Fatty Liver Is an Independent Risk Factor for Delayed Recovery from Anesthesia

Mark Shapses,[1] Lin Tang,[2] Austin Layne,[3] Andrea Beri,[3] and Yaron Rotman [1]

Fatty liver (FL) is associated with altered activity of hepatic drug-metabolizing enzymes, but the clinical significance is unknown. Many anesthetic agents are metabolized in the liver. We aimed to determine whether FL impacts recovery from anesthesia as a surrogate for altered drug metabolism. This was a single-center, retrospective, case-control study of all adults who underwent anesthesia and concurrent abdominal imaging (n = 2,021) in a hospital setting. FL (n = 234) was identified through radiology reports. Anesthesia recovery, the primary endpoint, was defined by Aldrete's recovery score (RS, 0-10), assessed following postanesthesia care unit (PACU) arrival, with RS ≥8 considered discharge eligible. FL and controls were compared using univariate and multivariate analyses, adjusting for confounders. A secondary matched-pairs analysis matched FL and controls 1:1 for confounders. Time from airway removal to discharge eligibility was compared using multivariate Cox regression. On PACU arrival, 54.1% of FL were discharge eligible compared to 61.7% of controls (P = 0.03), with lower activity scores on univariate (P = 0.03) and multivariate analysis (P = 0.03). On matched-pairs analysis, discharge eligibility, activity, consciousness, and total RSs were lower in FL ($P \leq 0.04$ for all). Median time from airway removal to discharge eligibility was 43% longer in FL (univariate, P = 0.01; multivariate hazard ratio, 1.32; P = 0.046). To further exclude confounding by obesity, we performed a sensitivity analysis limited to a body mass index <30, where FL was still associated with lower activity (P = 0.03) and total RS (P = 0.03). *Conclusion:* Patients with FL have delayed recovery from anesthesia, suggesting altered drug metabolism independent of metabolic risk factors. (*Hepatology Communications* 2021;5:1848-1859).

Fatty liver (FL), the excess accumulation of triglycerides in the liver, is the most common chronic liver condition in Western countries.[1] FL is a component of both alcohol-associated liver disease and nonalcoholic fatty liver disease (NAFLD), each with an estimated prevalence of 4%-5% and 20%-30%, respectively.[2-6]

The presence of FL is associated with hepatic and nonhepatic outcomes, such as cardiovascular disease.[1] In addition, FL has also been shown to impact hepatic drug-metabolizing enzymes.[7-11] Specifically, evidence suggests that NAFLD is associated with increased activity of cytochrome P450 family 2 subfamily E member 1 (CYP2E1) and decreased activity of CYP3A4.[7,10,12] Altered activity of drug-metabolizing enzymes in FL is predicted to affect drug pharmacokinetics and pharmacodynamics, but to date there is a paucity of data to show that these findings from basic research studies have clinically meaningful implications.[11,13] No study has evaluated the impact of FL on drug metabolism in a real-world setting.

Anesthesia frequently uses medications that are metabolized by the CYP450 system.[14,15] Postanesthesia recovery, after anesthetic agents have

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; CYP450, cytochrome P450; FL, fatty Liver; MAC, monitored anesthesia care; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PACU, postanesthesia care unit; RS, recovery score.

Received April 16, 2021; accepted June 9, 2021.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1772/suppinfo.

Supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH) (Y.R.) and the NIH Medical Research Scholars Program (M.S.).

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1772

Potential conflict of Interest: Nothing to report.

been withdrawn, can potentially serve as a surrogate for drug metabolism and elimination. Factors that lead to reduced recovery from anesthesia have been studied,[16,17] but the impact of FL on recovery has not yet been assessed. Based on the known altered activity of drug-metabolizing enzymes in patients with FL, we hypothesized that patients with FL will have delayed recovery from anesthesia compared to controls. Given the high prevalence of FL in the population, understanding whether patients with FL require special consideration for anesthetic management is highly relevant for management of these patients as well as for improving hospital patient flow. In this study, we aim to evaluate whether patients with FL have a delayed recovery from anesthesia compared to controls without FL, using postanesthetic recovery scores (RSs) as the outcome measure.

Participants and Methods

We conducted a single-center, retrospective, case-control study to evaluate the impact of FL on postoperative recovery. Data were collected using the National Institutes of Health (NIH) Biomedical Translational Research Information System. All periprocedural records and radiology reports for procedures requiring anesthesia at the NIH Clinical Center between July 2014 and December 2019 were extracted for analysis. This time frame was selected based on a power analysis of preliminary data. All patient information was obtained in a deidentified manner and was deemed exempt from institutional review board informed consent requirements.

