



Liver biopsy in patients with gall stone disease and concomitant non-alcoholic fatty liver disease undergoing cholecystectomy: A prospective observational study

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ABSTRACT

Objective: Gallstone disease (GSD) and non-alcoholic fatty liver disease (NAFLD) share common risk factors. NAFLD can progress to non-alcoholic steatohepatitis (NASH), which may lead to severe liver conditions. This study aimed to assess the prevalence of NASH and associated factors in patients with GSD and fatty liver undergoing cholecystectomy.

Material and Methods: This prospective observational study was conducted from March 2021 to June 2023 and included 134 patients diagnosed with GSD and fatty liver based on preoperative ultrasound. Core liver biopsies were obtained during cholecystectomy. Preoperatively, clinical, anthropometric, demographic, biochemical variables, and FibroScan parameters were recorded.

Results: NASH was found in 21 (15.67%) patients, while 50 (37.31%) patients had probable NASH, and 63 (47.01%) had non-NASH scores. Metabolic syndrome was present in 63.6% of the patients. Univariate analysis revealed significant differences in AST and ALT values between the NASH and non-NASH groups. In multivariate analysis, AST was statistically significant ($p=0.041$). Mean controlled attenuation parameter in patients with non-NASH was 219.40 ± 60.44 dB/m, and in patients with NASH, it was 265.48 ± 63.47 dB/m ($p=0.006$). Fibrosis was present in 33 of the 82 slides examined, with 17 patients having grade 2 and two patients with grade 3 fibrosis.

Conclusion: The high prevalence of NASH among GSD patients highlights a significant public health issue, prompting consideration for liver biopsy in individuals with NAFLD and GSD undergoing laparoscopic cholecystectomy.

Keywords: Gallstone disease, NAFLD, NASH, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis

INTRODUCTION

Symptomatic gallstone disease (GSD) stands as the most prevalent benign disorder of the gallbladder, with an incidence of up to 6% among Indian adults (1). Patients afflicted with GSD often exhibit a high prevalence of non-alcoholic fatty liver disease (NAFLD), characterized by significant fat deposition in hepatocytes (2). Cholesterol GSD shares several risk factors with NAFLD, notably age, obesity, diabetes mellitus, insulin resistance, hyperlipidemia, sedentary lifestyle, and metabolic syndrome (2-4). It remains uncertain whether NAFLD acts as a precursor to GSD, or if the presence of GSD signifies long-standing features of metabolic syndrome, thereby hastening the progression of NAFLD (5). NAFLD stands as the foremost cause of chronic liver disease and cryptogenic cirrhosis globally. Non-alcoholic steatohepatitis (NASH), encompassing 10%-20% of NAFLD cases, can advance to severe chronic liver disease, liver cirrhosis, and hepatocellular carcinoma (6).

As of today, non-alcoholic steatohepatitis (NASH) primarily relies on histological diagnosis due to the unreliability of non-invasive methods. Liver biopsy remains the gold standard for diagnosing and staging NAFLD. However, firm recommendations regarding when to perform a liver biopsy in NAFLD patients are lacking. In our present study, our objective was to estimate the prevalence of NASH in patients with symptomatic GSD and concomitant fatty liver diagnosed via US.

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This insight could aid in determining whether liver biopsy should be routinely conducted during cholecystectomy to assess the severity of NAFLD in GSD patients with concurrent fatty liver. The diagnosis of NASH upon biopsy would offer sufficient grounds for recommending lifestyle modifications, controlling metabolic risk factors, and implementing long-term liver disease monitoring in these patients. Additionally, we aimed to identify clinical predictors of NASH within this population, potentially facilitating timely evaluation and intervention. Previous studies have primarily focused on general patient populations, whereas our study exclusively concentrated on individuals with fatty liver and GSD to ascertain both prevalence rates and predictors of NASH in such patients.

