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BRIEF ARTICLE

Nonalcoholic fatty liver disease is associated with benign gastrointestinal disorders

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Abstract

AIM: To explore associations between nonalcoholic fatty liver disease (NAFLD) and benign gastrointestinal and pancreato-biliary disorders.

METHODS: Patient demographics, diagnoses, and hospital outcomes from the 2010 Nationwide Inpatient Sample were analyzed. Chronic liver diseases were identified using International Classification of Diseases, the 9th Revision, Clinical Modification codes. Patients with NAFLD were compared to those with other chronic liver diseases for the endpoints of total hospital charges, disease severity, and hospital mortality. Multivariable stepwise logistic regression analyses to assess for the independent association of demographic, comorbidity, and diagnosis variables with the event of NAFLD (*vs* other chronic liver diseases) were also performed.

RESULTS: Of 7800441 discharge records, 32347 (0.4%) and 271049 (3.5%) included diagnoses of NAFLD and other chronic liver diseases, respectively. NAFLD patients were younger (average 52.3 years *vs* 55.3 years), more often female (58.8% *vs* 41.6%), less often black (9.6% *vs* 18.6%), and were from higher income areas (23.7% *vs* 17.7%) compared to counterparts with other chronic liver diseases (all $P < 0.0001$). Diabetes mellitus (43.4% *vs* 28.9%), hypertension (56.9% *vs* 47.6%), morbid obesity (36.9% *vs* 8.0%), dyslipidemia (37.9% *vs* 15.6%), and the metabolic syndrome (28.75% *vs* 8.8%) were all more common among NAFLD patients (all $P < 0.0001$). The average total hospital charge ($39607 *vs* $51665), disease severity scores, and intra-hospital mortality (0.9% *vs* 6.0%) were lower among NALFD patients compared to those with other chronic liver diseases (all $P < 0.0001$). Compared with other chronic liver diseases, NAFLD was significantly associated with diverticular disorders [OR = 4.26 (3.89-4.67)], inflammatory bowel diseases [OR = 3.64 (3.10-4.28)], gallstone related diseases [OR = 3.59 (3.40-3.79)], and benign pancreatitis [OR = 2.95 (2.79-3.12)] on multivariable logistic regression (all $P < 0.0001$) when the latter disorders were the principal diagnoses on hospital discharge. Similar relationships were observed when the latter disorders were associated diagnoses on hospital discharge.

CONCLUSION: NAFLD is associated with diverticular, inflammatory bowel, gallstone, and benign pancreatitis disorders. Compared with other liver diseases, patients with NAFLD have lower hospital charges and mortality.

Key words: Nationwide inpatient sample; Nonalcoholic fatty liver disease; Chronic liver disease; Diverticular disease; Pancreatitis; Gallstones; Inflammatory

bowel disease

Core tip: This study analyzed the 2010 Nationwide Inpatient Sample to compare outcomes and associations between patients with nonalcoholic fatty liver disease (NAFLD) and other chronic liver diseases. Compared with other liver diseases, NAFLD is associated with diverticular, inflammatory bowel, gallstone, and benign pancreatitis disorders when these latter disorders are considered as either the principal or associated diagnoses on discharge. These associations suggest shared mechanisms of pathology between NAFLD and these benign gastrointestinal disorders. Furthermore, patients with NAFLD have lower hospital mortality and consume fewer healthcare resources compared to patients with other chronic liver diseases.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States[1]. Outpatient primary care and specialist cohort series report prevalence proportions of 25%-46%[2-4]. Yet the proportion of hospitalized patients diagnosed with NAFLD is unknown. The prevalence of NAFLD in hospitalized patients maybe similar to outpatient cohorts given the associations between NAFLD and disorders common among hospitalized patients--including diabetes, cardiovascular disease, venous thromboembolism, colorectal cancer, and inflammatory bowel disease[5-13]. Conversely, NAFLD may comprise a small percentage of chronic liver disease among hospitalized patients because hepatic complications (such as ascites, variceal bleeding, and hepatocellular carcinoma) are less common with NAFLD compared to hepatitis B, hepatitis C, and alcohol associated liver diseases[10,14-19]. Finally, it is unclear if NAFLD is widely recognized by health care providers. This knowledge gap is important given recent small, single institutional studies suggesting relationships between NAFLD and benign digestive and pancreato-biliary disorders including diverticular disease, gallstone disorders, and inflammatory bowel disease[20-23]. Recognition of associations between NAFLD and these conditions may reveal insights into the pathologic mechanisms of all disorders.

The objectives of this study were to estimate the prevalence of the diagnosis of NAFLD among hospitalized patients in the United States and to explore associations between NAFLD and benign gastrointestinal and pancreato-biliary disorders.

MATERIALS AND METHODS

Database

Data were abstracted from the 2010 Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (AHRQ). The 2010 NIS contains discharge information from 1051 non-Federal, short-term, general, and specialty hospitals located in 45 states; approximating a 20% stratified sample of United States community hospitals[24]. This study was deemed exempt by the Institutional Review Board at the University of Maryland School of Medicine.

Sample identification

This study comprised patients with a diagnosis of chronic liver disease and compared patients with NAFLD *vs* any other chronic liver disease. All 25 diagnoses listed in each record were searched in creating each subsample in this study. The International Classification of Diseases, the 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code of 571.8 ("other chronic nonalcoholic liver disease") was used to identify the NAFLD subsample. The "other chronic liver disease" subsample was identified using diagnosis codes describing other recognized etiologies of chronic liver disease, chronic liver disease of unknown etiology, and viral infections and errors in mineral metabolism which may lead to chronic liver disease (Table 1). Patient discharge records with diagnoses representing other liver diseases were eliminated from the NAFLD subsample. To eliminate records with possible alcoholic liver disease from the NAFLD subsample, records which included diagnoses pertaining to ethanol abuse, dependence, and/or overdose (Table 1) were removed from the NAFLD subsample. Similarly, records with an ICD-9-CM diagnosis code of 571.8 were eliminated from the "other chronic liver disease"subsample. Nationwide prevalence estimates were calculated using both unweighted and discharge weights, which account for the number of calendar quarters for which each hospital contributed discharges to the NIS[24,25].