Subjects were included in the analysis if they had at least one procedure requiring anesthesia and had abdominal imaging (see below) performed within 6 months of the procedure. Patients were excluded if they were younger than 18 years at the time of the procedure or if data were missing. Radiology text reports from abdominal computed tomography, magnetic resonance imaging, or ultrasound were interrogated using the terms "steatosis," "echogenicity," "fatty infiltration," "fat deposition," and derivative word terms to identify patients with radiologic evidence of FL, who were defined as cases. Patients without mention of FL on radiologic reports were considered controls. Due to the high likelihood of underreporting, subjects who had at least one imaging study reporting FL were not eligible to be included as controls if a subsequent imaging study did not report FL.

ASSESSMENT OF RECOVERY

Aldrete's scoring system,[18,19] a commonly used metric for assessing patient status postoperatively,[20] was used to establish the RS. The score is comprised of the following five subcomponents: activity, consciousness, respiration, oxygen saturation, and circulation. Each category is scored between 0 and 2, with higher scores denoting better outcomes and the total RS constituting an arithmetic sum of the five RS categories. Individual category scores were missing from the record, likely due to clerical error, in 3 subjects with FL (1%) and in 57 controls (3%) with no evidence of selection bias ($P = 0.15$); in these subjects, the total RS was not calculated. The scores were assessed in a standardized manner in the postanesthesia care unit (PACU) at the following time points: on arrival at the PACU, approximately 15 minutes after arrival, and following discharge. A total RS ≥8 is considered to signify discharge eligibility from the PACU.[20]

ARTICLE INFORMATION:

From the [1]Liver and Energy Metabolism Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA; [2]Department of Perioperative Medicine, National Institutes of Health Clinical Center, Bethesda, MD, USA; [3]Biomedical Translational Research Information System, National Institutes of Health Clinical Center, Bethesda, MD, USA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Yaron Rotman, M.D., M.Sc., F.A.A.S.L.D.
Liver and Energy Metabolism Section, Liver Diseases Branch
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
10 Center Drive, Building 10, Room 10N248C, MSC 1800
Bethesda, MD 20892-1800, USA
E-mail: rotmany@niddk.nih.gov
Tel.: +1-301-451-6553

The primary outcome of interest was RS at PACU arrival, with activity and consciousness RS expected to be a better surrogate of the anesthetic agent metabolism compared to respiration, circulation, and oxygen saturation.

For patients who underwent more than one procedure during the study period, only one procedure per patient, selected randomly to avoid bias and before any data analysis, was included in the analysis.

The following data were extracted for each subject: sex, age, race, ethnicity, body mass index (BMI), diagnoses (diabetes, cirrhosis, chronic hepatitis C, cancer, pulmonary disease, and cardiovascular disease), alcohol use, American Society of Anesthesiologists (ASA) physical status classification system (ASA score), procedure type, general anesthesia versus monitored anesthesia care (MAC), anesthesia duration, and airway removal time. Procedure type was classified into minor procedures, minor surgeries, and major surgeries. Minor procedures included gastrointestinal endoscopy, cystoscopy, catheter insertion, and biopsies. Minor surgeries included abscess incision and drainage, lymph node and soft tissue excision, and dental and ocular procedures. Major surgery included abdominopelvic, vascular, thyroid, and neurosurgery; debridements; and visceral organ resection. Data on diagnoses were obtained from the preanesthesia and anesthesia notes as well as from International Classification of Diseases-coded diagnoses.

Sensitivity analyses were performed to assess the impact of obesity, diabetes, anesthesia type, cirrhosis, and hepatitis C virus.

STATISTICAL ANALYSIS

Statistical analysis was performed using Prism version 8.4.2 (GraphPad Software, San Diego, CA). Descriptive statistics of baseline characteristics are presented as mean and SD for continuous variables or as number and percentage for categorical variables. Mann-Whitney U test was performed for comparison of non-normal continuous and noncontinuous variables, and the chi-squared test was performed for comparison of categorical variables. Differences between groups were evaluated using the Mann-Whitney U test for univariate analysis and binary logistic regression for multivariate analysis, adjusting for age, sex, ASA score, procedure type, anesthesia type, anesthesia duration, cardiovascular disease, diabetes, and BMI. For binary logistic regression, outcome measures for RS subcategories were classified as 2 (maximal score) versus <2. The time from airway removal to achieve RS ≥8 (discharge eligibility) was calculated for general anesthesia procedures, and the difference between groups was assessed using the Gehan-Breslow-Wilcoxon test for univariate analysis and a multivariate Cox proportional hazards model adjusted for age, sex, BMI, anesthesia duration, and ASA score. Patients were censored if they were discharged before receiving an RS ≥8. Covariates for multivariate analyses were selected *a priori* based on assumption of relevance.

