

# World Journal of *Gastrointestinal Pathophysiology*

*World J Gastrointest Pathophysiol* 2021 March 22; 12(2): 14-24



**ORIGINAL ARTICLE****Retrospective Study**

- 14 Association of non-alcoholic fatty liver disease with gallstone disease in the United States hospitalized patient population

*Kichloo A, Solanki S, Haq KF, Dahiya D, Bailey B, Solanki D, Singh J, Albosta M, Wani F, Aljadah M, Shah H, Khan H, Jafri SM*

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**Production Editor:** Ji-Hong Liu; **Production Department Director:** Yun-Xiaojuan Wu; **Editorial Office Director:** Jia-Ping Yan.

**NAME OF JOURNAL**

*World Journal of Gastrointestinal Pathophysiology*

**ISSN**

ISSN 2150-5330 (online)

**LAUNCH DATE**

April 15, 2010

**FREQUENCY**

Bimonthly

**EDITORS-IN-CHIEF**

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**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2150-5330/editorialboard.htm>

**PUBLICATION DATE**

March 22, 2021

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<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

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## Retrospective Study

**Association of non-alcoholic fatty liver disease with gallstone disease in the United States hospitalized patient population**

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**Author contributions:** Kichloo A and Solanki S are credited with substantial contribution to the design of the work, acquisition and interpretation of the data, drafting the manuscript, revision of important intellectual content, final approval of the version published, and agreement of accountability for all aspects of the work; Haq KF, Dahiya D and Solanki D are credited with substantial contribution to interpretation of data, literature review of all sections discussed, drafting of the manuscript, final approval of the version published, and agreement of accountability for all aspects of the work; Bailey B is credited with substantial contribution to acquisition, analysis, and

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**Abstract****BACKGROUND**

Gallstones and cholecystectomy have been proposed as risk factors for non-alcoholic fatty liver disease (NAFLD). The reason for this may be that both gallstones, as well as NAFLD share several risk factors with regards to their development. Currently, there is a lack of sufficient evidence showing an association between these clinical conditions.

**AIM**

To determine whether there is a meaningful association between gallstones and cholecystectomy with NAFLD.

interpretation of the data, revision of critically important intellectual content, final approval of the version to be published, and agreement of accountability for all aspects of the work; Singh J, Wani F, Albosta M and Aljadah M are credited with interpretation of the data, literature review of all sections, revision of important intellectual content, final approval of the version published, and agreement of accountability of all aspects of the work; Shah H, Khan H and Jafri SM are credited with interpretation of data, literature review, specifically for the discussion section, revision of the work for critically important intellectual content, final approval of the version published, and agreement of accountability for all aspects of the work.

#### Institutional review board

**statement:** The study presented in the current manuscript, which utilizes data from the Health Cost and Utilization Project, meets all relevant ethical and regulatory standards. These data, which were received by the investigators completely deidentified, required a local data custodian, and all investigators who accessed the data completed HCUP appropriate data use training and signed data use agreements. As such, our use of the HCUP data met the Central Michigan University IRB policy that such data use is not human subjects research, and does not require their review or approval.

#### Informed consent statement:

Consent was not obtained but the presented data are anonymized and risk of identification is low.

**Conflict-of-interest statement:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the Supplementary Material.

**Open-Access:** This article is an open-access article that was

## METHODS

We queried the National Inpatient Sample database from the years 2016 and 2017 using International Classification of Diseases, 10<sup>th</sup> revision, Clinical Modification diagnosis codes to identify hospitalizations with a diagnosis of gallstone disease (GSD) (includes calculus of gallbladder without cholecystitis without obstruction and acquired absence of gallbladder) as well as NAFLD (includes simple fatty liver and non-alcoholic steatohepatitis). Odds ratios (ORs) measuring the association between GSD (includes gallstones and cholecystectomy) and NAFLD were calculated using logistic regression after adjusting for confounding variables.