Demographics and diagnoses

The location of patient's residence included central counties of greater than one million population, fringe counties of metropolitan areas of greater than one million population, counties in metropolitan areas of 250000-999999 population, counties in metropolitan areas of 50000-249999 population, and micropolitan counties in areas of less than 50000 population. The reported median income is the median income for the population in the zip code from which the patient pertaining to that particular discharge record resides[25].

All diagnoses were searched to determine the presence of obesity (ICD-9-CM codes 278, 278.0, 278.00, 278.01, 278.02, or 278.03) and dyslipidemia (ICD-9-CM codes 272, 272.0, 272.1, 272.2, 272.3, 272.4, 272.5, 272.8, or 272.9). The presence of associated diagnoses (principal or secondary) were determined using the clinical classifi-

Table 1 International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes used to identify disease

	ICD-9-CM diagnosis	Diagnosis
The "other liver disease" cohort	571	Chronic liver disease and cirrhosis
	571	Alcoholic fatty liver
	571.1	Acute alcoholic hepatitis
	571.2	Alcoholic cirrhosis of liver
	571.3	Alcoholic liver damage, unspecified
	571.4	Chronic hepatitis
	571.4	Chronic hepatitis unspecified
	571.41	Chronic persistent hepatitis
	571.42	Autoimmune hepatitis
	571.49	Other chronic hepatitis
	571.5	Cirrhosis of liver without mention of alcohol
	571.6	Biliary cirrhosis
	571.9	Other unspecified chronic liver disease without mention of alcohol
	573	Other disorders of liver
	573.1	Hepatitis in viral diseases classified elsewhere
	573.2	Hepatitis in other infectious diseases classified elsewhere
	573.3	Hepatitis, unspecified
	573.8	Other specified disorders of liver
	573.9	Unspecified disorder of liver
	70	Viral hepatitis
	70	Viral hepatitis A with hepatic coma
	70.1	Viral hepatitis A without mention of hepatic coma
	70.2	Viral hepatitis B with hepatic coma
	70.2	Viral hepatitis B with hepatic coma, acute or unspecified without hepatitis delta
	70.21	Viral hepatitis B with hepatic coma, acute or unspecified with hepatitis delta
	70.22	Chronic viral hepatitis B with hepatic coma without hepatitis delta
	70.23	Chronic viral hepatitis B with hepatic coma with hepatitis delta
	70.3	Viral hepatitis b without mention of hepatic coma
	70.3	Viral hepatitis B without mention of hepatic coma, acute or unspecified, without mention of hepatitis delta
	70.31	Viral hepatitis B without mention of hepatic coma, acute or unspecified, with hepatitis delta
	70.32	Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta
	70.33	Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta
	70.4	Other specified viral hepatitis with hepatic coma
	70.41	Acute hepatitis C with hepatic coma
	70.42	Hepatitis delta without mention of active hepatitis B disease with hepatic coma
	70.43	Hepatitis E with hepatic coma
	70.44	Chronic hepatitis C with hepatic coma
	70.49	Other specified viral hepatitis with hepatic coma
	70.5	Other specified viral hepatitis without mention of hepatic coma
	70.51	Acute hepatitis C without mention of hepatic coma
	70.52	Hepatitis delta without mention of active hepatitis B disease or hepatic coma
	70.53	Hepatitis E without mention of hepatic coma
	70.54	Chronic hepatitis C without mention of hepatic coma
	70.59	Other specified viral hepatitis without mention of hepatic coma
	70.6	Unspecified viral hepatitis with hepatic coma
	70.7	Unspecified viral hepatitis c
	70.7	Unspecified viral hepatitis C without hepatic coma
	70.71	Unspecified viral hepatitis C with hepatic coma
	70.9	Unspecified viral hepatitis without mention of hepatic coma
	V02.6	Carrier or suspected carrier of viral hepatitis
	V02.60	Viral hepatitis carrier, unspecified
	V02.61	Hepatitis B carrier
	V02.62	Hepatitis C carrier
	V02.69	Other viral hepatitis carrier
	275	Disorders of iron metabolism
	275.01	Hereditary hemochromatosis
	275.02	Hemochromatosis due to repeated red blood cell transfusions
	275.03	Other hemochromatosis
	275.09	Other disorders of iron metabolism
	275.1	Disorders of copper metabolism
Alcohol abuse, dependence, and/or overdose	291	Alcohol-induced mental disorders
	291	Alcohol withdrawal delirium
	291.1	Alcohol-induced persisting amnestic disorder
	291.2	Alcohol-induced persisting dementia
	291.3	Alcohol-induced psychotic disorder with hallucinations
	291.4	Idiosyncratic alcohol intoxication
	291.5	Alcohol-induced psychotic disorder with delusions

291.8	Other specified alcohol-induced mental disorders
291.81	Alcohol withdrawal
291.82	Alcohol-induced sleep disorder
291.89	Other alcoholic psychosis
291.9	Unspecified alcohol-induced mental disorders
303	Alcohol dependence syndrome
303	Acute alcoholic intoxication
303	Acute alcoholic intoxication in alcoholism unspecified drinking behavior
303.01	Acute alcoholic intoxication in alcoholism continuous drinking behavior
303.02	Acute alcoholic intoxication in alcoholism episodic drinking behavior
303.03	Acute alcoholic intoxication in alcoholism in remission
303.9	Other and unspecified alcohol dependence
303.9	Other and unspecified alcohol dependence unspecified drinking behavior
303.91	Other and unspecified alcohol dependence continuous drinking behavior
303.92	Other and unspecified alcohol dependence episodic drinking behavior
303.93	Other and unspecified alcohol dependence in remission

ICD-9-CM: International classification of diseases, 9th revision, clinical modification.