MATERIAL and METHODS

This prospective observational study was conducted on consecutive adult patients aged 18-70 years diagnosed with symptomatic GSD and fatty liver via ultrasound (US) undergoing cholecystectomy at a tertiary care center in Northeastern India from March 2021 to June 2023. Ethics approval was obtained from the Institutional Ethics Committee (AIIMS/Pat/IEC/PGTh/Jan20/09), and research approval was taken from the institutional research board (AIIMS/Pat/IRC/2020/PGTh/Jan20/09) on 01/03/2021. Patients positive for HBV and HCV, with a history of alcohol intake exceeding 20 g per day for females and 30 g per day for males, diagnosed with liver cirrhosis, autoimmune hepatitis, or other liver diseases, pregnant individuals, and those with a history of drug intake (including oral contraceptive pills, steroids, methotrexate, amiodarone, tamoxifen, highly active antiretroviral therapy, and chemotherapy agents) were excluded from the study. Written informed consent was obtained from all included patients, and the study was conducted in accordance with the declaration of Helsinki.

Demographic details, clinical history of comorbidities, and anthropometric parameters were recorded. All patients underwent blood investigations, including fasting blood sugar, glycated hemoglobin (HbA1c), liver function tests [bilirubin, albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), prothrombin time international normalized ratio (INR)], thyroid stimulating hormone (TSH), lipid profile [triglycerides (TG), cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL)], and serology for hepatitis B and C. Preoperatively, all patients underwent USG to document gallstones and assess the presence of fatty liver, as well as Fibroscan® (Echosens, Paris, France) for calculating controlled attenuation parameter (CAP).

Liver biopsies were performed during laparoscopic cholecystectomy using a 16 g × 20 cm, BARD Max-Core™ Core Biopsy Instrument (Arizona, USA) from the right lobe of the liver. Hematoxylin-eosin stained and Masson trichrome stained

paraffin-embedded liver biopsy sections were examined and interpreted by a single experienced pathologist. Severity was assessed using the NAFLD activity score (NAS) as proposed by the clinical research network (7). A NAS score of less than three was categorized as non-NASH, 3-4 as borderline NASH, and five or more as NASH. Fibrosis was staged on a scale of zero to four according to the clinical research network (7).

The sample size was determined based on a survey by Monzon et al., which reported a 10.2% prevalence of NASH in adult patients with GSD (8). To achieve a 95% confidence level and a 5% absolute precision, the study required a sample size of 131 participants. Clinical demographic data collected were analyzed using descriptive statistics. Qualitative variables were presented as absolute [number, (n)] and relative [percentage, (%)] frequencies. Standard deviations, means, and frequencies for each group with categorical variables were calculated. Qualitative data between the groups were compared using Pearson's Chi-square test or Fisher's exact test as appropriate. Quantitative variables were analyzed using ANOVA for normally distributed data (confirmed by Shapiro-Wilk test) and equal variances (confirmed by Levene's test). Ordinal logistic regression analysis was adjusted for confounding variables to identify independent predictors of NASH in the entire study population. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for the Social Sciences, version 20, SPSS Inc., Chicago, IL, United States (SPSS) for Microsoft Windows.

RESULTS

Among the 550 patients initially evaluated for laparoscopic cholecystectomy, 150 patients with fatty liver on US who met the inclusion and exclusion criteria were enrolled in the study. A further 16 patients with inadequate liver tissue for quantifying fatty liver on liver biopsy were excluded from the final analysis.

The demographic details of the patients are summarized in Table 1. Mean age of the patients was 43.22 ± 11.54 years (range 20 - 72 years), with ninety (67.2%) of the study participants being female. Mean body mass index (BMI) was 26.53 ± 3.99 kg/m². Among all patients, 49 (36.6%) were obese, and 52 (38.8%) were overweight. Additionally, twenty patients (16.3%) were diabetic, 23 (17.2%) were hypertensive, 16 (11.9%) had hypothyroidism, and four had other comorbidities, including bronchial asthma and coronary artery disease. According to the International Diabetes Federation (IDF) consensus definition, metabolic syndrome was present in 63.6% of the study population (9).

Upon analysis of liver biopsy samples from 134 patients with fatty liver on preoperative US, NASH (i.e., NAS score ≥ 5) was found in 21 (15.67%) patients with GSD. Fifty (37.31%) patients had probable NASH (i.e., NAS scores of 3 and 4), while sixty-three (47.01%) patients had non-NASH scores (i.e., NAS scores ≤ 2) (Table 2).