## RESULTS

Out of 14294784 hospitalizations in 2016-2017, 159259 were found to have NAFLD. The prevalence of NAFLD was 3.3% in patients with GSD and 1% in those without. NAFLD was prevalent in 64.3% of women with GSD as compared to 35.7% of men with GSD. After controlling for various confounders associated with NAFLD and GSD, multivariate-adjusted analysis showed that there was an association between NAFLD with gallstones [OR = 6.32; 95% confidence interval (CI): 6.15-6.48] as well as cholecystectomy (OR = 1.97; 95%CI: 1.93-2.01). The association between NAFLD and gallstones was stronger in men (OR = 6.67; 95%CI: 6.42-6.93) than women (OR = 6.05; 95%CI: 5.83-6.27). The association between NAFLD and cholecystectomy was stronger in women (OR = 2.01; 95%CI: 1.96-2.06) than men (OR = 1.85; 95%CI: 1.79-1.92). *P* value was less than 0.001 for all comparisons.

## CONCLUSION

NAFLD is more prevalent in women with GSD than men. The association between NAFLD and cholecystectomy/gallstones indicates that they may be risk factors for NAFLD.

**Key Words:** Gallstones; Non-alcoholic fatty liver disease; Gastroenterology; Hepatology; Non-alcoholic steatohepatitis; Cholecystectomy

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**Core Tip:** We have identified a significant association between gallstone disease and non-alcoholic fatty liver disease. This association is stronger in women with gallstone disease than men. Further, this association is strongest in the Caucasian population. It is believed that this association is due to both physiologic changes post-cholecystectomy as well as the presence of metabolic derangement common to the development of both disorders. Lifestyle modification, including weight loss, dietary alterations, exercise, decreasing alcohol intake, and screening for the development of hepatic malignancy are important in preventing the development/progression of non-alcoholic fatty liver disease.

**Citation:** Kichloo A, Solanki S, Haq KF, Dahiya D, Bailey B, Solanki D, Singh J, Albosta M, Wani F, Aljadah M, Shah H, Khan H, Jafri SM. Association of non-alcoholic fatty liver disease with gallstone disease in the United States hospitalized patient population. *World J Gastrointest Pathophysiol* 2021; 12(2): 14-24

**URL:** <https://www.wjgnet.com/2150-5330/full/v12/i2/14.htm>

**DOI:** <https://dx.doi.org/10.4291/wjgp.v12.i2.14>

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis in the absence of other etiologies responsible for secondary fatty deposition in the liver. NAFLD is a spectrum of disease characterized initially by hepatic steatosis with gradual progression to liver fibrosis and ultimately, end stage liver disease. It is

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**Manuscript source:** Unsolicited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): C, C  
Grade D (Fair): 0  
Grade E (Poor): 0

**Received:** November 27, 2020

**Peer-review started:** November 27, 2020

**First decision:** December 20, 2020

**Revised:** December 27, 2020

**Accepted:** January 14, 2021

**Article in press:** January 14, 2021

**Published online:** March 22, 2021

**P-Reviewer:** Kanda T, Li CP

**S-Editor:** Gao CC

**L-Editor:** A

**P-Editor:** Yuan YY



one of the most frequent causes of liver disease in the United States (US), with recent studies reporting a prevalence as high as 20%-30%. Additionally, the prevalence of NAFLD continues to rise globally in line with the obesity epidemic<sup>[1,2]</sup>. Although believed to be a slowly progressive disease, it is currently the third most common reason for liver transplant in the US<sup>[3]</sup>.