As a secondary analysis, we performed matched-pair comparisons to control for baseline parameters. Patients with FL were matched with controls in a 1:1 ratio for age (in decades), sex, ASA score, anesthesia type, and BMI category. When more than one control could be matched to a case, only one was randomly selected. Statistical significance was assessed using Wilcoxon's signed-rank test or McNemar's test, as appropriate. $P < 0.05$ was considered significant.

Results

Between 2015 and 2019, there were 3,648 procedures with administered anesthesia and available documents (Supporting Fig. S1). After exclusion of pediatric patients and random selection of one procedure per adult subject, 2,021 procedures of unique patients were available for analysis. Of these, there were 234 FL cases and 1,787 controls. Baseline characteristics of the cohort are shown in Table 1. FL and control groups were similar for sex, ASA score, and anesthesia duration. The FL group was slightly younger, had a higher proportion of MAC procedures, and, as expected, had higher BMI and higher prevalence of type 2 diabetes and cardiovascular disease.

Patients with FL were significantly less likely than controls to be discharge eligible (defined as total RS ≥8) following arrival at the PACU (54.1% vs. 61.7%, $P = 0.03$) (Fig. 1A). On multivariate logistic regression, the association between FL and reduced eligibility for discharge persisted after adjusting for age, sex, BMI, diabetes, cardiovascular disease, procedure type, anesthesia type, anesthesia duration, and ASA score (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.52-0.93; $P = 0.015$) (Table 2). Furthermore,

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY COHORT

	All Patients (n = 2,021)	FL Group (n = 234)	Control Group (n = 1,787)	*P* Value
Age, years	49.7 ± 16.3	47.0 ± 14.3	50.0 ± 16.5	0.003
Sex, female	887 (44%)	107 (46%)	780 (44%)	0.55
BMI, kg/m^2	27.6 ± 7.6	31.3 ± 8.2	27.1 ± 7.3	<0.0001
<25	784 (39%)	47 (20%)	737 (41%)	<0.0001
25-29.99	595 (29%)	57 (24%)	538 (30%)	
30-34.99	320 (16%)	59 (25%)	261 (15%)	
≥35	241 (12%)	62 (26%)	179 (10%)	
Unknown	81 (4%)	9 (4%)	72 (4%)	
Type 2 diabetes	239 (11.8%)	47 (20.1%)	192 (10.7%)	<0.0001
Race				0.004
White	1,353 (67%)	154 (66%)	1,199 (67%)	
Black/African American	320 (16%)	28 (12%)	292 (16%)	
Asian	115 (6%)	10 (4%)	105 (6%)	
Multiple race	65 (3%)	4 (2%)	11 (1%)	
Other	19 (1%)	8 (3%)	61 (3%)	
Unknown	149 (7%)	30 (13%)	119 (7%)	
Ethnicity				<0.0001
Hispanic	259 (13%)	56 (24%)	203 (11%)	
ASA score				0.85
1	2 (0%)	0 (0%)	2 (0%)	
2	354 (18%)	40 (17%)	314 (18%)	
3	1,560 (77%)	184 (79%)	1,376 (77%)	
4	105 (5%)	10 (4%)	95 (5%)	
Procedure type				0.04
Minor procedure	1,324 (66%)	171 (73%)	1,153 (65%)	
Minor surgery	248 (12%)	22 (9%)	226 (13%)	
Major surgery	449 (22%)	41 (18%)	408 (23%)	
Anesthesia type				0.01
MAC	713 (35%)	100 (43%)	613 (34%)	
General	1,308 (65%)	134 (57%)	1,174 (66%)	
Anesthesia duration, minutes	194.4 ± 120.8	183.1 ± 117.7	195.9 ± 121.2	0.08
Alcohol use				0.15
None to moderate alcohol use	1,235 (61%)	139 (59%)	1,096 (61%)	
Excess alcohol use	31 (2%)	7 (3%)	24 (1%)	
Unknown	755 (37%)	88 (38%)	667 (37%)	
Diagnoses				
Cancer	1,119 (55.4%)	119 (50.9%)	1,000 (56%)	0.14
Pulmonary disease	720 (35.6%)	94 (40.2%)	626 (35.0%)	0.12
Cardiovascular disease	1,013 (50.1%)	142 (60.7%)	871 (48.7%)	0.001
Cirrhosis	73 (3.6%)	15 (6.4%)	58 (3.2%)	0.02
Chronic hepatitis C	60 (3.0%)	10 (4.3%)	50 (2.8%)	0.22

