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Progressive Rise in Hepatic Steatosis and Fibrosis with Longer Time Since Cholecystectomy: Findings from a Nationally Representative Survey

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ABSTRACT

Background Cholecystectomy is a common surgical procedure, yet its long-term metabolic consequences on liver health remain poorly understood. The temporal association between time since cholecystectomy and hepatic steatosis and fibrosis was evaluated using data from a nationally representative US population. **Methods** We analyzed data from the 2017~2020 National Health and Nutrition Examination Survey (NHANES) cycles, focusing on participants with available data on vibration-controlled transient elastography (VCTE), liver stiffness measurements (LSM), controlled attenuation parameter (CAP), and the FIB-4 index. Adults aged ⩾20 years without viral hepatitis, malignancy, or liver disease were included. Cholecystectomy exposure was categorized by time since surgery: no cholecystectomy, 0~5 years, 6~10 years, and >10 years. Weighted linear and logistic regression models assessed associations with CAP, LSM, and FIB-4, adjusting for demographic, metabolic, and lifestyle factors. Sensitivity analyses using inverse probability of treatment weighting (IPTW) were conducted to assess robustness. **Results** Among 6,246 eligible adults, cholecystectomy was independently associated with increased odds of hepatic steatosis (CAP > 248 dB/m), particularly with longer postoperative durations (OR: 1.141 for >10 years, $p<0.001$). However, no significant association was found for log-transformed CAP values after full covariate adjustment. In contrast, cholecystectomy showed a dose-response relationship with liver stiffness: compared to controls, log-LSM values progressively increased with time since surgery (β for >10 years = 0.179, $p<0.001$), corresponding with higher odds of LSM-defined fibrosis (OR: 1.713~2.005, $p<0.001$). Associations with FIB-4 were mixed: early postoperative periods were associated with lower FIB-4 levels, while longer-term periods showed slight increases in fibrosis classification. All key findings remained consistent in IPTW analyses, with E-values indicating robustness to unmeasured confounding. **Conclusions** In this cross-sectional analysis of a nationally representative US population, cholecystectomy was associated with increased hepatic steatosis and fibrosis, with distinct time-related patterns. The risk of steatosis appeared to rise progressively with longer postoperative durations, while fibrosis was most prominent in the early postoperative period. These findings highlight the potential need for liver health monitoring in individuals with a history of cholecystectomy, especially those with metabolic risk factors.

1. Introduction

Cholecystectomy represents the definitive treatment for symptomatic gallstone disease, with approximately 750,000 procedures performed annually in the United States alone and over 2 million globally [1]. While traditionally considered a benign intervention with minimal long-term consequences, emerging evidence challenges this paradigm by demonstrating potential metabolic sequelae following gallbladder removal. The gallbladder functions beyond simple bile storage—it orchestrates critical aspects of bile acid metabolism through rhythmic storage, concentration, and postprandial release mechanisms that maintain enterohepatic homeostasis [2]. Disruption of these precisely regulated processes may precipitate unintended metabolic consequences, particularly affecting hepatic lipid metabolism.

Metabolic dysfunction-associated steatotic liver disease (MASLD, previously NAFLD) affects 32% of the global population and represents the

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most rapidly increasing cause of chronic liver disease worldwide [3][4]. The pathophysiology of gallstone disease and hepatic steatosis demonstrates striking overlap, with both conditions sharing metabolic risk factors including insulin resistance, dyslipidemia, and central obesity [5]. However, distinguishing between the metabolic consequences of underlying gallstone disease versus the independent effects of cholecystectomy itself remains a major challenge in epidemiological investigations, creating significant confounding by indication that complicates causal inference.

The biological rationale linking cholecystectomy to hepatic steatosis centers on fundamental alterations in bile acid signaling pathways. Following gallbladder removal, bile acids flow continuously from liver to intestine, disrupting the normal pulsatile pattern essential for optimal farnesoid X receptor (FXR) activation [6]. This continuous bile acid exposure fundamentally alters the FXR-fibroblast growth factor 19 (FGF19) axis, a critical regulatory system governing hepatic lipogenesis and gluconeogenesis [7]. Simultaneously, loss of gallbladder-mediated bile acid storage increases enterohepatic circulation frequency, potentially overwhelming intestinal G protein-coupled bile acid receptor (TGR5) signaling and disrupting incretin hormone release patterns [8][9]. These molecular perturbations create conditions favoring hepatic triglyceride accumulation and metabolic dysfunction.