Table 1. Patient demographics

Category	Mean/Count	Standard Deviation/ Percentage
Age, years	43.22	11.54
Sex		
Male	44	32.8%
Female	90	67.2%
BMI, kg/m ²	26.53	3.99
BMI categories		
Normal (18.5-22.49)	20	14.9%
Overweight (22.5-27.49)	52	38.8%
Obese (>27.5)	49	36.6%
Comorbidity status	52	42.3%
Diabetes mellitus	20	16.3%
Hypertension	23	17.2%
Thyroid disease	16	11.9%
Other comorbidities	4	3.3%

BMI: Body mass index.

Table 2. Prevalence of NASH

Liver Biopsy	n= 134
Non-NASH	63 (47.01%)
Probable NASH	50 (37.31%)
NASH	21 (15.67%)

NASH: Non-alcoholic steatohepatitis.

Table 3. Prevalence of fibrosis

Grade	n
0	49
1a	2
1b	1
1c	11
2	17
3	2
4	0
Total	82

Masson trichrome staining was performed on 82 samples, revealing hepatic fibrosis in 33 of them, with 17 patients having stage 2 and two patients with grade 3 fibrosis. None of the patients had underlying cirrhosis (Table 3). Among patients with NASH, 23% exhibited significant hepatic fibrosis (F2 or higher).

A higher percentage of patients with NASH had metabolic syndrome (86.7%) although it did not achieve statistical significance as a risk factor for NASH (p= 0.114). NASH patients had higher AST levels (41.19 ± 20.53 IU/L) compared to non-

NASH subjects (28.95 ± 12.66 IU/L) (p= 0.028). ALT levels in non-NASH subjects were 28.36 ± 17.88 IU/L, while in NASH subjects, they were 44.71 ± 27.92 IU/L (p= 0.047). The remaining biochemical parameters, such as ALP, albumin, INR, cholesterol, HDL, VLDL, LDL, triglycerides, FBS, HbA1c, and TSH, did not achieve statistical significance. CAP increased from 219.40 ± 60.44 dB/m in non-NASH subjects to 265.48 ± 63.47 dB/m in NASH patients (p= 0.006) (Table 4).

For multivariate analysis, the following variables were considered: age, sex, comorbidities, BMI, AST, ALT, INR, HDL, triglycerides, and CAP. In this model, only AST reached statistical significance (p= 0.041) (Table 5). No morbidity or mortality were reported secondary to intra-operative liver biopsy in any patient.

DISCUSSION

GSD and NAFLD share common risk and pathogenic factors, and several studies have reported a significant association between them. The clinical spectrum of NAFLD includes steatosis, NASH, fibrosis, and cirrhosis. Given the high prevalence of NAFLD in patients with GSD, our study aimed to determine the prevalence of NASH and identify contributing risk factors in patients with fatty liver undergoing cholecystectomy.

Our study found NASH in 21 (15.67%) out of 134 patients undergoing cholecystectomy with fatty liver detected on preoperative US. Fifty percent of the patients with NASH were obese, while 43.5% of the probable NASH group and 42.9% of the non-NASH group were obese. Univariate analysis revealed significant differences in AST, ALT, and CAP between the NASH and non-NASH groups (p= 0.028), (p= 0.008), and (p= 0.006), respectively. Multivariate analysis showed that only AST was significant (p= 0.041).

The prevalence of NAFLD varies depending on the diagnostic test and population studied. Indian data indicates a prevalence of NAFLD between 6.7%-55.1% in adults (10). The variation in prevalence results from different diagnostic methods such as US, magnetic resonance imaging, and biopsy. A meta-analysis has found the pooled odds ratio of NAFLD in patients with gallstone disease to be 1.55 (95% CI 1.31-1.82) (11). In studies on patients undergoing cholecystectomy, NAFLD has shown a prevalence of 35%-55% in persons with GSD (8,12-15). The prevalence of NASH varies from 6%-11% in patients undergoing cholecystectomy (8,14,16,17). However, these studies were conducted on a general cohort of patients undergoing cholecystectomy. Our study specifically targeted patients with a preoperative diagnosis of NAFLD on US, revealing a 15.67% prevalence of NASH in this population. This high prevalence justifies considering liver biopsy during cholecystectomy to detect NASH early and implement necessary interventions such as lifestyle modifications and treatment of metabolic comorbidities can help reduce the