Data presented as mean ± SD or n (%).

in patients undergoing general anesthesia, the median time from airway removal to RS ≥8 was 43% longer in the FL group compared to controls (20 vs. 14 minutes, P = 0.01; Gehan-Wilcoxon-Breslow test) (Fig. 1B). This association persisted after adjusting for age, sex, BMI, ASA score, and anesthesia type and duration (adjusted hazard ratio,1.36; 95% CI, 1.005-1.842; P = 0.046) (Supporting Table S1). Thus, patients with FL had delayed recovery from anesthesia compared to controls.

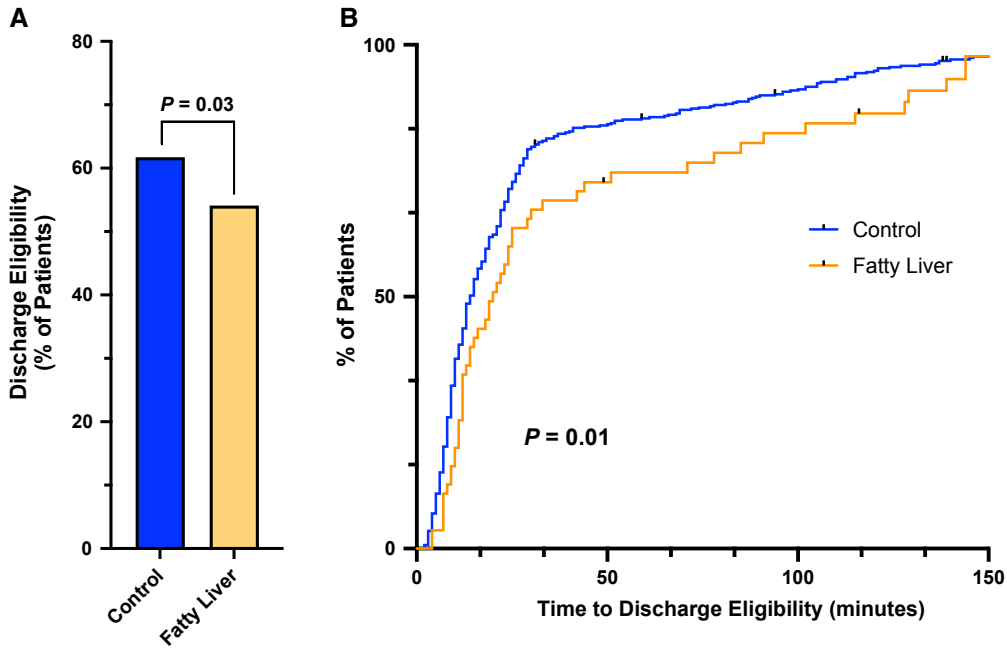

FIG. 1. Association of FL with discharge eligibility from the PACU. (A) Percentage of patients eligible for discharge on PACU admission (RS ≥8) (FL, n = 231; controls, n = 1,730); chi-squared test. (B) Time from airway removal to discharge eligibility in FL (n = 53) and control (n = 425) groups; Gehan-Breslow-Wilcoxon test.

Patients with FL had significantly lower activity scores on arrival at the PACU compared to controls (Fig. 2A; P = 0.04). On arrival at the PACU, 38.0% of patients with FL were assigned an activity score of 0 or 1 versus 30.9% in the control group (Supporting Table S2). Other subcomponents of the RS did not differ significantly between the groups (Supporting Table S2; Fig. 2B,C). On multivariate logistic regression, the association between FL and lower activity score on PACU entry persisted after adjusting for age, sex, BMI, diabetes, cardiovascular disease, procedure type, anesthesia type, anesthesia duration, and ASA score (OR, 0.71; 95% CI, 0.53-0.97; P = 0.03) (Table 3).