Multiple co-morbidities closely associated with NAFLD have been identified, including visceral obesity, type 2 diabetes mellitus (T2DM), dyslipidemia and the metabolic syndrome. Other potential risk factors that may contribute to the development of NAFLD including gallstone disease (GSD), cholecystectomy, sleep deprivation, polycystic ovarian syndrome, hypertension and pituitary disorders are not well understood<sup>[4]</sup>. However, it has been well established that some degree of metabolic derangement and insulin resistance are involved in the core pathophysiology of the development of NAFLD. Our study evaluates GSD, which includes both a diagnosis of cholelithiasis as well as sequelae associated with this diagnosis, including cholecystectomy, and its' association with the development of NAFLD. Cholesterol gallstones are the most common type of gallstones and the risk factors for their formation are largely similar to those associated with NAFLD<sup>[4]</sup>. Hepatic insulin resistance is implicated in supersaturation and excessive production of bile salts. It is not clear whether the presence of gallstones are merely a reflection of the presence of risk factors for the metabolic syndrome, which accelerate NAFLD progression, or whether NAFLD leads to gallstone formation<sup>[5]</sup>. On the other hand, cholecystectomy is believed to alter the metabolism of the enterohepatic circulation of bile acids leading to an increased risk for the development of NAFLD. In 2013, Ruhl *et al*<sup>[6]</sup> used the US National Health and Nutrition Examination Survey (NHANES) from 1988 to 1994 to report that having had a cholecystectomy may be a risk factor for the development of NAFLD. More recently, Kakati *et al*<sup>[7]</sup> found an increased prevalence of cholecystectomy among NAFLD patients than non-NAFLD patients at a tertiary care center in the US. However, the sample size of this study was small (379 patients) and it was confined to one center. Hence, a direct correlation between cholecystectomy and NAFLD has yet to be proven.

There is a paucity of literature and data in terms of large-scale multicenter retrospective studies investigating an association between GSD and NAFLD. The purpose of our study is to determine whether an association between GSD and NAFLD exists, identify the prevalence of multiple co-morbidities associated with NAFLD, and discuss risk factor modification for the prevention of the development of NAFLD in addition to halting its progression to end stage liver disease.

## MATERIALS AND METHODS

### Data source

The National Inpatient Sample (NIS) is a publicly available all-payer Healthcare Cost and Utilization Project (HCUP) database designed to produce US regional and national estimates<sup>[8,9]</sup>. HCUP is a family of healthcare databases and related software tools and products released by the Agency for Healthcare Research and Quality. The NIS contains data from more than 7 million hospital stays every year and approximates a 20% stratified sample of discharges from US community hospitals<sup>[9]</sup>. HCUP databases are limited data sets. Under the Health Insurance Portability and Accountability Act, review by an Institutional Review Board (IRB) is not required for the use of limited data sets<sup>[10]</sup>. Therefore, our study was exempt from IRB review.

### Study design

This is a retrospective study utilizing the NIS dataset from 2016 and 2017 using International Classification of Diseases, 10<sup>th</sup> Revision, Clinical Modification (ICD-10-CM) diagnosis codes. GSD was identified using the codes K80.20 (calculus of gallbladder without cholecystitis without obstruction) and Z90.49 (acquired absence of gallbladder). The NAFLD cohort was then generated using the codes K76.0 (simple fatty liver) and K75.81 (non-alcoholic steatohepatitis, NASH) as depicted in [Supplementary Table 1](#). Co-morbidities and known risk factors were identified using the ICD-10 codes depicted in [Supplementary Table 1](#).

### Statistical analysis

SAS 9.3 (SAS Institute, Cary, NC, United States) was used for data analysis. Statistical review was performed by a biomedical statistician. We used NIS designated weights to produce nationally representative estimates of disease prevalence and demographic

variations. A two-tailed *P* value of less than 0.05 was considered statistically significant. Age and sex standardized prevalence of NAFLD and GSD were generated. The unadjusted prevalence of NAFLD by GSD status was compared using the chi-square ( $\chi^2$ ) test. The differences in demographics and co-morbidities by GSD status were also compared using the  $\chi^2$  test. We used multivariate logistic regression analysis to determine odds ratios (ORs) for NAFLD comparing GSD to those without GSD after adjusting for age, gender, race, alcohol abuse, diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, nicotine dependence, and obesity. Owing to the gender differences in the prevalence of NAFLD and GSD, ORs for men and women were also calculated separately.