Table 2 Clinical classification software categories used to identify comorbidities and associated diagnoses

CCS Category	Diagnosis
98 and 99	Hypertension
49 and 50	Diabetes mellitus
138	Esophageal disorders (excluding ICD-9-CM diagnoses f.or varices)
139	Gastroduodenal ulcer
140	Gastritis and/or duodenitis
141	Other disorders of stomach and duodenum
142	Appendicitis
143	Abdmoninal and groin hernia
144	Inflammatory bowel diseases
145	Intestinal obstruction
146	Diverticular disease
147	Anal and rectal conditions
148	Peritonitis and intestinal abscess
149	Benign biliary tract disease
152	Benign pancreatic disorders excluding diabetes mellitus
153	Gastrointestinal hemorrhage
154	Noninfectious gastroenteritis

CCS: Clinical classification software categories; ICD-9-CM: International classification of diseases, 9th revision, clinical modification.

Table 3 Disease Staging© (Thomson Reuters) classification system used to identify principal discharge diagnoses

Discharge category	Description
GIS03, GIS04, GIS18	Benign anal-rectal disorders
GIS05	Appendicitis
GIS09 or GIS37	Inflammatory bowel disease
GIS10	Diverticular disease
GIS17 or GIS84	Gastroduodenitis
GIS19	Hernia
GIS20	Esophagitis
GIS25-30, HEP11, GIS82-83	Upper gastrointestinal cancers
GIS31	Gastroduodenal ulcer
HEP01 or HEP 84	Gallstone related disorders
HEP12 or HEP85	Non-malignant pancreatitis
HEP81 or HEP82	Hepatobiliary malignancies

cation software provided by the AHRQ[26] (Table 2). Criteria for the metabolic syndrome include the presence of any three of obesity, diabetes mellitus, hypertension, and dyslipidemia[27,28]. Principal discharge diagnoses were also identified by the Disease Staging© (Thomson Reuters) classification system[29] (Table 3). The all patient refined diagnosis related group (APR-DRG© 3M) assesses severity of illness and mortality risk of the DRG pertaining to each patient discharge record[30].

Statistical analysis

Discrete and continuous variables were compared using χ^2 and Student's *t* tests with two-sided *P* values. Multivariable stepwise logistic regression analyses to assess for the independent association of each variable with the event of NAFLD were performed. The *P* value for variable entry and stay was 0.05. OR point estimates with 95% Wald confidence limits are reported. Results for those variables that did not stay in each model were not reported. Two multivariable analyses were performed-one using associated diagnoses and another using principal diagnoses. SAS© Version 9.2 (SAS Institute, Inc., Cary, NC, United States) was used to perform all analyses.

RESULTS

Patient demographics and comorbidities

Of the 7800441 discharge records in the 2010 NIS, 314109 (4.0%) included a diagnosis describing any chronic liver disease (Figure 1). After excluding patients with diagnoses describing ethanol abuse, dependence, and/or overdose and those with other chronic liver diseases in addition to NAFLD, 32347 (0.4%) records contained the NAFLD diagnosis. Similarly, 271049 (3.5%) records included diagnosis codes describing other chronic liver diseasesand did not include NAFLD. When using discharge weighted analyses, 3.9% of all discharge records included a principal or secondary diagnosis describing any chronic liver disease. 0.4% and 3.4% records included diagnoses describing NAFLD and other chronic liver diseases excluding NAFLD, respectively.

NAFLD patients were younger, more often female, and less often black compared to counterparts with other chronic liver diseases (Table 4). Diabetes mellitus, hypertension, obesity, and dyslipidemia were all more common

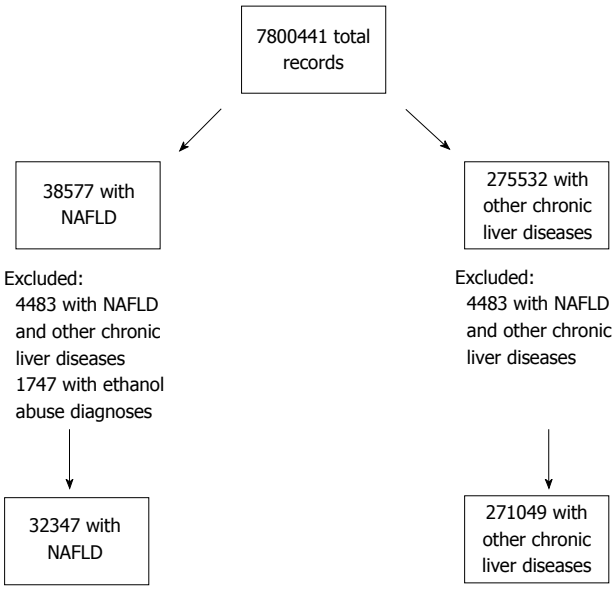

Figure 1 Identification of nonalcoholic fatty liver disease and "other chronic liver diseases" subsamples from the Nationwide Inpatient Sample. NAFLD: Nonalcoholic fatty liver disease.

among NAFLD patients. Nearly 29% of the patients in the NAFLD subsample had the metabolic syndrome. NAFLD patients were from higher income areas and more often had private health insurance. The average total hospital charge and length of hospital stay were significantly shorter than among patients with other chronic liver diseases. Rates of NAFLD intra-hospital mortality and advanced APRDRG mortality and disease severity scores were all significantly lower than among patients with other chronic liver diseases.