To demonstrate that the findings are robust to analysis method, we performed a secondary matched-pairs analysis, matching for age, sex, ASA score, anesthesia type, and BMI as potential confounders. We matched 211 patients with FL with 211 controls, while 23 patients with FL could not be matched. The baseline characteristics of the matched cohort (Table 4) were similar for the matched variables but did differ in ethnicity and race. Discharge eligibility following PACU arrival was significantly lower in the FL group compared to controls; while 64.2% of control patients were eligible for discharge (RS ≥8), only 52.6% of patients with FL met the same criterion (P = 0.009; Fig. 3A). When arriving at the PACU, patients with FL had significantly lower activity, consciousness, and total RSs compared to their matched controls (P = 0.02, P = 0.04, and P = 0.02, respectively) (Fig. 3B-D).

To establish whether the association of FL with delayed recovery is independent of obesity, we performed a sensitivity analysis, separating patients with BMI <30 kg/m^2 (FL, n = 104; controls, n = 1,266) or ≥30 kg/m^2 (FL, n = 121; controls, n = 438). In the group with BMI <30 kg/m^2, eligibility for discharge was significantly lower in the patients with FL compared to controls (P = 0.005; Fig. 4A). Additionally, patients with FL had significantly lower activity and total RSs (P = 0.02, P = 0.03, respectively) (Fig. 4B,D). In those with BMI ≥30 kg/m^2, a greater proportion of patients with FL had a lower RS compared to controls numerically, but the difference was not significant (Fig. 4E-H).

To establish whether the association of FL with delayed recovery is independent of diabetes, we

TABLE 2. UNIVARIATE AND MULTIVARIATE ASSOCIATIONS WITH DISCHARGE ELIGIBILITY

	Univariate Analysis*		Multivariate Analysis*	
Covariate	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
FL	0.73 (0.56-0.97)	0.03	0.69 (0.52-0.93)	0.015
Age (per year)	1.01 (1.00-1.01)	0.007	1.01 (0.999-1.01)	0.08
Male sex	0.90 (0.75-1.07)	0.23	0.85 (0.70-1.03)	0.11
BMI	1.01 (1.00-1.03)	0.035	1.02 (1.00-1.03)	0.02
Type 2 diabetes	1.24 (0.93-1.66)	0.15	1.16 (0.85-1.58)	0.36
Cardiovascular disease	1.06 (0.89-1.27)	0.52	1.02 (0.83-1.24)	0.87
Procedure type				
Minor procedures	Reference		Reference	
Minor surgery	1.65 (1.23-2.22)	0.001	1.39 (1.02-1.91)	0.04
Major surgery	1.23 (0.98-1.54)	0.07	1.08 (0.78-1.49)	0.64
General anesthesia	1.63 (1.35-1.97)	<0.0001	1.74 (1.39-2.18)	<0.001
Anesthesia duration (per 10 minutes)	1.00 (0.997-1.01)	0.24	0.99 (0.98-1.00)	0.07
ASA score	1.07 (0.88-1.30)	0.48	1.01 (0.81-1.24)	0.96

*Binary logistic regression for total RS ≥8.