## RESULTS

The total sample size of the study population for the years 2016-2017 was  $n = 14294784$ . The total number of hospitalizations with GSD as a primary diagnosis was  $n = 534015$  (87769 gallstone diagnoses and 448932 cholecystectomy diagnoses). The sample size of the NAFLD cohort was  $n = 159259$ , with simple fatty liver accounting for 123549 hospitalizations and NASH accounting for 36440 hospitalizations.

The prevalence of NAFLD was 3.3% in GSD hospitalizations and 1.0% in non-GSD hospitalizations. Patients with GSD and NAFLD were more likely to be older, and more likely to be women (Table 1). In white patients, GSD hospitalizations (72.1%) were more common than non-GSD hospitalizations (64.9%). For other racial groups, the percentage of non-GSD hospitalizations was higher than GSD hospitalizations. Medicare was the primary payor for 58% of hospitalizations with GSD in contrast to 39.4% of non-GSD hospitalizations. Alcohol abuse, diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, and nicotine dependence were seen in a higher proportion of GSD hospitalizations than non-GSD hospitalizations. In contrast, obesity was more common in non-GSD hospitalizations than GSD hospitalizations (Table 1). All the differences between the two groups were significant at  $P < 0.001$ .

After adjusting for age (Table 2), patients with gallstones were 6.85 times more likely to have NAFLD [OR = 6.85; 95% confidence interval (CI): 6.67-7.03,  $P < 0.001$ ] whereas those with cholecystectomy were 2.14 times more likely to have NAFLD. In addition, after adjusting for age, men with gallstones were more likely to have NAFLD than women, whereas women with cholecystectomy were more likely to have NAFLD than men.

In multivariate-adjusted analysis (Table 2), patients with gallstones were 6.32 times more likely to have NAFLD (OR = 6.32; 95% CI: 6.15-6.48,  $P < 0.001$ ) and patients with cholecystectomy were 1.97 times more likely to have NAFLD (OR = 1.97; 95% CI: 1.93-2.01,  $P < 0.001$ ). Also, in the sex-adjusted analysis, the association of NAFLD with gallstones was found to be stronger in men (OR = 6.67; 95% CI: 6.42-6.93,  $P < 0.001$ ) than in women (OR = 6.05; 95% CI: 5.83-6.27,  $P < 0.001$ ). The association of NAFLD with cholecystectomy was found to be stronger in women (OR = 2.01; 95% CI: 1.96-2.06,  $P < 0.001$ ) than in men (OR = 1.85; 95% CI: 1.79-1.92,  $P < 0.001$ ).

## DISCUSSION

It has previously been established that gallstones and cholecystectomy are independently associated with NAFLD after adjustment for metabolic risk factors, especially in Asian populations<sup>[11,12]</sup>. In our study we report that the prevalence of NAFLD is 3.3% in patients with GSD, which includes both the presence of gallstones and history of cholecystectomy, and 1% in those without GSD. After controlling for various confounders associated with NAFLD and GSD, a multivariate-adjusted analysis showed that there was significant association between NAFLD with gallstones as well as cholecystectomy. The exact pathophysiology behind the presence of gallstones leading to NAFLD is not well understood, however, the association between gallstones and NAFLD might stem from the common pathogenic factors shared by both gallstone formation and NAFLD, given that the risk for gallstones is high in patients with central obesity, type 2 diabetes and insulin resistance<sup>[13]</sup>. The removal of the gallbladder has a metabolic impact on NAFLD initiation and progression. Once the gallbladder is removed, bile is continuously secreted into the small intestine. This leads to quicker enterohepatic circulation of bile acids, consequently leading to a greater influx of bile acids into the liver<sup>[6]</sup>. Also, the gallbladder is the main site of fibroblast growth factor 19 (FGF19) expression in the