Current epidemiological evidence linking cholecystectomy to MASLD remains contradictory and methodologically limited. While retrospective cohort studies suggest increased MAFLD risk following cholecystectomy [10][11], these investigations suffer from significant limitations including reliance on biochemical surrogates rather than validated imaging assessments, inadequate confounding control, and absence of temporal analysis. Most critically, the temporal relationship between surgery and hepatic changes remains unexplored, despite growing recognition that bile acid-mediated metabolic effects may evolve over years following gallbladder removal. Recent large-scale studies have yielded conflicting results, with some demonstrating increased MASLD risk [12] while others report null associations [13].

Recent advances in non-invasive hepatic assessment have created unprecedented opportunities to address these knowledge gaps with precision. Transient elastography provides simultaneous quantification of hepatic steatosis via CAP and liver fibrosis through LSM, offering standardized metrics that overcome limitations of traditional imaging modalities [14][15]. The integration of validated serum biomarkers such as FIB-4 further enhances diagnostic accuracy for detecting clinically significant liver disease [16]. To address these critical knowledge gaps, we conducted a comprehensive analysis of 6,246 adults from the NHANES 2017-March 2020, stratified by time since cholecystectomy. Using transient elastography-derived parameters and multivariable regression modeling with inverse probability of treatment weighting, we tested the hypothesis that cholecystectomy associates with time-dependent increases in hepatic steatosis and fibrosis risk.

2. Materials and methods

2.1. Study Population

We analyzed data from the 2017-March 2020 NHANES, representing the pre-pandemic cycle with complete transient elastography assessments. From the initial 15,560 participants, we systematically excluded individuals under 20 years of age (n = 6,328), those lacking complete cholecystectomy history (n = 4), participants without valid CAP and LSM data (n = 1,310), and individuals missing essential biochemical parameters required for FIB-4 calculation—specifically alanine aminotransferase (n = 535), aspartate aminotransferase (n = 29), or platelet count (n = 4). We further excluded participants with active liver disease (n = 195), current viral hepatitis infections including hepatitis B (n = 31), hepatitis C (n = 59), or hepatitis E (n = 149), and those reporting a history of malignancy (n = 670). The final analytic cohort comprised 6,246 adults, representing a weighted U.S. population of approximately 158 million adults. All NHANES procedures received approval from the National Center for Health Statistics Ethics Review Board, and participants provided written informed consent. Details of the exclusion process are shown in Figure 1.

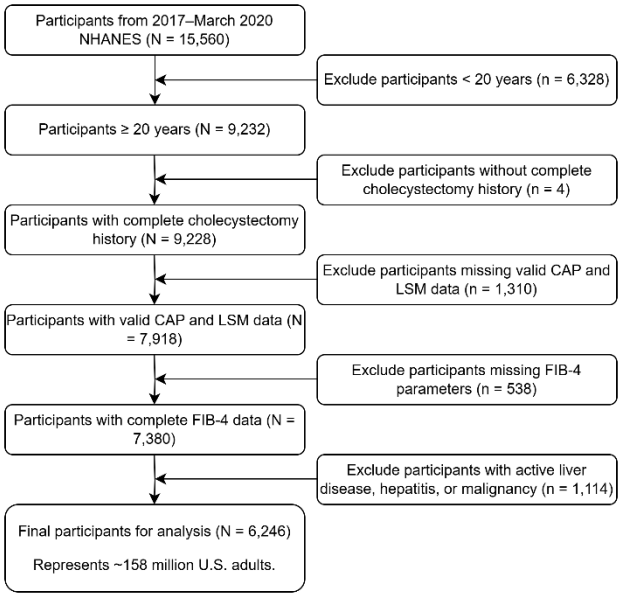

Fig. 1 - Participant Selection and Exclusion Process

2.2. Transient Elastography Parameters

Hepatic steatosis and fibrosis were quantified using the FibroScan® 502 V2 Touch system (Echosens, Paris, France) with the M probe, administered by trained technicians following standardized protocols. The CAP served as our primary steatosis metric, measured in decibels per meter (dB/m), while LSM provided our fibrosis assessment, recorded in kilopascals (kPa). Quality control criteria mandated a minimum of 10 valid measurements with an interquartile range-to-median ratio $\leqslant$ 30% and a success rate $\geqslant$ 60%.

For analytical purposes, we examined these parameters both as continuous variables (natural log-transformed to address right-skewed distributions) and as clinically relevant binary classifications. Steatosis was defined as CAP > 248 dB/m, corresponding to moderate-to-severe hepatic fat accumulation based on histological validation studies [17][18]. Significant fibrosis was defined as LSM $\geqslant$ 8.2 kPa, representing the established threshold for stage 2 or higher fibrosis in the general population [19][20].