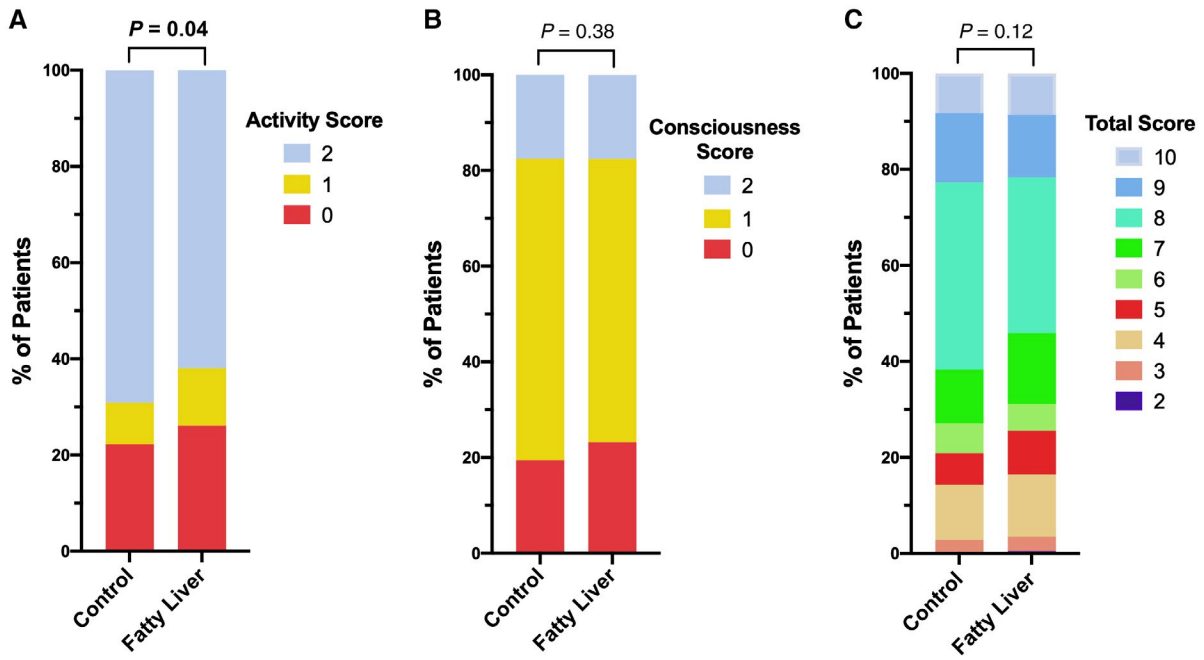

FIG. 2. Association of FL with postprocedural RSs. (A) Activity, (B) consciousness, and (C) total RSs on arrival at the PACU in patients with FL and controls; Mann-Whitney U test.

performed a sensitivity analysis limited to patients without diabetes (FL, n = 188; controls, n = 1,596) (Supporting Fig. S2). Similar to the results of the primary analysis, patients without diabetes but with FL had significantly lower discharge eligibility compared to controls (53.2% vs. 61.1%; OR, 0.73; 95% CI, 0.53-0.99; P = 0.046) as well as lower activity scores (OR, 0.67; 95% CI, 0.49-0.92; P = 0.01). We found that 40.6% of the patients without diabetes but with FL had an activity score <2 compared to 31.5% in the nondiabetic control group.

Steatosis is frequently underreported by radiologists, especially when imaging is done for other indications[21]; noting the absence of steatosis as a pertinent

TABLE 3. UNIVARIATE AND MULTIVARIATE ASSOCIATIONS WITH THE ACTIVITY COMPONENT OF THE RS

	Univariate Analysis*		Multivariate Analysis*	
Covariate	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
FL	0.73 (0.55-0.97)	0.03	0.71 (0.53-0.97)	0.03
Age (per year)	1.01 (1.01-1.02)	0.0003	1.01 (1.00-1.01)	0.03
Male sex	0.88 (0.72-1.06)	0.17	0.81 (0.66-0.99)	0.04
BMI	1.02 (1.01-1.03)	0.01	1.02 (1.004-1.03)	0.01
Type 2 diabetes	1.37 (1.01-1.87)	0.46	1.27 (0.92-1.77)	0.15
Cardiovascular disease	1.07 (0.88-1.29)	0.50	0.98 (0.80-1.21)	0.88
Procedure type				
Minor procedures	Reference		Reference	
Minor surgery	1.85 (1.34-2.54)	<0.001	1.50 (1.07-2.10)	0.02
Major surgery	1.49 (1.17-1.89)	0.001	1.25 (0.88-1.76)	0.21
General anesthesia	1.96 (1.61-2.38)	<0.001	1.94 (1.52-2.45)	<0.001
Anesthesia duration (per 10 minutes)	1.01 (1.00-1.02)	0.005	0.99 (0.98-1.00)	0.16
ASA score	1.13 (0.92-1.38)	0.24	1.10 (0.88-1.37)	0.40

*Binary logistic regression for activity score 2 versus <2.

negative is even less common. Therefore, it is plausible that some of the subjects classified as controls actually had unreported FL. We therefore compared subjects from the control group whose radiology reports explicitly stated the absence of FL (n = 78) to those with FL. Similar to the main analysis, patients with FL were significantly less likely to be eligible for discharge following arrival at the PACU compared to the confirmed controls (54.1% in FL vs. 67.1% in controls, $P = 0.047$) (Supporting Fig. S3A). Patients with FL also had significantly decreased activity, consciousness, and total RSs on arrival at the PACU compared to controls with confirmed absence of FL ($P = 0.045$, $P = 0.035$, $P = 0.03$, respectively) (Supporting Fig. S3B-D).