Associated gastrointestinal and pancreato-biliary disorders

As a *principal or secondary* (*e.g.,* associated) diagnoses, abdominal hernia, appendiceal disorders, benign biliary and pancreatic disorders, diverticular disease, non-variceal esophageal disorders, gastritis/duodenitits, gastroduodenal ulcer, inflammatory bowel disease, and intestinal infection were all significantly more common among NAFLD patients (Table 5). Conversely, gastrointestinal and hepatobiliary malignancies, gastrointestinal hemorrhage, and peritonitis/intra-abdominal abscess were all more common among patients with other chronic liver diseases. NAFLD patients were more likely to have a *principal* diagnosis on discharge of appendicitis, benign pancreatitis, diverticular disease, esophagitis, gallstone disorders, gastroduodenitis, and inflammatory bowel disease. In contrast, benign ano-rectal disorders, gastroduodenal ulcers, and hepatobiliary cancers were more common among patients with other chronic liver diseases.

All variables with statistically significant differences ($P < 0.05$) on univariable analysis (Table 4) were included in multivariable logistic regression models. When considering each gastrointestinal, hepatic, or pancreato-biliary diagnosis as an associated diagnosis, the patterns of association observed on univariable comparisons were maintained on multivariable logistic regression (Table 5). When considering each disorder as the *principal* diagnosis, appendicitis, benign pancreatitis, diverticular disease, esophagitis, gallstone disorders, Gastroduodenitis, and hernia were all associated with NAFLD on multivariable logistic regression (Table 6). Hepatobiliary cancers were independently associated with other liver diseases. In both analyses, female gender, younger patient age, diabetes mellitus, obesity, dyslipidemia, higher income, and private health insurance were independently associated with NAFLD.

Subgroup analysis for selected disorders

We performed subgroup analyses of records with a principal discharge diagnosis of diverticular disease, gallstone related disordersor benign pancreatitis. We chose these disorders because of their high prevalence in our sample. When stratified by type of background liver disease, similar differences in ethnicity, gender, comorbidities, health insurance payer, age, hospital charges, and income existed for each subgroupas in the overall sample (Table 7). As in the overall sample, total hospital charges, length of hospital stay, discharge disposition, rates of hospital death and APRDRG mortality and disease severity scores were all greater among patients with other chronic liver diseases in each subgroup.

DISCUSSION

The diagnosis of NAFLD among hospitalized patients is much less common compared to that noted in outpatient cohort studies[2-4]. Our findings that patients with NAFLD were more likely to be female, obese, and non-Black and more likely have diabetes mellitus, hypertension, dyslipidemia, and the metabolic syndrome compared to patients with other chronic liver diseases is in agreement with other studies[10,14-19]-suggesting that our methods to identify these patients were accurate. Similarly, patients with other liver diseases were more frequently from low-income regions and less likely to have private insurance as the primary health care payer; reflecting the higher prevalence of hepatitis C viral infections and alcohol abuse in low-income areas. The discrepancy in prevalence of NAFLD in outpatient series compared with hospitalized patients shows that NAFLD is underrecognized in hospital patients and that the impact of NAFLD on clinical outcomes and health care resource utilizationis unrecognized.

NAFLD is associated with several benign gastrointestinal and pancreato-biliary disorders. The exceptions were gastrointestinal hemorrhage and peritonitis, which are expected to occur in patients with decompensated liver disease and thus are less likely in NAFLD patients compared to those with other chronic liver diseases[10,14-19]. Several studies have established the role of bacterial translocation in nonalcoholic steatohepatitis and severe steatosis[20,21,31-33]. This could be a potential mechanism

Table 4 Demographics and hospital outcomes of discharge records stratified by background liver disease *n* (%)