**Table 1** Age- and sex-standardized characteristics of hospitalizations

	No gallstone disease (n = 13760769)	All gallstone disease (n = 534015)	P value
NAFLD (%)	1.0	3.3	< 0.001
Age, yr (mean ± SD)	48.8 ± 27.6	63.2 ± 18.1	< 0.001
Gender (%)			
Male	43.7	35.7	< 0.001
Female	56.3	64.3	< 0.001
Race (%)			
White	64.9	72.1	< 0.001
Black	15.4	11.8	< 0.001
Hispanic	12.4	11.2	< 0.001
Others	7.3	4.9	< 0.001
Payment (%)			
Medicare	39.4	58.0	< 0.001
Medicaid	23.5	13.6	< 0.001
Private insurance	29.9	22.8	< 0.001
Others (includes self-pay)	7.1	5.5	< 0.001
Co-morbidities (%)			
Alcohol abuse	1.6	2.3	< 0.001
Diabetes mellitus	13.2	18.9	< 0.001
Dyslipidemia	22.6	33.4	< 0.001
Hypertension	29.8	43.0	< 0.001
Metabolic syndrome	0.1	0.2	< 0.001
Nicotine dependence	29.6	40.1	< 0.001
Obesity	7.5	5.4	< 0.001

NAFLD: Non-alcoholic fatty liver disease.

enterohepatobiliary system<sup>[14]</sup>. FGF19 suppresses the ability of insulin to promote synthesis of hepatic fatty acid<sup>[15]</sup>. Barrera *et al*<sup>[16]</sup> found that cholecystectomy leads to reduced serum FGF19 levels and increased bile acid synthesis. Animal studies have shown that cholecystectomy leads to increased serum triglycerides and very low-density lipoprotein, which may contribute to increased triglyceride accumulation in the liver, and ultimately, NAFLD<sup>[11]</sup>. Because of this, we postulate that cholecystectomy may contribute to NAFLD initiation or progression.

Gender differences in NAFLD continues to be a debated topic, however, it is well known that NAFLD is a sexually dimorphic condition<sup>[17]</sup>. After analysis of the NHANES data, most studies reported a higher prevalence of NAFLD in men than women<sup>[18]</sup>. However, the study by Younossi *et al*<sup>[19]</sup>, which divides individuals into lean or obese-overweight subgroups, reported that the lean NAFLD cohort was more commonly female. Our study also focused on these gender differences. We report that NAFLD was prevalent in 64.3% of women with GSD as compared to 35.7% of men with GSD. The association between NAFLD with gallstones was found to be stronger in men (OR = 6.67; 95%CI: 6.42-6.93) than in women (OR = 6.05; 95%CI: 5.83-6.27) and the association between NAFLD with cholecystectomy was found to be stronger in women (OR = 2.01; 95%CI: 1.96-2.06) than in men (OR = 1.85; 95%CI: 1.79-1.92). The pathophysiology behind this difference is attributed to natural changes in female physiology, especially in the post-menopausal years, such as increased rates of insulin resistance, central obesity, and alterations in adipose tissue distribution as a result of fluctuations in estrogen levels<sup>[20]</sup>. It has also been noted that early menarche may predispose women to an increased risk of NAFLD in adulthood, due to the association between obesity and early onset of menses<sup>[17]</sup>. Animal studies in over nourished

**Table 2** Logistic regression odds ratios for the association of non-alcoholic fatty liver disease with gallstone disease

	Age-adjusted			Multivariate-adjusted <sup>1</sup>		
	OR	95%CI	P value	OR	95%CI	P value
All						
Gallstone disease <sup>2</sup>	2.99	2.94-3.03	< 0.001	2.75	2.70-2.79	< 0.001
Gallstones	6.85	6.67-7.03	< 0.001	6.32	6.15-6.48	< 0.001
Cholecystectomy	2.14	2.10-2.18	< 0.001	1.97	1.93-2.01	< 0.001
Men						
Gallstone disease	3.09	3.01-3.17	< 0.001	2.90	2.82-2.97	< 0.001
Gallstones	7.32	7.05-7.59	< 0.001	6.67	6.42-6.93	< 0.001
Cholecystectomy	1.95	1.88-2.02	< 0.001	1.85	1.79-1.92	< 0.001
Women						
Gallstone disease	2.93	2.88-3.00	< 0.001	2.63	2.58-2.69	< 0.001
Gallstones	6.48	6.26-6.72	< 0.001	6.05	5.83-6.27	< 0.001
Cholecystectomy	2.25	2.20-2.30	< 0.001	2.01	1.96-2.06	< 0.001

<sup>1</sup>Adjusted for age, gender, race, alcohol abuse, diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, nicotine dependence, and obesity.