Table 4. Characteristics of the patients with gallstones studied according to diagnosis on liver histology

Risk factors	Levels	Liver biopsy			p
		Non NASH (n= 63)	Probable NASH (n= 50)	NASH (n= 21)	
Age (in years)		41.35 ± 12.26	44.08 ± 10.51	46.76 ± 11.11	0.142
Sex	Male	18 (40.9%)	22 (50%)	4 (9.1%)	0.076
	Female	45 (50%)	28 (31.1%)	17 (18.9%)	
BMI (kg/m ²)		25.86 ± 4.11	27.34 ± 3.69	26.65 ± 4.15	0.169
BMI category	Normal	14 (23.7)	3 (6.5%)	3 (18.8%)	0.158
	Overweight	24 (35.6%)	23 (50%)	5 (31.3%)	
	Obese	21 (42.9%)	20 (43.5%)	8 (50%)	
Presence of comorbidity	Absent	39 (54.9%)	22 (31%)	10 (14.1%)	0.206
	Present	21 (40.4%)	24 (46.2%)	7 (13.5%)	
Metabolic syndrome	Absent	21 (42.9%)	17 (37%)	2 (13.3%)	0.114
	Present	28 (57.1%)	29 (53%)	13 (86.7%)	
Bilirubin (mg/dL)		0.73 ± 0.54	0.67 ± 0.42	0.63 ± 0.39	0.652
AST (IU/L)		28.95 ± 12.66	33.12 ± 14.75	41.19 ± 20.53	0.028
ALT (IU/L)		28.36 ± 17.88	39.78 ± 27.45	44.71 ± 27.92	0.008
ALP (IU/L)		92.18 ± 44.44	98.25 ± 46.44	88.76 ± 25.20	0.633
Albumin (g/dL)		4.00 ± 0.40	4.03 ± 0.39	3.90 ± 0.57	0.492
INR		0.99 ± 0.13	0.94 ± 0.08	0.93 ± 0.10	0.073
Cholesterol (mg/dL)		168.0 ± 29.9	172.2 ± 44.2	172.4 ± 50.3	0.832
HDL (mg/dL)		50.45 ± 40.25	42.85 ± 19.48	38.20 ± 10.19	0.212
VLDL (mg/dL)		32.56 ± 13.30	29.99 ± 15.49	34.05 ± 9.96	0.480
LDL (mg/dL)		93.50 ± 29.38	99.30 ± 36.40	93.10 ± 42.66	0.651
Triglycerides (mg/dL)		161.77 ± 62.7	149.38 ± 76.7	219.97 ± 251.3	0.077
FBS (mg/dL)		104.50 ± 25.5	105.50 ± 27.4	106.32 ± 16.5	0.958
HbA1c (%)		5.72 ± 0.85	5.72 ± 1.41	5.66 ± 0.59	0.974
TSH (m IU/L)		3.82 ± 2.42	3.42 ± 3.39	5.33 ± 10.15	0.319
CAP (dB/m)		219.40 ± 60.4	243.64 ± 59.7	265.48 ± 63.47	0.006

BMI: Body mass index, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, INR: International normalized ratio, HDL: High density lipoprotein, VLDL: Very low density lipoprotein, LDL: Low density lipoprotein, FBS: Fasting blood sugar, HbA1c: Glycated hemoglobin, TSH: Thyroid stimulating hormone, CAP: Controlled attenuation parameter.

advanced liver disease burden in the population. We utilized a core liver biopsy instead of a wedge biopsy because fibrous septa from a subcapsular sample in a wedge biopsy may mimic cirrhosis and potentially overestimate the stage of liver disease (18). Previous studies have primarily employed wedge biopsies rather than core biopsies (13,15,16).

In patients with NAFLD, liver fibrosis plays a crucial role in overall morbidity and mortality. Our study revealed significant liver fibrosis in 23% of NASH subjects, although advanced fibrosis was rare, and none had compensated cirrhosis. These findings suggest that patients were likely identified during the relatively early phase of NAFLD progression. Typically, fibrosis progression in NAFLD is slow, with approximately seven years required for one stage of fibrosis to progress (19).