2.3. Biochemical Fibrosis Assessment

The FIB-4 index was calculated using the standard formula: [age × AST] / [platelet count × $\sqrt{}$ ALT], where AST and ALT are expressed in U/L and platelet count in 10^9/L. Elevated FIB-4 was defined as $\geqslant$ 1.45, consistent with current guidelines for identifying individuals at increased risk of ad-

vanced fibrosis [21][22]. This non-invasive biomarker served as a complementary assessment to transient elastography, providing additional validation of our fibrosis determinations.

2.4. Covariate Assessment

We systematically collected potential confounding variables across multiple domains based on established risk factors for hepatic steatosis and fibrosis. Demographic characteristics included age (continuous), sex (male/female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Hispanic, Other Race), and family poverty-income ratio stratified as low income (≤ 1.00), middle income (1.01~3.00), and high income (> 3.00).

Anthropometric and metabolic variables encompassed body mass index categories (< 25.0, 25.0~29.9, ≥ 30.0 kg/m²), diabetes mellitus defined as either self-reported diagnosis or laboratory evidence of fasting plasma glucose ≥ 7.0 mmol/L or HbA1c ≥ 6.5% [23], hypertension determined by self-reported diagnosis or an average of three measured blood pressure readings ≥ 130/80 mmHg [24], and dyslipidemia identified by self-report or laboratory evidence of total cholesterol ≥ 200 mg/dL, triglycerides ≥ 150 mg/dL, LDL-C ≥ 130 mg/dL, or HDL-C < 40 mg/dL for men and < 50 mg/dL for women [25].

Lifestyle factors included smoking history (never vs. ever/current), Alcohol use patterns categorized as non-drinker, light drinker (≤ 1 drink/day for women, ≤ 2 drinks/day for men), moderate drinker (1~2 drinks/day for women, 2~3 drinks/day for men), and heavy drinker (> 2 drinks/day for women, > 3 drinks/day for men).

2.5. Statistical Analysis

All analyses incorporated appropriate survey weights (WTMECPRP), strata, and primary sampling units to account for NHANES' complex multistage probability sampling design, ensuring nationally representative estimates. Missing data for covariates were handled using multiple imputation techniques to ensure robust and unbiased estimates. We confirmed non-normal distributions for log-transformed hepatic parameters using Anderson-Darling normality tests prior to analysis selection.

We constructed hierarchical survey-weighted regression models with sequential covariate adjustment to minimize confounding while preserving statistical power:

- Model 1 (crude): examined cholecystectomy associations without covariate adjustment.
- Model 2 (demographic): incorporated age, sex, race/ethnicity, and family poverty-income ratio.
- Model 3 (fully adjusted): additionally included BMI categories, diabetes, hypertension, dyslipidemia, Alcohol use, and smoking status.

For continuous outcomes (log-transformed CAP, LSM, and FIB-4), we employed survey-weighted linear regression, reporting regression coefficients (β) with 95% confidence intervals and two-sided p-values. For binary outcomes (steatosis, fibrosis classifications), we utilized survey-weighted logistic regression, presenting odds ratios (OR) with corresponding confidence intervals.

2.6. Sensitivity Analyses

To address potential confounding by indication and strengthen causal inference, we conducted IPTW analyses. Propensity scores for cholecystectomy were estimated using all Model 3 covariates in a multinomial logistic regression framework, with stabilized weights applied to minimize extreme values. We calculated E-values to quantify the minimum strength of association that unmeasured confounders would require to fully explain observed associations.

2.7. Model Performance Assessment

For binary outcomes, we evaluated model discrimination using receiver operating characteristic (ROC) curve analysis, calculating areas under the curve (AUC) with 95% confidence intervals. Model calibration was assessed through Hosmer-Lemeshow goodness-of-fit tests where appropriate. All analyses were conducted using Python version 3.10 (Python Software Foundation, USA), with appropriate methods to account for complex survey design and implement propensity score weighting. Statistical significance was defined as two-sided $p < 0.05$.

3. Results

3.1. Baseline characteristics of the participants

The analytic cohort comprised 6,246 adults, representing a weighted U.S. population of approximately 158 million adults. Participants were stratified by cholecystectomy status: no history (n = 5,654, 90.52%), 0~5 years post-surgery (n = 164, 2.63%), 6-10 years post-surgery (n = 109, 1.75%), and >10 years post-surgery (n = 319, 5.11%).

Significant demographic disparities emerged across groups. Mean age differed significantly across groups (48.04, 51.93, 51.60, and 60.54 years, respectively; $p < 0.001$), with the >10 years group being substantially older. Gender distribution showed marked female predominance in post-cholecystectomy groups: 48.27% female in controls versus 64.63%, 76.15%, and 82.76% in successive post-surgical intervals ($p < 0.001$). Racial composition varied significantly ($p < 0.001$), with Non-Hispanic White representation increasing from 30.74% in controls to 47.65% in the >10 years group.