<sup>2</sup>Gallstone disease includes both gallstones and cholecystectomy. OR: Odds ratio; CI: Confidence interval.

zebrafish models have shown that ovarian senescence causing hypoestrogenemia facilitates the development of hepatic steatosis and the fibrotic progression of liver disease<sup>[21]</sup>. Understanding gender differences in NAFLD is crucial as it will allow us to target specific groups to improve primary prevention and health promotion, as well as provide treatment strategies which may help reduce morbidity and mortality associated with NAFLD and its associated pathologies.

Significant racial differences exist with regards to the prevalence of NAFLD. Our study reports that the prevalence of NAFLD with GSD was 72.1% in the Caucasian population, followed by 11.8% in African Americans, 11.2% in Hispanics and 4.9% in other races ( $P < 0.001$ ). This is most likely attributed to complex interactions between environmental, behavioral, and genetic factors<sup>[3,18]</sup>. One explanation for the racial variance may be a higher average BMI and visceral adiposity in the Caucasian population as compared to their African American counterparts. The most recent literature suggests that the East Asian Indian population may be at the highest risk of NAFLD<sup>[22]</sup>.

Our study reports a higher prevalence of NAFLD in the GSD group. Numerous comorbidities have been identified in the GSD disease group which could possibly be linked to the development of NAFLD, with most having some form of metabolic derangement or insulin resistance as the core pathophysiology. We analyzed some of the common co-morbidities associated with GSD, as follows:

#### **T2DM or insulin resistance**

NAFLD and T2DM often co-exist, leading to adverse outcomes<sup>[23]</sup>. The presence of NAFLD is also associated with an increased incidence of the microvascular complications of T2DM. We found that T2DM had a prevalence of 18.9% in the GSD group as compared to 13.2% in the group without GSD ( $P < 0.001$ ). Therefore, patients with T2DM should be screened for NAFLD. Elastography, a technique used to measure tissue stiffness, can be used as a screening tool for NAFLD.

#### **Metabolic syndrome**

This is defined as a cluster of conditions that occur in conjunction leading to an increased risk of developing cardiovascular disease, diabetes, and stroke. There is a strong association between the metabolic syndrome and NAFLD<sup>[24]</sup>. Metabolic syndrome is characterized by the presence of 3 out of the following 5 criteria: (1) Abdominal obesity; waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women; (2) Serum triglycerides  $\geq 150$  mg/dL or drug treatment for elevated triglycerides; (3) Serum high-density lipoprotein (HDL) cholesterol  $< 40$  mg/dL in men and  $< 50$

mg/dL in women or drug treatment for low HDL cholesterol; (4) Blood pressure  $\geq$  130/85 mmHg or drug treatment for elevated blood pressure; and (5) Fasting plasma glucose  $\geq$  100 mg/dL or drug treatment for elevated blood glucose.

We found that there was a higher prevalence of patients having metabolic syndrome in the GSD group (0.2%) *vs* the group without GSD (0.1%) ( $P < 0.001$ ). Therefore, Metabolic syndrome may be closely associated with NAFLD.

### **Dyslipidaemia**

Elevated levels of free fatty acids promote insulin resistance leading to NAFLD<sup>[25]</sup>. We found that dyslipidaemia was more common in patients in the GSD group (33.4%) compared to the non-GSD group (22.6%) ( $P < 0.001$ ). Hypertriglyceridemia is known to be an independent risk factor for NAFLD and therefore requires appropriate screening. The Framingham Heart study also revealed that patients with fatty liver had a high prevalence of hypertriglyceridemia and low HDL levels<sup>[26]</sup>.