	NAFLD (*n* = 32347)	Other liver diseases (*n* = 271049)	*P* value	Missing
Average age (yr)	52.3 ± 16.5	55.3 ± 15.4	< 0.0001	0
Female gender	19027 (58.8)	112788 (41.6)	< 0.0001	78 (0.0003)
Non-elective admission	25291 (78.4)	231024 (85.4)	< 0.0001	521 (0.2)
Ethnicity			< 0.0001	29349 (9.7)
White	20536 (70.7)	152778 (62.4)		
Black	2798 (9.6)	45634 (18.6)		
Hispanic	4135 (14.2)	32124 (13.1)		
Asian/Pacific Islander	592 (2.0)	5720 (2.3)		
Native American	191 (0.7)	2075 (0.9)		
Other	797 (2.7)	6667 (2.7)		
Diabetes mellitus	14027 (43.4)	78011 (28.9)	< 0.0001	
Hypertension	18413 (56.9)	129031 (47.6)	< 0.0001	
Obesity	11920 (36.9)	21677 (8.0)	< 0.0001	
Dyslipidemia	12262 (37.9)	42299 (15.6)	< 0.0001	
Metabolic syndrome	9286 (28.7)	23888 (8.8)	< 0.0001	
Location			< 0.0001	13512 (4.4)
Central Metropolitan	9115 (28.8)	91426 (35.4)		
Fringe Metropolitan	8540 (27.0)	58794 (22.8)		
Metro below one million	6003 (19.0)	48308 (18.7)		
50000-250000 population	2563 (8.1)	19519 (7.6)		
Micropolitan	3482 (11.0)	24641 (9.5)		
Other	1948 (6.2)	15545 (6.0)		
Median zip code income ($)			< 0.0001	13104 (4.3)
< 39000	8003 (25.3)	89265 (34.5)		
39000-47999	8140 (25.7)	65082 (25.2)		
48000-62999	8006 (25.3)	58595 (22.7)		
⩾ 63000	7488 (23.7)	45713 (17.7)		
Primary payer			< 0.0001	870 (0.3)
Medicare	10429 (32.3)	104892 (38.8)		
Medicaid	4461 (13.8)	65829 (24.4)		
Private	13602 (42.1)	59410 (22.0)		
Self-pay	2454 (7.6)	24729 (9.2)		
No charge	244 (0.8)	2917 (1.1)		
Other	1107 (3.4)	12452 (4.6)		
Major operative procedure	9804 (30.3)	47187 (17.4)	< 0.0001	0
Average total hospital charges ($)	39607.3 ± 52512	51665 ± 90685	< 0.0001	0
Average length of hospital stay (d)	4.7 ± 6.0	6.6 ± 9.7	< 0.0001	0
Discharge disposition			< 0.0001	420 (0.001)
Routine	25703 (79.5)	167545 (61.9)		
Acute care	660 (2.0)	9190 (3.4)		
Another health facility	2273 (7.0)	39311 (14.5)		
Home Health	3114 (9.6)	30276 (11.2)		
AMA	269 (0.8)	7691 (2.8)		
Other	10 (0.03)	479 (0.2)		
Died in hospital	301 (0.9)	16154 (6.0)	< 0.0001	571 (0.2)
Aprdrg mortality risk			< 0.0001	347 (0.1)
Minor	14347 (44.4)	82849 (30.4)		
Moderate	11678 (36.1)	84343 (31.1)		
Major	4921 (15.2)	63614 (23.5)		
Extreme	1377 (4.3)	40280 (14.9)		
Aprdrg severity			< 0.0001	347 (0.1)
Minor functional loss	814 (2.5)	12242 (4.5)		
Moderate functional loss	18105 (56.0)	88446 (32.6)		
Major functional loss	11156 (35.0)	116365 (43.0)		
Extreme functional loss	2248 (7.0)	53673 (19.8)		
Associated Diagnoses				
Abdominal Hernia	3459 (10.7)	12755 (4.7)	< 0.0001	
Appendiceal disorders	254 (0.8)	728 (0.3)	< 0.0001	
Benign anus-rectum disorders	174 (0.5)	1401 (0.5)	0.62	
Benign biliary disorders	5421 (16.8)	19306 (7.1)	< 0.0001	
Benign pancreatic disorders	3379 (10.5)	15898 (5.9)	< 0.0001	
Diverticular disease	2845 (8.8)	8697 (3.2)	< 0.0001	
Esophageal disorders (non-variceal)	9114 (28.2)	41835 (15.4)	< 0.0001	
Gastritis/duodenitis	2163 (6.7)	11220 (4.1)	< 0.0001	
Gastroduodenal ulcer	1011 (3.1)	7477 (2.8)	0.002	
Gastrointestinal hemorrhage	1119 (3.5)	23651 (8.7)	< 0.0001	
Gastrointestinal malignancies	688 (2.1)	6871 (2.5)	< 0.0001	

Hepatobiliary malignancies	84 (0.3)	7903 (2.9)	< 0.0001
Inflammatory bowel disease	555 (1.7)	2659 (1.0)	< 0.0001
Intestinal infection	886 (2.7)	5904 (2.2)	< 0.0001
Intestinal obstruction	1346 (4.2)	7898 (2.9)	< 0.0001
Peritonitis-abscess	326 (1.0)	5772 (2.1)	< 0.0001
Principal discharge diagnoses			
Appendicitis	217 (0.7)	554 (0.2)	< 0.0001
Benign anus-rectal disorders	163 (0.5)	1694 (0.6)	0.008
Benign pancreatitis	2224 (6.9)	7074 (2.6)	< 0.0001
Diverticular disease	898 (2.8)	1805 (0.7)	< 0.0001
Esophagitis	306 (1.0)	1762 (0.7)	< 0.0001
Gallstone disorders	2622 (8.1)	5978 (2.2)	< 0.0001
Gastroduodenal ulcer	232 (0.7)	2572 (1.0)	< 0.0001
Gastroduodenitis	713 (2.2)	3481 (1.3)	< 0.0001
Gastrointestinal malignancies	338 (1.0)	3017 (1.1)	0.27
Hepatobiliary malignancies	68 (0.2)	2837 (1.1)	< 0.0001
Hernia	204 (0.6)	1497 (0.6)	0.07
Inflammatory bowel disease	242 (0.8)	696 (0.3)	< 0.0001
Intestinal Infection	235 (0.7)	1999 (0.7)	0.83

NAFLD: Nonalcoholic fatty liver disease; AMA: American medical association.