Metabolic comorbidity burden escalated with longer post-cholecystectomy duration. Obesity prevalence (BMI ≥ 30 kg/m²) rose from 40.56% in controls to 54.88%, 66.06%, and 63.32% across post-surgical groups ($p < 0.001$). Similarly, hypertension increased from 53.82% to 70.53% ($p < 0.001$), diabetes from 34.95% to 47.96% ($p < 0.001$), and dyslipidemia from 75.20% to 81.82% ($p = 0.044$).

Hepatic parameters demonstrated progressive deterioration. Log-transformed CAP values increased from 5.54 in controls to 5.65 in the >10 years group ($p < 0.001$), with hepatic steatosis prevalence (CAP > 248 dB/m) rising from 57.61% to 76.49% ($p < 0.001$). Log-transformed LSM values showed similar patterns (1.64 to 1.82; $p < 0.001$), with liver fibrosis prevalence (LSM ≥ 8.2 kPa) increasing from 8.90% to 18.50% ($p < 0.001$). FIB-4 index elevation (≥1.45) prevalence rose from 18.38% in controls to 30.09% in the >10 years group ($p < 0.001$). Alcohol use patterns differed significantly ($p < 0.001$), with post-cholecystectomy participants showing higher abstinence rates. No significant differences emerged for smoking status or family income distribution (both $p > 0.05$) (Table 1).

Table 1 - Baseline characteristics of the selected participants

Variables	n (%)	No surgery	0~5 years post- surgery	6~10 years post-surgery	＞10 years post-surgery	*P*
Age (Mean ± SD)	48.84 ± 16.90	48.04 ±16.86	51.93 ± 17.41	51.60±14.47	60.54±13.27	<.001
CAP Log (Mean ± SD)	5.55 ± 0.25	5.54 ± 0.25	5.56 ± 0.27	5.63 ± 0.29	5.65 ± 0.22	<.001
LSM Log (Mean ± SD)	1.66 ± 0.41	1.64 ± 0.40	1.71 ± 0.46	1.79 ± 0.45	1.82 ± 0.53	<.001
FIB-4 log (Mean ± SD)	-0.14 ± 0.57	-0.15 ± 0.57	-0.13 ± 0.63	-0.11 ± 0.54	0.06 ± 0.54	<.001
CAP Group						<.001
＞248 dB/m	3685 (59.00)	3257 (57.61)	105 (64.02)	79 (72.48)	244 (76.49)	
≤248 dB/m	2561 (41.00)	2397 (42.39)	59 (35.98)	30 (27.52)	75 (23.51)	
LSM Group						<.001
≥8.2 kPa	610 (9.77)	503 (8.90)	26 (15.85)	22 (20.18)	59 (18.50)	
＜8.2 kPa	5636 (90.23)	5151 (91.10)	138 (84.15)	87 (79.82)	260 (81.50)	
FIB-4 group						<.001
≥1.45	1194 (19.12)	1039 (18.38)	39 (23.78)	20 (18.35)	96 (30.09)	
＜1.45	5052 (80.88)	4615 (81.62)	125 (76.22)	89 (81.65)	223 (69.91)	
Gender						<.001
Male	3064 (49.06)	2925 (51.73)	58 (35.37)	26 (23.85)	55 (17.24)	
Female	3182 (50.94)	2729 (48.27)	106 (64.63)	83 (76.15)	264 (82.76)	
Race						<.001
Mexican American	802 (12.84)	724 (12.81)	20 (12.20)	16 (14.68)	42 (13.17)	
Other Hispanic	687 (11.00)	620 (10.97)	17 (10.37)	13 (11.93)	37 (11.60)	
Non-Hispanic White	2006 (32.12)	1738 (30.74)	66 (40.24)	50 (45.87)	152 (47.65)	
Non-Hispanic Black	1648 (26.38)	1540 (27.24)	34 (20.73)	17 (15.60)	57 (17.87)	
Other Race	1103 (17.66)	1032 (18.25)	27 (16.46)	13 (11.93)	31 (9.72)	
Smoking						0.065
Ever/Current	2507 (40.14)	2241 (39.64)	70 (42.68)	53 (48.62)	143 (44.83)	
Never	3739 (59.86)	3413 (60.36)	94 (57.32)	56 (51.38)	176 (55.17)	
Alcohol Use						<.001
Non-drinker	1141 (18.27)	983 (17.39)	37 (22.56)	27 (24.77)	94 (29.47)	
Light drinker	1732 (27.73)	1546 (27.34)	51 (31.10)	36 (33.03)	99 (31.03)	
Moderate drinker	1708 (27.35)	1568 (27.73)	42 (25.61)	32 (29.36)	66 (20.69)	
Heavy drinker	1665 (26.66)	1557 (27.54)	34 (20.73)	14 (12.84)	60 (18.81)	
Family PIR						0.760
Low income	1127 (18.04)	1021 (18.06)	27 (16.46)	17 (15.60)	62 (19.44)	
Middle income	2535 (40.59)	2280 (40.33)	69 (42.07)	48 (44.04)	138 (43.26)	
High income	2584 (41.37)	2353 (41.62)	68 (41.46)	44 (40.37)	119 (37.30)	
BMI						<.001
Normal or underweight	1605 (25.70)	1527 (27.01)	26 (15.85)	9 (8.26)	43 (13.48)	
Overweight	1984 (31.76)	1834 (32.44)	48 (29.27)	28 (25.69)	74 (23.20)	
Obesity	2657 (42.54)	2293 (40.56)	90 (54.88)	72 (66.06)	202 (63.32)	
Hypertension						<.001
Yes	3434 (54.98)	3043 (53.82)	96 (58.54)	70 (64.22)	225 (70.53)	
No	2812 (45.02)	2611 (46.18)	68 (41.46)	39 (35.78)	94 (29.47)	
Diabetes						<.001
Yes	2244 (35.93)	1976 (34.95)	63 (38.41)	52 (47.71)	153 (47.96)	
No	4002 (64.07)	3678 (65.05)	101 (61.59)	57 (52.29)	166 (52.04)	
Dyslipidemia						0.044
Yes	4720 (75.57)	4252 (75.20)	121 (73.78)	86 (78.90)	261 (81.82)	
No	1526 (24.43)	1402 (24.80)	43 (26.22)	23 (21.10)	58 (18.18)	

