 2017-2018 transient elastography data and application of machine learning. *Hepatol Commun* 2022;**6**:1537-1548.
16. Magrì S, Paduano D, Chicco F, et al. Nonalcoholic fatty liver disease in patients with inflammatory bowel disease: Beyond the natural history. *World J Gastroenterol* 2019;**25**:5676-5686.
17. Zamani M, Alizadeh-Tabari S, Singh S, Loomba R. Meta-analysis: prevalence of, and risk factors for, non-alcoholic fatty liver disease in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2022;**55**:894-907.
18. Bessissow T, Le NH, Rollet K, Afif W, Bitton A, Sebastiani G. Incidence and predictors of nonalcoholic fatty liver disease by serum biomarkers in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2016;**22**:1937-1944.
19. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011;**34**:274-285.
20. Principi M, Iannone A, Lasurdo G, et al. Nonalcoholic fatty liver disease in inflammatory bowel disease: prevalence and risk factors. *Inflamm Bowel Dis* 2018;**24**:1589-1596.
21. Dong F, Zhang Y, Huang Y, et al. Long-term lifestyle interventions in middle-aged and elderly men with nonalcoholic fatty liver disease: a randomized controlled trial. *Sci Rep* 2016;**6**:36783.
22. Lonardo A, Nascimbeni F, Ballestri S, et al. Sex differences in nonalcoholic fatty liver disease: state of the art and identification of research gaps. *Hepatology* 2019;**70**:1457-1469.
23. Fried SK, Lee MJ, Karastergiou K. Shaping fat distribution: new insights into the molecular determinants of depot- and sex-dependent adipose biology. *Obesity (Silver Spring)* 2015;**23**:1345-1352.
24. Kubiliun MJ, Cohen JC, Hobbs HH, Kozlitina J. Contribution of a genetic risk score to ethnic differences in fatty liver disease. *Liver Int* 2022;**42**:2227-2236.
25. Samji NS, Snell PD, Singal AK, Satapathy SK. Racial disparities in diagnosis and prognosis of nonalcoholic fatty liver disease. *Clin Liver Dis (Hoboken)* 2020;**16**:66-72.
26. Tricò D, Caprio S, Rosaria Umano G, et al. Metabolic features of nonalcoholic fatty liver (NAFL) in obese adolescents: findings from a multiethnic cohort. *Hepatology* 2018;**68**:1376-1390.
27. Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. *Am J Epidemiol* 2013;**178**:38-45.
28. Kasarala G, Sheri G, Harvin G. Non-alcoholic fatty liver disease in inflammatory bowel disease. *Am Coll Gastroenterol* 2017;**112**:S352.
29. Riazi K, Swain MG, Congly SE, Kaplan GG, Shaheen AA. Race and ethnicity in non-alcoholic fatty liver disease (NAFLD): a narrative review. *Nutrients* 2022;**14**:4556.
30. Behairy MA, Sherief AF, Hussein HA. Prevalence of non-alcoholic fatty liver disease among patients with non-diabetic chronic kidney disease detected by transient elastography. *Int Urol Nephrol* 2021;**53**:2593-2601.
31. Vajravelu RK, Copelovitch L, Osterman MT, et al. Inflammatory bowel diseases are associated with an increased risk for chronic kidney disease, which decreases with age. *Clin Gastroenterol Hepatol* 2020;**18**:2262-2268.
32. Alqahtani SA, Schattenberg JM. NAFLD in the elderly. *Clin Interv Aging* 2021;**16**:1633-1649.
33. Chen B, Collen LV, Mowat C, et al. Inflammatory bowel disease and cardiovascular diseases. *Am J Med* 2022;**135**:1453-1460.
34. Zou ZY, Shen B, Fan JG. Systematic review with meta-analysis: epidemiology of nonalcoholic fatty liver disease in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2019;**25**:1764-1772.
35. Barron L, Courtney C, Bao J, et al. Intestinal resection-associated metabolic syndrome. *J Pediatr Surg* 2018;**53**:1142-1147.
36. Barron LK, Bao JW, Aladegbami BG, et al. Toll-like receptor 4 is critical for the development of resection-associated hepatic steatosis. *J Pediatr Surg* 2017;**52**:1014-1019.
37. Opstelten JL, Vaartjes I, Bots ML, Oldenburg B. Mortality after first hospital admission for inflammatory bowel disease: a nationwide registry linkage study. *Inflamm Bowel Dis* 2019;**25**:1692-1699.
38. Roberts SE, Williams JG, Yeates D, Goldacre MJ. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. *BMJ* 2007;**335**:1033.
39. Abomhya A, Mahmoodurrahman M, Ayaz S, Hamad H, Khan F. Burden and predictors of non-alcoholic fatty liver disease in a retrospective cohort of patients with Crohn's disease. *Gastroenterology Res* 2022;**15**:82-90.
40. Noorian S, Jeon Y, Nguyen MT, Sauk J, Limketkai BN. The impact of NAFLD on hospitalization outcomes in patients with inflammatory bowel diseases: nationwide analysis. *Inflamm Bowel Dis* 2022;**28**:878-887.
41. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;**363**:1341-1350.
42. Ma W, Wu W, Wen W, et al. Association of NAFLD with cardiovascular disease and all-cause mortality: a large-scale prospective cohort study based on UK Biobank. *Ther Adv Chronic Dis* 2022;**13**:20406223221122478.
43. Lin Y, Gong X, Li X, et al. Distinct cause of death profiles of hospitalized non-alcoholic fatty liver disease: a 10 years' cross-sectional multicenter study in China. *Front Med (Lausanne)* 2020;**7**:584396.
44. Chen L, Lv X, Kan M, Wang R, Wang H, Zang H. Critical overview of hepatic factors that link non-alcoholic fatty liver disease and acute kidney injury: physiology and therapeutic implications. *Int J Mol Sci* 2022;**23**:12464.
45. Gjurašin B, Jeličić M, Kutleša M, Papić N. The impact of nonalcoholic fatty liver disease on severe community-acquired pneumonia outcomes. *Life (Basel)* 2022;**13**:36.
46. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2018. *Gastroenterology* 2019;**156**:254-272.