Table 5 Multivariable logistic regression for factors associated with nonalcoholic fatty liver disease compared to other liver diseases using associated diagnoses

Variable	*P* value	OR (95%CI)
Age (reference ⩽ 70 yr)	< 0.0001	0.79 (0.76-0.83)
Gender (reference female)	< 0.0001	0.58 (0.57-0.60)
Diabetes	< 0.0001	1.41 (1.37-1.45)
Hypertension	0.05	0.97 (0.94-1.0)
Obesity	< 0.0001	4.47 (4.34-4.61)
Dyslipidemia	< 0.0001	2.35 (2.28-2.42)
Location (reference central metropolitan)	< 0.0001	
50000-250000 population		1.2 (1.1-1.3)
Fringe metropolitan		1.1 (1.1-1.2)
Metro 250000 - one million population		1.2 (1.1-1.2)
Micropolitan		1.4 (1.4-1.5)
Other		1.4 (1.3-1.4)
Income (reference ⩾ $63000)	< 0.0001	
$39000-$47999		0.80 (0.77-0.83)
$48000-$62999		0.86 (0.82-0.89)
< $39000		0.64 (0.62-0.67)
Payer (reference private insurance)	< 0.0001	
Medicaid		0.42 (0.41-0.43)
Medicare		0.46 (0.44-0.47)
No charge		0.61 (0.53-0.70)
Other		0.55 (0.51-0.59)
Self-pay		0.65 (0.62-0.68)
Associated diagnoses		
Abdominal hernia	< 0.0001	1.70 (1.63-1.79)
Appendiceal disorders	< 0.0001	2.58 (2.19-3.04)
Benign biliary disorders	< 0.0001	2.11 (2.03-2.19)
Benign pancreatic disorders	< 0.0001	1.57 (1.50-1.64)
Diverticular disease	< 0.0001	2.22 (2.11-2.34)
Esophageal disorders (non-variceal)	< 0.0001	1.52 (1.48-1.57)
Gastroduodenal ulcer	< 0.0001	1.41(1.33-1.49)
Gastrointestinal hemorrhage	< 0.0001	0.41 (0.38-0.44)
Gastrointestinal malignancies	< 0.0001	0.83 (0.76-0.91)
Hepatobiliary malignancies	< 0.0001	0.12 (0.10-0.15)
Inflammatory bowel disease	< 0.0001	1.68 (1.52-1.86)
Intestinal infection	< 0.0001	1.29 (1.19-1.40)
Intestinal obstruction	< 0.0001	1.30 (1.22-1.39)
Peritonitis-abscess	< 0.0001	0.47 (0.42-0.53)

Table 6 Multivariable logistic regression for factors associated with nonalcoholic fatty liver disease compared to other liver diseases using principal diagnoses

Variable	*P* value	OR (95%CI)
Age (reference ⩽ 70 yr)	< 0.0001	0.84 (0.81-0.88)
Gender (reference female)	< 0.0001	0.55 (0.53-0.56)
Diabetes	< 0.0001	1.38 (1.35-1.42)
Obesity	< 0.0001	4.75 (4.61-4.89)
Dyslipidemia	< 0.0001	2.51 (2.44-2.58)
Location (reference central metropolitan)	< 0.0001	
50000-250000 population		1.21 (1.14-1.27)
Fringe metropolitan		1.12 (1.09-1.17)
Metro 250000 - one million population		1.15 (1.11-1.20)
Micropolitan		1.44 (1.37-1.51)
Other		1.37 (1.29-1.45)
Income (reference > $63000)	< 0.0001	
$39000-$47999		0.80 (0.77-0.83)
$48000-$63000		0.86 (0.83-0.89)
< $39000		0.64 (0.62-0.67)
Payer (reference private insurance)	< 0.0001	
Medicaid		0.42 (0.40-0.43)
Medicare		0.47 (0.46-0.49)
No charge		0.60 (0.52-0.69)
Other		0.54 (0.50-0.58)
Self-pay		0.62(0.59-0.65)
Principal discharge diagnosis		
Appendicitis	< 0.0001	3.53 (2.96-4.22)
Benign pancreatitis	< 0.0001	2.95 (2.79-3.12)
Diverticular disease	< 0.0001	4.26 (3.89-4.67)
Esophagitis	< 0.0001	1.69 (1.48-1.93)
Gallstone disorders	< 0.0001	3.59 (3.40-3.79)
Gastroduodenitis	< 0.0001	2.09 (1.91-2.29)
Hepatobiliary malignancies	< 0.0001	0.29 (0.22-0.37)
Hernia	0.01	1.23 (1.04-1.45)
Inflammatory bowel disease	< 0.0001	3.64 (3.10-4.28)

for which diverticular disorders in particular are more commonly associated with NAFLD compared to other chronic liver diseases[21].Our finding of the association between NAFLD and gallstone disease is in agreement that a recent Italian study which noted a high prevalence of gallstone disease among patients with NAFLD[22]. Other series have noted similar findings[23,34].

Patients with NAFLD have better hospital outcomes, less severe disease severity and mortality risk, and utilize

Table 7 Demographics and hospital outcomes of discharge records of patients with a principal discharge diagnosis of diverticular disease, gallstone disease or benign pancreatitis stratified by background liver disease *n* (%)