Abbreviations: SD, standard deviation; PIR, poverty income ratio; BMI, body mass index; CAP, Controlled Attenuation Parameter; LSM, Liver Stiffness Measurement; FIB-4, Fibrosis-4 Index.

3.2. Visual Distribution of Log-Transformed Hepatic Parameters by Cholecystectomy History

Shapiro-Wilk tests indicated that the CAP, LSM, and FIB-4 values significantly deviated from normality ($p < 0.001$ for all), prompting the application of natural logarithmic transformations. Boxplots of the log-transformed CAP (CAP log), LSM (LSM log), and FIB-4 (FIB-4 log) values showed that participants with a history of cholecystectomy, particularly those within 0–5 years post-surgery, had higher median values compared to those without surgery. A clear upward trend in median values was observed over time, with the most significant increase occurring in the first 0~5 years post-surgery. In this early postoperative period, wider interquartile ranges

(IQR) and more extreme outliers were also observed, indicating greater variability in hepatic conditions (Figure 2, showing boxplots of log-transformed hepatic parameters by cholecystectomy history).

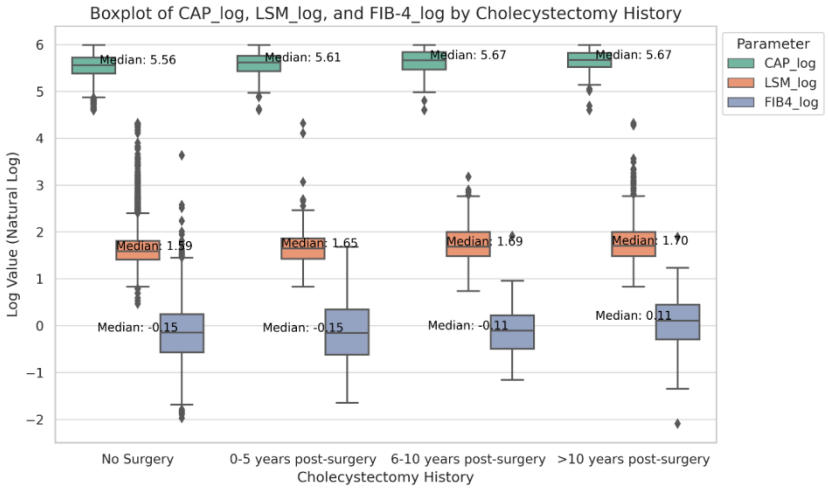

Fig. 2 - Distribution of CAP log, LSM log, and FIB-4 log by Cholecystectomy History

3.3. Hepatic Steatosis Outcomes

3.3.1 Continuous CAP Analysis: In fully adjusted weighted linear regression (Model 3), controlling for age, sex, race/ethnicity, poverty-income ratio, BMI, diabetes, hypertension, dyslipidemia, Alcohol use, and smoking, no statistically significant associations emerged between cholecystectomy timing and log-transformed CAP values. Compared to participants without cholecystectomy history, the 0~5 years post-surgical group showed a marginal log-CAP reduction (β = -0.029; 95% CI: -0.059~0.002; p = 0.065), while the 6-10 years group demonstrated a non-significant increase (β = 0.033; 95% CI: -0.005~0.070; p = 0.085). The >10 years post-cholecystectomy group exhibited minimal effect (β = 0.012; 95% CI: -0.011~ 0.034; p = 0.315).