Obesity is a common risk factor for both NAFLD and GSD. Both excessive BMI and visceral obesity are recognized risk factors for NAFLD. In studies conducted on patients undergoing cholecystectomy, some have found a statistically significant difference in BMI between the NASH and non-NASH groups (14,16). In contrast, other studies have reported no significant difference in BMI among NASH and non-NASH patients (17). The presence of 50% of the patients in the non-obese group might be attributed to the lower BMI in our population compared to other parts of the country. NAFLD has been reported in lean subjects residing in developing countries, suggesting that lean NAFLD may represent a distinct entity that could contribute to NAFLD in our population.

Table 5. Summary of ordinal regression analysis

Variable	Estimate (b)	Standard Error	p
Age	0.038	2.513	0.265
Sex	-0.354	0.460	0.442
BMI	0.060	0.054	0.270
Comorbidity	0.041	0.450	0.928
AST	0.050	0.024	0.041
ALT	0.004	0.015	0.792
INR	-2.108	1.858	0.257
HDL	-0.015	0.011	0.165
Triglycerides	0.001	0.002	0.688
CAP	0.003	0.004	0.416

BMI: Body mass index, AST: Aspartate transaminase, ALT: Alanine transaminase, INR: International normalized ratio, HDL: High density lipoprotein, CAP: Controlled attenuation parameter.

Metabolic syndrome is prevalent in patients with symptomatic gallstones, with a significant association with NAFLD. It remains unclear whether NAFLD serves as a precursor to GSD or if the presence of GSD indicates the presence of longstanding features of metabolic syndrome, potentially accelerating the progression of NAFLD. In our study, metabolic syndrome was present in 63.6% of NAFLD patients, with 20 patients (16.3%) diagnosed with diabetes mellitus and 23 (17.2%) with hypertension. A higher percentage of patients with NASH exhibited metabolic syndrome (86.7%) although it did not achieve statistical significance as a risk factor for NASH ($p=0.114$). The prevalence of metabolic syndrome in the non-NASH group was 57.1%, and in the probable-NASH group, it was 53%. The close association between metabolic syndrome and GSD has led some researchers to propose GSD as another manifestation of metabolic syndrome (19). However, its role as a risk factor for NASH in our study did not reach statistical significance. Routine assessment of metabolic syndrome components is essential to mitigate NASH progression and liver-related complications.

Identifying subsets with NASH and liver fibrosis in NAFLD patients is crucial for disease management. While several non-invasive validated non-invasive markers for liver fibrosis such as AST/platelet ratio index, fibrosis-4 index, non-alcoholic fatty liver disease fibrosis score, BMI AST/ALT ratio, and diabetes score (BARD), exist for liver fibrosis, none reliably indicate the presence of NASH (20). In studies comparing NAFLD and NASH patients with normal controls based on liver biopsies, AST and ALT were found to correlate with the presence of NASH (15,21). In our univariate analysis, AST and ALT levels were significant in both NASH and non-NASH populations, with only AST showing independent association with NASH in the multivariate analysis.

High serum triglyceride levels and low serum HDL levels are commonly observed in patients with NAFLD (15,22-24). Our results were consistent with this observation although statistical significance was not achieved.

CAP is a valid method for the non-invasive detection and quantification of hepatic steatosis. Its measurement has been validated by multiple studies, and CAP scores have shown good correlation with hepatic steatosis observed on liver biopsies (25-28). In our study as well, CAP was significantly different between the NASH and non-NASH groups in the univariate analysis.

Liver biopsy during cholecystectomy was well-tolerated in our study, with no significant complications reported. This may be attributed to the fact that the liver biopsy procedure is performed under laparoscopic visualization, allowing for immediate coagulation of any bleeders using electrocautery. We can observe for any further bleeding from the biopsy site.

This study highlights the importance of screening for NASH in patients with GSD and fatty liver undergoing cholecystectomy. Liver biopsy emerges as a vital diagnostic tool to assess NASH and fibrosis presence and severity. Close monitoring of metabolic syndrome components is warranted to mitigate NASH progression and liver-related complications. Routine assessment of liver enzymes and evaluation of fibrosis status can aid in early detection and management strategies for patients with GSD and fatty liver undergoing cholecystectomy.