To address whether anesthesia type affected outcomes, we separately analyzed patients undergoing general anesthesia (134 FL and 1,174 controls; Supporting Fig. S4A-D) and MAC (100 FL and 613 controls; Supporting Fig. S4E-H). The groups were underpowered to establish statistical significance, but the directionality of the findings persisted, with subjects with FL having numerically lower RS compared to controls in both types of anesthesia.

Finally, we performed a sensitivity analysis limited to patients without cirrhosis or chronic hepatitis C (FL, n = 212; controls, n = 1,705; Supporting Fig. S5). Similar to the results of the primary analysis, patients with FL had significantly lower discharge eligibility compared to controls (54.5% vs. 61.8%; OR, 0.74; 95% CI, 0.55-0.99; $P = 0.04$) (Supporting Fig. S5A) as well as significantly longer median time from airway withdrawal to RS ≥8 compared to controls (20 vs. 14 minutes, $P = 0.01$; Gehan-Wilcoxon-Breslow test) (Supporting Fig. S5B).

Discussion

Based on existing data suggesting that FL alters drug-metabolizing enzymes,[7-10] we hypothesized that the presence of FL will have a clinical implication by impacting the metabolism of anesthetic agents. Indeed, in this study we show for the first time that patients with FL undergoing anesthesia have a delayed recovery. Specifically, we found that patients with FL were assigned lower early postprocedural RSs compared to controls without FL, that patients with FL had delayed recovery to discharge eligibility, and that these findings are independent of obesity and diabetes.

Our findings have direct clinical implications. The global prevalence of NAFLD, estimated at 20%-30%, is increasing.[1] Further, an estimated 312 million surgical procedures were performed worldwide in 2012, which has increased substantially from 226 million in 2004.[22,23] Given the large and rising volume of procedures globally, surgical safety is a critical public health concern. Periprocedural management must be able to take into account all factors that impact care

TABLE 4. BASELINE CHARACTERISTICS OF THE MATCHED COHORT

	FL Group (n = 211)	Control Group (n = 211)	*P* Value
Age, years	47.0 ± 14.1	47.2 ± 14.1	0.38
Sex, female	98 (45%)	98 (45%)	1
BMI, kg/m^2	31.3 ± 8.3	31.3 ± 9.1	0.08
<25	43 (20%)	43 (20%)	1.0
25-29.99	57 (27%)	57 (27%)	
30-34.99	53 (25%)	53 (25%)	
≥35	58 (27%)	58 (27%)	
Type 2 diabetes	42 (20%)	30 (14%)	0.15
Race			0.03
White	139 (66%)	139 (66%)	
Black/African American	26 (12%)	40 (19%)	
Asian	10 (5%)	4 (2%)	
Multiple race	6 (3%)	1 (0%)	
Other	4 (2%)	9 (4%)	
Unknown	26 (12%)	18 (9%)	
Ethnicity			0.01
Hispanic	46 (22%)	29 (14%)	
ASA score			1.0
1			
2	31 (15%)	31 (15%)	
3	175 (83%)	175 (83%)	
4	5 (2%)	5 (2%)	
Procedure type			0.55
Minor procedure	155 (73%)	147 (70%)	
Minor surgery	18 (9%)	17 (8%)	
Major surgery	38 (18%)	47 (22%)	
Anesthesia type			1.0
MAC	90 (43%)	90 (43%)	
General	121 (57%)	121 (57%)	
Anesthesia duration, minutes	184.4 ± 121.7	191.1 ± 121.6	0.47
Alcohol use			0.94
None to moderate alcohol use	127 (60%)	129 (61%)	
Excess alcohol use	5 (2%)	4 (2%)	
Unknown	79 (37%)	78 (37%)	
Diagnoses			
Cancer	111 (53%)	110 (52%)	0.92
Pulmonary disease	86 (41%)	80 (38%)	0.55
Cardiovascular disease	128 (61%)	118 (56%)	0.32
Cirrhosis	14 (7%)	7 (3%)	0.12
Chronic hepatitis C	9 (4.0%)	5 (2%)	0.28

Data presented as mean ± SD or n (%).

to guide decision making. These data suggest that FL is one such factor, and additional consideration for patients with FL may be prudent.