### **Obesity**

Weight gain is a modifiable risk factor believed to be strongly associated with the development of NAFLD. The distribution of the adipose tissue, rather than the amount, is more clearly associated with NAFLD. However, our study found a higher prevalence of obesity (7.5%) in the group without GSD compared to the GSD group (5.4%) ( $P < 0.001$ ). Nevertheless, it has been well established that visceral adipose tissue predisposes patients to the development of NAFLD even at lower body mass index<sup>[27]</sup>.

### **Hypertension**

Essential hypertension has been known to be associated with metabolic syndrome which in-turn is associated with the development of NAFLD. Other mechanisms for hypertension leading to NAFLD development are poorly understood<sup>[28]</sup>. Our study reported a 43% prevalence of hypertension in the GSD group and a 29.8% prevalence in the group without GSD ( $P < 0.001$ ). Hence, we advocate for a more aggressive approach to screening and treatment for hypertension.

### **Nicotine dependence**

Some studies on humans and animal models indicate that smoking has some association with NAFLD. However, the clinical correlation of these findings remains controversial<sup>[29]</sup>. We looked at nicotine dependence and found that the prevalence of NAFLD is 40.1% in nicotine dependent patients in the GSD group *vs* 29.6% in the group without GSD ( $P < 0.001$ ). More studies are needed to establish a significant relationship between the use of nicotine and NAFLD.

Patients with NAFLD tend to have a decreased survival rate when compared to the general population. Cardiovascular disease is a major cause of death in these patients, followed by malignancies such as hepatocellular carcinoma, as well as increased morbidity and mortality due to the sequela of chronic liver disease itself<sup>[30]</sup>. Despite a thorough investigation into available clinical trials, no effective treatment therapy or protocol currently exists for NAFLD. Therefore, a non-pharmacological approach for controlling the co-morbidities leading to not only NAFLD but also cardiovascular risk and overall mortality becomes crucial in the management of the NAFLD population. Correcting the core pathophysiology (often underlying metabolic derangement or insulin resistance) is the basis of the management of NAFLD. It can be achieved through a patient-tailored approach of risk factor modification through lifestyle changes, which consists of:

### **Weight loss**

Weight loss of 3%-5% in patients with steatosis and 7%-10% in patients with NASH is recommended, with the long-term goal of achieving a normal BMI<sup>[31]</sup>. A 5% weight loss is associated with about a 75% rate of remission of NAFLD<sup>[32]</sup>.

### **Diet**

Patients with dyslipidaemia benefit from a low-fat diet, whereas patients with insulin resistance or Diabetes Mellitus should be advised to follow a low carbohydrate diet. Patients with NAFLD and NASH eat a lower polyunsaturated *vs* saturated Fatty Acid ratio, a lower omega-3 *vs* omega-6 ratio, and a higher amount of cholesterol, as compared to the general population<sup>[3]</sup>. Therefore, it is recommended to modify the diet to include more polyunsaturated fatty acids, omega-3 fatty acids, and decrease cholesterol consumption to less than 200 mg a day.

**Exercise**

The literature suggests that exercise alone has a beneficial effect in NAFLD. Exercise along with dietary modification may play a synergistic role in the management of NAFLD. Aerobic exercise, about 3-4 times a week with > 400 kcal per session is currently recommended.

**Alcohol intake**

The literature suggests a U-relationship between alcohol consumption, with lower intake associated with decreased overall mortality, decreased rates of cardiovascular events, lower risk of Diabetes Mellitus, and decreased incidence of the metabolic syndrome<sup>[3]</sup>. Studies have also shown a possible beneficial effect of mild alcohol consumption in NAFLD. However, we do not actively recommend alcohol consumption in NAFLD patients especially in those suffering from progressive NAFLD.

**Coffee consumption**

Animal and epidemiological studies reveal a possible beneficial effect of coffee consumption in terms of metabolic control and development of NAFLD<sup>[33]</sup>. Because of this, coffee consumption should not be restricted.

**Cancer screening**

Patients with NAFLD are at increased risk for developing malignancies. The literature does report the incidence of liver cancer in patients with NAFLD without fibrosis but not enough evidence exists to recommend a screening protocol<sup>[9]</sup>. Patients with NAFLD should also be monitored in regular screening programs for breast, prostate, colorectal and cervical cancer.