3.3.2 Binary Steatosis Risk: Weighted logistic regression analysis (Model 3) revealed significant dose-response associations between cholecystectomy timing and hepatic steatosis risk (CAP > 248 dB/m). Compared to non-surgical controls, odds ratios for steatosis progressively increased: 0-5 years post-cholecystectomy (OR 1.053; 95% CI: 1.050~1.055; p < 0.001), 6~10 years (OR 1.137; 95% CI: 1.134~1.140; p < 0.001), and >10 years (OR 1.141; 95% CI: 1.139~1.143; p < 0.001) (Table 2, presenting steatosis associations across models).

Table 2 - Association between Cholecystectomy and Liver Outcomes (CAP, LSM, FIB-4) by Time Since Surgery - Model 3

Outcome	0-5 years post- surgery	p	6-10 years post-surgery	p	>10 years post-surgery	*P*
CAP Log	β = -0.0288 (-0.0594, 0.0018)	0.0653	β = 0.0329 (-0.0046, 0.0704)	0.0852	β = 0.0116 (-0.0110, 0.0341)	0.3148
CAP Group	OR = 1.0531 (1.0509, 1.0553)	<0.001	OR = 1.1370 (1.1340, 1.1401)	<0.001	OR = 1.1407 (1.1388, 1.1426)	<0.001
LSM Log	β = 0.0836 (0.0264, 0.1408)	0.0042	β = 0.1291 (0.0590, 0.1992)	<0.001	β = 0.1788 (0.1366, 0.2210)	<0.001
LSM Group	OR = 2.0051 (1.9996, 2.0106)	<0.001	OR = 1.9485 (1.9426, 1.9543)	<0.001	OR = 1.7127 (1.7094, 1.7161)	<0.001
FIB-4 Log	β = -0.0726 (-0.1232, -0.0220)	0.0049	β = -0.0006 (-0.0626, 0.0614)	0.9847	β = -0.0522 (-0.0895, -0.0150)	0.0061
FIB-4 Group	OR = 0.7750 (0.7728, 0.7772)	<0.001	OR = 1.0113 (1.0074, 1.0153)	<0.001	OR = 1.0102 (1.0084, 1.0120)	<0.001

Abbreviations: β, regression coefficient; CI, confidence interval; OR, odds ratio; CAP, Controlled Attenuation Parameter; LSM, Liver Stiffness Measurement; FIB-4, Fibrosis-4 Index.

3.4. Hepatic Fibrosis Outcomes

3.4.1 Continuous LSM Analysis: Fully adjusted analyses demonstrated progressively increasing log-transformed liver stiffness values with longer post-cholecystectomy intervals. Relative to non-surgical participants, mean log-LSM increased by 0.084 units at 0~5 years (β = 0.084; 95% CI: 0.026~0.141; p = 0.004), 0.129 units at 6~10 years (β = 0.129; 95% CI: 0.059~0.199; p < 0.001), and 0.179 units at >10 years post-surgery (β = 0.179; 95% CI: 0.137~0.221; p < 0.001), establishing a clear temporal gradient.

3.4.2 Binary Fibrosis Risk: Correspondingly, weighted logistic regression identified substantial elevated fibrosis risk (LSM ⩾ 8.2 kPa) across all post-cholecystectomy intervals: 0-5 years (OR 2.005; 95% CI: 1.999-2.011; p < 0.001), 6~10 years (OR 1.948; 95% CI: 1.943~1.954; p < 0.001), and >10 years (OR 1.713; 95% CI: 1.709~1.716; p < 0.001).

3.5. FIB-4 Index Associations

3.5.1 Continuous FIB-4 Analysis: Multivariable adjusted analyses yielded mixed findings for log-transformed FIB-4 values. The 0~5 years post-cholecystectomy group demonstrated significantly lower mean log-FIB-4 (β = -0.073; 95% CI: -0.123 to -0.022; p = 0.005), while the 6-10 years group showed no significant difference (β = -0.001; 95% CI: -0.063 to 0.061; p = 0.985). The >10 years group exhibited a modest reduction (β = -0.052; 95% CI: -0.090 to -0.015; p = 0.006).