	Diverticular disease (*n* = 2703)			Gallstone disease (*n* = 8600)			Benign pancreatitis (*n* = 9298)		
	NAFLD (*n* = 898)	OLD (*n* = 1805)	*P* value	NAFLD (*n* = 2622)	OLD (*n* = 5978)	*P* value	NAFLD (*n* = 2224)	OLD (*n* = 7074)	*P* value
Average age (yr)	55.1 ± 13.5	62.7 ± 14.2	< 0.0001	50.5 ± 16.7	57.7 ± 17.4	< 0.0001	47.8 ± 15.5	51.9 ± 14.0	< 0.0001
Female Gender	501 (55.8)	897 (49.7)	< 0.003	1606 (61.3)	3056 (51.2)	< 0.0001	1058 (47.6)	2796 (39.5)	< 0.0001
Non-elective admission	791 (88.3)	1612 (89.5)	0.36	2305 (88.4)	5137 (86.0)	< 0.0001	2110 (95.1)	6680 (94.5)	< 0.0001
Ethnicity			< 0.0001			< 0.0001			< 0.0001
White	610 (74.5)	1174 (72.1)		1575 (65.3)	3532 (65.5)		1376 (67.8)	3910 (60.8)	
Black	48 (5.9)	236 (14.5)		166 (6.9)	633 (11.7)		196 (9.7)	1355 (21.1)	
Hispanic	128 (15.7)	159 (9.8)		519 (21.5%)	882 (16.4)		339 (16.7)	854 (13.3)	
Other	33 (4.0)	60 (3.7)		152 (6.3)	344 (6.4)		119 (5.9)	313 (4.9)	
Diabetes mellitus	276 (30.7)	440 (24.4)	0.0004	816 (31.1)	1603 (26.8)	< 0.0001	984 (44.2)	1974 (27.9)	< 0.0001
Hypertension	490 (54.6)	1021 (56.6)	0.32	1285 (49.0)	2892 (48.4)	< 0.0001	1222 (55.0)	3524 (49.8)	< 0.0001
Obesity	252 (28.1)	200 (11.1)	< 0.0001	1010 (38.5)	770 (12.9)	< 0.0001	680 (30.6)	561 (7.9)	< 0.0001
Dyslipidemia	319 (35.5)	451 (25.0)	< 0.0001	818 (31.2)	1233 (20.6)	< 0.0001	1093 (49.2)	1359 (19.2)	< 0.0001
Metabolic syndrome	178 (19.8)	195 (10.8)	< 0.0001	567 (21.6)	638 (10.7)	< 0.0001	662 (29.8)	721 (10.2)	< 0.0001
Location			0.02			< 0.0001			< 0.0001
Central Metro	268 (30.6)	537 (30.7)		835 (32.5)	1775 (30.7)		603 (27.8)	2184 (32.6)	
Fringe Metro	247 (28.2)	436 (24.9)		707 (27.5)	1379 (23.9)		600 (27.6)	1554 (23.2)	
Metro below one million	185 (21.1)	322 (18.4)		505(19.7)	1132 (19.6)		406 (18.7)	1373 (20.5)	
50000-250000	53 (6.1)	147 (8.4)		160 (6.2)	427 (7.4)		185 (8.5)	536 (8.0)	
Micropolitan	81 (9.3)	187 (10.7)		237 (9.2)	651 (11.3)		238 (11.0)	626 (9.3)	
Other	42 (4.8)	119 (6.8)		124 (4.8)	411 (7.1)		140 (6.5)	437 (6.5)	
Median zip code income ($)			0.0008			< 0.0001			< 0.0001
< 39000	202 (22.8)	502 (28.5)		632 (24.6)	166 (28.9)		556 (25.6)	2334 (34.4)	
39000-47999	209 (23.5)	437 (24.8)		640 (24.9)	1550 (26.9)		534 (24.6)	1734 (25.5)	
48000-63000	233 (26.2)	445 (25.2)		676 (26.3)	1446 (25.1)		564 (25.9)	1527 (22.5)	
> 63000	244 (27.5)	380 (21.5)		618 (24.1)	1107 (19.2)		520 (23.9)	1196 (17.6)	
Primary payer			< 0.0001			< 0.0001			< 0.0001
Medicare	256 (28.5)	866 (48.1)		659 (25.2)	2461 (41.2)		523 (23.6)	2028 (28.8)	
Medicaid	60 (6.7)	181 (10.1)		382 (14.6)	1016 (17.0)		320 (14.4)	1682 (23.9)	
Private	469 (52.2)	562 (31.2)		1229 (46.9)	1687 (28.3)		971 (43.7)	1742 (24.7)	
Self-pay	75 (8.4)	119 (6.6)		215 (8.2)	531 (8.9)		295 (13.3)	1054 (15.0)	
No charge	6 (0.7)	15 (0.8)		27 (1.0)	53 (0.9)		24 (1.1)	128 (1.8)	
Other	32 (3.6)	58 (3.2)		106 (4.1)	219 (3.7)		87 (3.9)	418 (5.9)	
Major operative procedure	109 (12.1)	333 (18.5)	< 0.0001	2002 (76.4)	3327 (55.7)	< 0.0001	294 (13.2)	652 (9.2)	< 0.0001
Average total hospital charges ($)	26868.7 ± 26364.6	46666.9 ± 80222.8	< 0.0001	40016.5 ± 32898.6	49682.8 ± 65425.9	< 0.0001	32680.5 ± 42691.0	45115.5 ± 83193.4	< 0.0001
Average length of hospital stay (d)	4.2 ± 3.4	6.0 ± 8.3	< 0.0001	4.0 ± 3.4	5.6 ± 6.1	< 0.0001	4.9 ± 4.4	6.2 ± 8.4	< 0.0001
Discharge Disposition			< 0.0001			< 0.0001			< 0.0001
Routine	821 (91.4)	1355 (75.2)		2403 (91.8)	4492 (75.3)		2013 (90.5)	5396 (76.3)	
Acute care	2 (0.2)	33 (1.8)		32 (1.2)	240 (4.0)		45 (2.0)	209 (3.0)	
Another health facility	25 (2.8)	158 (8.8)		66 (2.5)	503 (8.4)		47 (2.1)	480 (6.8)	
Home Health	44 (4.9)	184 (10.2)		101 (3.9)	487 (8.2)		86 (3.9)	361 (5.1)	
AMA	5 (0.6)	17 (0.9)		14 (0.5)	81 (1.4)		22 (1.0)	325 (4.6)	
Other	0	3 (0.2)		0	7 (0.1)		0	4 (0.1)	
Died in hospital	1 (0.1)	53 (2.9)	< 0.0001	3 (0.1)	157 (2.6)	< 0.0001	11 (0.5)	296 (4.2)	< 0.0001
APRDRG Mortality risk			< 0.0001			< 0.0001			< 0.0001
Minor	530 (59.0)	783 (43.4)		1457 (55.6)	2123 (35.5)		1177 (52.9)	2658 (37.6)	
Moderate	278 (31.0)	563 (31.2)		936 (35.7)	2095 (35.1)		746 (33.5)	2308 (32.6)	
Major	82 (9.1)	291 (16.1)		188 (7.2)	1187 (19.9)		238 (10.7)	1318 (18.6)	
Extreme	8 (0.9)	167 (9.3)		37 (1.4)	571 (9.6)		61 (2.7)	785 (11.1)	
APRDRG Severity			< 0.0001			< 0.0001			< 0.0001
Minor functional loss	0	163 (9.0)		1 (0.04%)	377 (6.3)		1 (0.04)	347 (4.9)	
Moderate functional loss	645 (71.8)	747 (41.4)		1828 (69.7)	2371 (39.7)		1318 (59.3)	2721 (38.5)	
Major functional loss	231 (25.7)	697 (38.6)		715 (27.3)	2393 (40.0)		791 (35.6)	2855 (40.4)	
Extreme functional loss	22	197 (10.9)		74	835 (14.0)		112 (5.0)	1146 (16.2)	
	-2.5			-2.8					