Supplementary material

Supplementary Table 1 ICD-10 Codes

Condition	Codes
Ulcerative colitis	K51 (K51.1, K51.2, K51.3, K51.5, K51.8, K51.9), K51.013, K51.213, K51.313, K51.913, K51.813
Crohn's disease	K50 (K50.1, K50.8, K50.9), K50.913, K50.113, K50.813, K50.112, K50.012
Nonalcoholic fatty liver disease	(K72.1x, K72.9x, K74.0-2, K74.6x, K75.8x, K75.9, K76.0, K76.89, K76.9, and K77)
Alcohol use disorder	G621×x, F10×x, I426, Elixhauser comorbidity
Chronic liver disease with mention of alcohol	K70×x
Autoimmune hepatitis	K754
Budd-Chiari syndrome	I820
Chronic passive congestion of liver	K761
Clonorchiasis	B661
Disorders of porphyrin and bilirubin metabolism	E80×x
Echinococcus of liver	B670, B675, B678
Fascioliasis	B663
Fabry disease	E7521
Gaucher disease	E7522, E770, E771
Hemochromatosis	E8311.xx
Hepatitis A virus	B15×x
Hepatitis B virus	B16×x, B180, B181, B191×x
Hepatitis C virus	B171×x, B192×x, B182
Unspecified and other disorders of lipoprotein metabolism	E788×x, E789
Opisthorchiasis	B660
Non-alcoholic steatohepatitis	K75.81
Cirrhosis	K74.6, K70.3, K70.2, K76.1, K71.7, K74.69

Amyloidosis	E85×x
Defects in the complement system	D841
Other specified/ unspecified disorders of the liver	K71.xx, K74.4, K75.0-4, K76.2-5, K73×x
Primary biliary cholangitis	K74.3, K74.5
Primary sclerosing cholangitis	K83.01
Syphilis of the liver	A52.74
Wilson's disease	E8301
Other viral hepatitis	B170, B172, B178, B179, B188, B189, B190, B1991
Dyslipidemia	E78.0, E78.00, E78.01, E78.1, E78.2, E78.3, E78.4, E78.5, E78.81, E78.89, E88.89, E78.9
Smoking	Z72.0, Z87.891, F17.200, O99.33x
Known/prior coronary artery disease	I25.10, I25.11x, I25.5, I25.6, I25.70x, I25.71x, I25.72x, I25.73x, I25.75x, I25.76x, I25.79x, I25.81x, I25.82, I25.83, I25.84, I25.89, I25.9
Chronic kidney disease	N18.1, N18.2, N18.3, N18.4
Atrial fibrillation	I48.0, I48.1, I48.2, I48.91
Prior myocardial infarction	I25.2
Colorectal cancer	C18.X

Comorbidities	Corresponding ICD-10 codes
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, 142.5-I42.9, I43.x, I50.x, P29.0
Peripheral vascular disorders	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Hypertension	110.x, I11.x-I13.x, I15.x
Chronic pulmonary disease	I27.8, 127.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Diabetes, uncomplicated	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes, complicated	E10.2-E10.8, E11.2-E11.8, E12.2-E12.8, E13.2-E13.8, E14.2-E14.8
Obesity	E66.x

Outcomes	ICD 10 codes
Acute kidney Injury	N17/N17.9 , N17.1 , N17.2 , N17.8 , N17.0
Acute respiratory failure	J96.0, J96.01, J96.02
Acute liver failure	K72.0 , K72.01
Shock	R57.0, R57.8, R57.9, R57
Need for pressors	3E030XZ, 3E033XZ, 3E040XZ, 3E043XZ, 3E050XZ, 3E053XZ, 3E060XZ, 3E063XZ
Need for dialysis	5A1D00Z, 5A1D60Z, 3E1M39Z
Need for mechanical ventilation/need for endotracheal intubation	OBH17EZ
Intestinal perforation	K63.
Intestinal strictures	K56.60, K56.69, K56.5
Megacolon	K59.39, K59.3 , K59.31
Intestinal fistula	K31.6, K63.2, K60.3, K60.5, N82.3, N82.2
Intestinal abscess	K63.0
Clostridioides difficile colitis	A04.72, A04.7
Malnutrition	E44.0, E44.1