3.5.2 Binary FIB-4 Classification: For categorical FIB-4 analysis (≥1.45), the 0~5 years post-cholecystectomy group showed reduced odds (OR 0.775; 95% CI: 0.773-0.777; p < 0.001), while both 6-10 years (OR 1.011; 95% CI: 1.007-1.015; p < 0.001) and >10 years groups (OR 1.010; 95% CI: 1.008-1.012; p < 0.001) demonstrated marginally increased risk.

3.6. Sensitivity Analyses

IPTW analyses using propensity scores derived from Model 3 covariates yielded results consistent with the primary analyses. For hepatic steatosis (CAP > 248 dB/m), a history of cholecystectomy was associated with increased odds (OR = 1.191; 95% CI: 1.108~1.281; E-value = 1.668). Similar associations were observed for liver fibrosis (OR = 1.776; 95% CI: 1.590~1.985; E-value = 2.950) and elevated FIB-4 scores (OR = 1.216; 95% CI: 1.114~1.327; E-value = 1.728). Additional analyses with weight trimming at the 1st and 99th percentiles showed comparable results: hepatic steatosis (OR = 1.358; 95% CI: 1.257~1.466), liver fibrosis (OR = 1.896; 95% CI: 1.691~2.125), and FIB-4 elevation (OR = 1.383; 95% CI: 1.264~1.514). (Table 3, summarizing sensitivity analyses).

Table 3 - Sensitivity Analysis of IPTW-Adjusted Associations between Cholecystectomy and Liver Outcomes (CAP, LSM, FIB-4)

Outcome	OR (95% CI)	E-value	*P*
CAP > 248 dB/m	OR = 1.191 (1.108, 1.281)	1.668	<0.001
LSM ≥ 8.2 kPa	OR = 1.776 (1.590, 1.985)	2.950	<0.001
FIB-4 Index ≥ 1.45	OR = 1.216 (1.114, 1.327)	1.728	<0.001
CAP > 248 dB/m - Weight Trimmed	OR = 1.358 (1.257, 1.466)	-	-
LSM ≥ 8.2 kPa - Weight Trimmed	OR = 1.896 (1.691, 2.125)	-	-
FIB-4 Index≥ 1.45 - Weight Trimmed	OR = 1.383 (1.264, 1.514)	-	-

Abbreviations: OR, odds ratio; CI, confidence interval; E-value, E-value for robustness of results; CAP, Controlled Attenuation Parameter; LSM, Liver Stiffness Measurement; FIB-4, Fibrosis-4 Index.

3.7. Model Performance

Receiver operating characteristic curve analysis demonstrated good discriminative performance for the fully adjusted models. Area under the curve values reached 0.797 for hepatic steatosis prediction, 0.796 for liver fibrosis, and 0.890 for FIB-4 elevation, indicating robust classification accuracy across all hepatic endpoints.

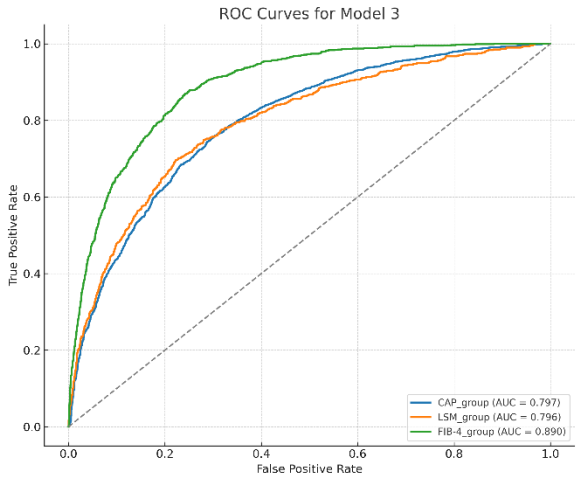

Fig. 3 - ROC Curves for Model 3: Evaluation of CAP, LSM, and FIB-4 Group Classifications

4. Discussion

This analysis of 6,246 adults from NHANES 2017-March 2020 provides the largest elastography-based examination of cholecystectomy's association with hepatic metabolic dysfunction. Our findings reveal distinct temporal patterns: progressive steatosis risk increase over time (OR 1.053~1.141) versus early-peaking fibrosis risk (OR 2.005 at 0-5 years) with subsequent attenuation. These observations challenge assumptions about the metabolic neutrality of gallbladder removal and carry implications for the 750,000 Americans undergoing annual cholecystectomy.