NAFLD: Nonalcoholic fatty liver disease; OLD: Other liver diseases; AMA: American medical association.

fewer health care resources compared to patients with other chronic liver diseases (Table 4). These relationships occurred despite the fact that more NAFLD patients underwent major operations, and were maintained in subgroup analysis of diverticular disease, gallstone disease, and benign pancreatitis (Table 7). Given that hepatic related morbidity more often occurs with other chronic liver diseases (such as hepatitis C and alcoholic liver dis-

ease) compared to NAFLD[10,14-19], these findings suggest that the type and severity of background liver disease plays a vital role in determining overall patient outcomes and health care resource utilization.

There are several limitations to this study. It is unknown how background liver disease diagnoses were derived. Thus, the accuracy of NAFLD in this sample cannot be verified-especially when discharge abstracts used to construct this database were intended for reimbursement and not clinical research purposes. Similar problems regarding the accuracy of entered codes may exist when using ICD-9 diagnosis codes for elements of the metabolic syndrome, gastrointestinal disorders, and pancreatobiliary diseases. Distinctions between simple hepatic steatosis, steatohepatitis, and degrees of fibrosis cannot be made in the NIS. Because medications were not included in the NIS, we were not able to account for drug induced fatty liver disease. This limitation has minimal influence on our conclusions since less than 2% of steatohepatitis is drug induced[9]. We attempted to homogenize the NAFLD subsample by using only one ICD-9-DM identifier and eliminating any records listing any other major potential etiology of background liver disease. We focused on patients with any diagnosis of chronic liver disease and postulated that these patients are the most likely to have undergone evaluation for NAFLD. NAFLD may coexist with other chronic liver diseases in a minority of patients[35-37]. It is therefore possible that we may have included patients with undiagnosed NAFLD in the "other liver disease"sample. The NIS is a discharge level database where each entry represents a hospital admission and not an individual patient-thus multiple readmissions for a single patient may have biased our results.

In conclusion, NAFLD is widely under diagnosed among hospitalized patients in the United States. NAFLD is associated with diverticular, gallstone, and benign pancreatic disorders. The type of background liver disease is a key factor in hospital outcomes and healthcare resource utilization among hospitalized patients.

COMMENTS

Background

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the developed world. While prevalence proportions among outpatient series are well described, the proportion of hospitalized patients diagnosed with NAFLD is unknown. Moreover, associations of NAFLD to other gastrointestinal disorders are not well established.

Research frontiers

The important research hotspots related to this article include (1) the prevalence of NAFLD diagnosis among hospitalized patients; (2) outcomes among hospitalized patients with NAFLD; and (3) relationships between NAFLD and other gastrointestinal disorders.

Innovations and breakthroughs

Most prior reports examining the prevalence of NAFLD are based on outpatient or cohort registry studies-data regarding the prevalence of NAFLD among hospitalized patients are sparse. Few studies have examined hospital outcomes among patients with NAFLD-most focus on long-term survival related to hepatic or cardiovascular complications. Previous studies looking at associations between NAFLD and other gastrointestinal disorders are small, single institution based, and often biased by patient selection and particular care settings. To overcome these obstacles, the authors used a large database that provides an accurate estimate of the prevalence of NALFD diagnosis among hospitalized patients across the United States. Analyses of these data show that patients with NAFLD have a lower frequency of hospital mortality and consume fewer healthcare resources compared to those with other chronic liver diseases. Finally, authors' study demonstrates that NAFLD is associated with diverticular, inflammatory bowel, gallstone, and benign pancreatitis disorders independent of demographics or other comorbidities.

Applications

The study results suggest that suggest that the type of background liver disease plays a vital role in determining overall patient outcomes and health care resource utilization among hospitalized patients. The results also suggest shared mechanisms of disease pathology between NAFLD and diverticular, inflammatory bowel, gallstone, and benign pancreatitis disorders.

Terminology

A principal diagnosis is the one diagnosis describing the main indication for admission and/or the condition which was the central focus of management during hospitalization. Associated diagnoses include the principal diagnosis, comorbid conditions, and disorders previously managed but not the focus of the particular hospitalization.

Peer review

The authors mentioned the prevalence of NAFLD and the associations between NAFLD and other common gastrointestinal and pancreato-biliary disorders among hospitalized patients. The authors also discussed the impact of NAFLD on healthcare resource utilization.

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