In addition to lifestyle modification, pharmacological therapies such as orlistat may be considered for assistance with weight reduction. Bariatric surgery may be considered in moderately to severely obese patients. In fact, a systematic review by Bower *et al.*<sup>[34]</sup> found that among 16 studies evaluating steatosis before and after bariatric surgery, the weighted mean decrease in the incidence of steatosis was 50.2%.

There are limitations to the current study, in particular with regards to the utilization of the Healthcare Utilization Project database, including errors in relation to the ICD9 and ICD10 coding system. In order to prevent this, we have utilized codes that have been validated in previous studies. We have performed a retrospective analysis and given insight into an association between these conditions and the studied outcomes, however the nature of observational studies does not allow for the determination of causation between the variables being studied. An additional limitation is that the ICD coding system is unable to identify when patients are readmitted with the same condition. Because of this, every admission is considered a separate case and therefore a new patient encounter. A final limitation of the study is that it was not performed on the general population.

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**CONCLUSION**

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We conclude that NAFLD is more prevalent in women with GSD than men. The association of NAFLD with cholecystectomy and GSD indicates that they may be risk factors for NAFLD. Lifestyle modification through physical exercise, diet, and weight reduction can prevent gallstone formation and the subsequent need for cholecystectomy. We know that gallstones are a common disease process and cholecystectomy is a commonly performed procedure. Their impact on NAFLD should be further evaluated through prospective studies and randomized clinical trials.

**ARTICLE HIGHLIGHTS****Research background**

Non-alcoholic fatty liver disease (NAFLD) is one of the most frequent causes of liver disease in the United States. The prevalence of NAFLD is rising globally in line with the obesity epidemic. The pathophysiology of the development of NAFLD is rooted in metabolic derangement and insulin resistance. In addition, the development of gallstones shares several common risk factors with that of NAFLD. Cholecystectomy, a

sequela of gallstone disease (GSD), may alter the metabolism of the enterohepatic circulation of bile acids and contribute to an increased risk of NAFLD.

### Research motivation

There is a paucity of literature and data in terms of large-scale multicenter retrospective studies that have investigated an association between GSD and NAFLD.

### Research objectives

To determine whether an association between GSD and NAFLD exists, identify the prevalence of multiple co-morbidities associated with NAFLD, and discuss risk factor modification for the prevention of the development of NAFLD in addition to halting its progression to end stage liver disease.

### Research methods

We queried the National Inpatient Sample database from the years 2016 and 2017 using International Classification of Diseases, 10<sup>th</sup> revision, Clinical Modification diagnosis codes to identify hospitalizations with a diagnosis of GSD as well as NAFLD. Odds ratios (ORs) measuring the association between GSD and NAFLD were calculated using logistic regression after adjusting for confounding variables.

### Research results

The prevalence of NAFLD was 3.3% in patients with GSD and 1% in those without. NAFLD was prevalent in 64.3% of women with GSD as compared to 35.7% of men with GSD. After controlling for confounders, multivariate-adjusted analysis showed that there was an association between NAFLD with gallstones [OR = 6.32; 95% confidence interval (CI): 6.15-6.48] as well as cholecystectomy (OR = 1.97; 95%CI: 1.93-2.01). The association between NAFLD and gallstones was stronger in men (OR = 6.67; 95%CI: 6.42-6.93) than women (OR = 6.05; 95%CI: 5.83-6.27). The association between NAFLD with cholecystectomy was stronger in women (OR = 2.01; 95%CI: 1.96-2.06) than men (OR = 1.85; 95%CI: 1.79-1.92).

### Research conclusions

NAFLD is more prevalent in women with GSD than men. The association between NAFLD and cholecystectomy/gallstones indicates that they may be risk factors for NAFLD.

### Research perspectives

There is a need for further prospective studies and randomized clinical trials to evaluate the impact of gallstones and cholecystectomy on the development of NAFLD.

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