The temporal dynamics suggest different pathophysiological mechanisms. Progressive steatosis risk indicates cumulative metabolic disruption, consistent with bile acid signaling disruption following gallbladder removal. Gallbladder cholangiocytes express FGF19 at 250-fold higher levels than terminal ileum, with bile containing 23-fold higher FGF19 concentrations than serum [7][26]. Cholecystectomy eliminates this critical metabolic regulator, fundamentally altering enterohepatic feedback mechanisms governing hepatic lipogenesis.

Early fibrosis risk peaking followed by gradual attenuation suggests acute metabolic stress and inflammatory cascades triggered by sudden bile acid dysregulation, with partial adaptive compensation over time [27][28]. Continuous bile acid flow may overwhelm intestinal FXR capacity, leading to preferential hepatic FXR activation that paradoxically promotes fibrogenesis when chronically stimulated [29].

Our findings extend previous epidemiological observations. The landmark NHANES III analysis by Ruhl and Everhart first demonstrated cholecystectomy-fatty liver associations (OR 2.4) [10]. Subsequent population studies from Korea, China, and Europe consistently reported elevated metabolic syndrome and hepatic steatosis risks [30]. However, these investigations were limited by cross-sectional designs, subjective imaging, or insufficient power for temporal analysis.

Biological plausibility is supported by extensive experimental evidence. Beyond lipid absorption, bile acids function as metabolic hormones regulating glucose homeostasis and hepatic metabolism through FXR and TGR5 pathways [35][36]. Cholecystectomy replaces normal pulsatile concentrated bile acid delivery with continuous dilute flow, fundamentally altering signaling cascades. Animal studies consistently demonstrate increased hepatic steatosis and metabolic dysfunction following experimental cholecystectomy [37][38].

Additional mechanisms include gut microbiome alterations. Cholecystectomy changes intestinal bile acid exposure, promoting bacteria producing deoxycholic acid and other secondary bile acids that antagonize FXR signaling and promote hepatic lipogenesis [39][40]. Loss of gallbladder-derived FGF19 also disrupts circadian hepatic metabolism rhythms [41].

Our IPTW sensitivity analyses strengthen causal inference despite cross-sectional limitations. E-values (1.668~2.950) indicate unmeasured confounders would need substantial strength to fully explain findings. Comprehensive adjustment for demographic, metabolic, and lifestyle factors supports association independence.

Clinical implications are immediate. Current surgical guidelines provide minimal long-term metabolic monitoring guidance [42]. Our findings support structured surveillance protocols, particularly during peak fibrosis risk periods. Excellent ROC discrimination (AUC 0.796~0.890) suggests existing variables can identify high-risk patients requiring enhanced monitoring. For prevention, results raise questions about surgical decision-making for asymptomatic/minimally symptomatic gallstones. Recent trials demonstrate substantial practice variation with 10-41% persistent post-operative symptoms [43]. Given questionable indications for many cholecystectomies, identified metabolic risks support more restrictive surgical criteria.

Global burden implications are substantial. With NAFLD affecting 25% globally and representing the fastest-growing liver transplantation indication [44][45], factors accelerating progression merit serious consideration. Advanced fibrosis confers 3-15fold mortality increases [46], suggesting cholecystectomy history should be incorporated into prognostic algorithms.

Future research should focus on longitudinal studies with pre-surgical baselines, mechanistic investigations examining bile acid profiles and gut microbiota, and intervention studies testing FGF19 analogs or FXR agonists for post-cholecystectomy metabolic dysfunction [47][48].

In conclusion, cholecystectomy is associated with clinically significant, time-dependent hepatic steatosis and fibrosis risks persisting decades post-surgery. These associations remained robust after adjustment for demographic and metabolic risk factors, suggesting opportunities for improved surveillance and prevention strategies. Recognizing cholecystectomy as an independent risk factor represents an important step toward precise risk stratification and targeted prevention in the expanding global burden of metabolic liver disease.

5. Conclusion

In this nationally representative analysis of 6,246 U.S. adults, cholecystectomy was associated with increased risks of hepatic steatosis and fibrosis, with distinct temporal patterns suggesting different underlying mechanisms. Steatosis risk progressively increased over time (OR 1.053~1.141), while fibrosis risk peaked early post-surgery and gradually attenuated (OR 2.005 declining to 1.716). These associations persisted after comprehensive covariate adjustment and sensitivity analyses based on propensity scores. Given the high prevalence of cholecystectomy and the increasing burden of metabolic liver disease, these findings underscore the potential need for post-operative hepatic surveillance, particularly in metabolically vulnerable populations. However, the cross-sectional design limits causal inference, and further longitudinal studies with pre-operative liver assessments are necessary to confirm temporal relationships and refine evidence-based surveillance strategies.

A.1. Data Availability

All data analyzed in this study are available from the NHANES repository, maintained by the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/).

A.2. Competing interests

The authors declare no competing interests.

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