Our study had limitations, including being hospital-based and single-centered, posing a risk of referral bias. Additionally, as a cross-sectional study, causality cannot be determined. Our study group consisted of patients who were optimized for surgery; hence, the biochemical parameters obtained may reflect optimized rather than typical values found in the general population. Consequently, the prediction of risk factors may have been influenced. Nonetheless, our findings underscore the importance of considering liver biopsy in NAFLD patients with GSD undergoing cholecystectomy, particularly in those with elevated liver enzymes.

Ethics Committee Approval: This study was obtained from All India Institute of Medical Sciences Institutional Ethics Committee (Decision no: AIIMS/Pat/IEC/PGTh/Jan20/09 Date: 01.03.2021).

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**ORJİNAL ÇALIŞMA-ÖZET**

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Kolesistektomi yapılan safra taşı hastalığı ve eşlik eden alkolik olmayan yağlı karaciğer hastalığı olan hastalarda karaciğer biyopsisi: Prospektif gözlemsel bir çalışmaAaron John¹, Utpal Anand², Tarun Kumar³, Rohith Kodali², Kunal Parasar², Ramesh Kumar⁴, Rajeev Priyadarshi⁵, Basant Singh², Kislay Kant²¹ Rajagiri Hastanesi, Gastrointestinal, HPB, Çoklu Organ Nakli Cerrahisi Kliniği, Kochi, Hindistan² Tüm Hindistan Tıp Bilimleri Enstitüsü, Cerrahi Gastroenteroloji Anabilim Dalı, Patna, Hindistan³ Tüm Hindistan Tıp Bilimleri Enstitüsü, Patoloji Anabilim Dalı, Patna, Hindistan⁴ Tüm Hindistan Tıp Bilimleri Enstitüsü, Tıbbi Gastroenteroloji Anabilim Dalı, Patna, Hindistan⁵ Tüm Hindistan Tıp Bilimleri Enstitüsü, Radyodiagnostik Anabilim Dalı, Patna, Hindistan**ÖZET**

Giriş ve Amaç: Safra taşı hastalığı (STH) ve alkolik olmayan yağlı karaciğer hastalığı (AOYKH) ortak risk faktörlerini paylaşmaktadır. Alkolik olmayan yağlı karaciğer hastalığı, ciddi karaciğer rahatsızlıklarına yol açabilen alkol dışı steatohepatit (ADS)'ye ilerleyebilir. Bu çalışmada, kolesistektomi yapılan STH ve yağlı karaciğer hastalarında NASH prevalansını ve ilişkili faktörleri değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu prospektif gözlemsel çalışma Mart 2021-Haziran 2023 tarihleri arasında yürütülmüş ve preoperatif ultrasonografiye göre STH ve yağlı karaciğer tanısı koyulan 134 hasta dahil edilmiştir. Kolesistektomi sırasında kor karaciğer doku biyopsileri alınmıştır. Ameliyat öncesi klinik, antropometrik, demografik, biyokimyasal değişkenler ve FibroScan parametreleri kaydedilmiştir.

Bulgular: Hastaların 21'inde (%15,67) NASH, 50'sinde (%37,31) olası NASH ve 63'ünde (%47,01) NASH dışı skorlar saptandı. Hastaların %63,6'sında metabolik sendrom mevcuttu. Tek değişkenli analizde AST ve ALT değerleri NASH ve NASH olmayan gruplar arasında anlamlı farklılıklar göstermiştir. Çok değişkenli analizde, AST istatistiksel olarak anlamlıydı ($p=0,041$). NASH olmayan hastalarda ortalama kontrollü zayıflama parametresi $219,40 \pm 60,44$ dB/m iken NASH olan hastalarda $265,48 \pm 63,47$ dB/m idi ($p=0,006$). İncelenen 82 lamin 33'ünde fibrozis mevcuttu ve 17 hastada evre 2 ve iki hastada evre 3 fibrozis vardı.

Sonuç: Safra taşı hastalığı olan hastalar arasında NASH prevalansının yüksek olması, önemli bir halk sağlığı sorununa işaret etmekte ve laparoskopik kolesistektomi geçiren NAFLD ve STH'li bireylerde karaciğer biyopsisinin dikkate alınmasını gerektirmektedir.

Anahtar Kelimeler: Safra taşı hastalığı, NAFLD, NASH, alkolik olmayan yağlı karaciğer hastalığı, alkol dışı steatohepatit

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