Several studies have indicated that FL is associated with changes in drug-metabolizing enzymes.[7,10-13] Kolwanker et al.[8] found that degree of steatosis inversely correlated with CYP3A4 activity in cadaveric liver samples. Woolsey et al.[9] found that patients with NAFLD had reduced clearance of midazolam, a CYP3A4 substrate, compared to controls. The mechanism by which steatosis or associated hepatocellular injury interferes with CYP activity is still unclear but may be related to zonality. Zone 3 of the liver acinus, where steatosis and ballooning predominantly occur, houses the

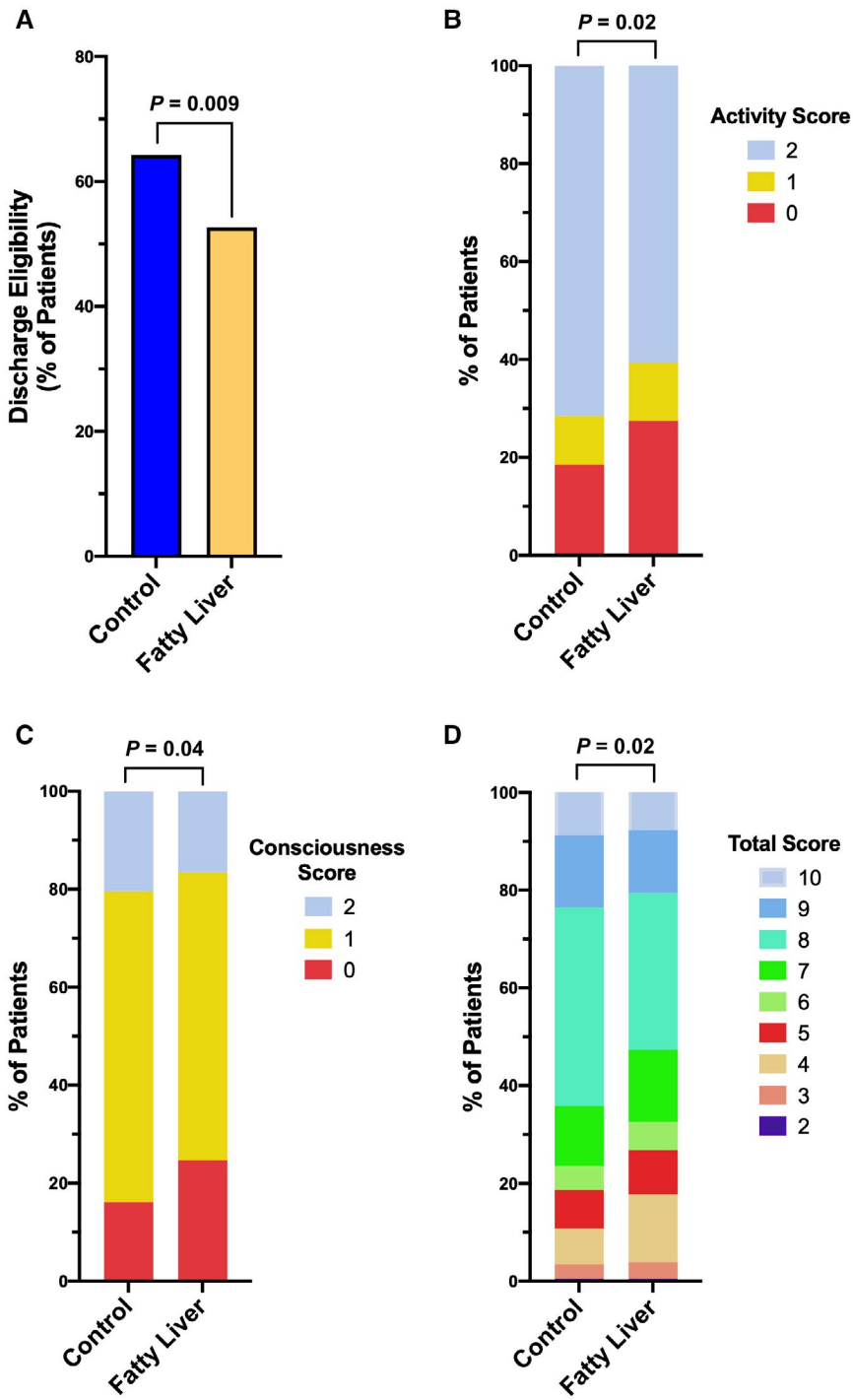

FIG. 3. Association of FL with postprocedural recovery within the matched cohort. FL (n = 211) and control (n = 211) groups were matched for age, sex, BMI, ASA score, and anesthesia type. (A) Discharge eligibility on PACU admission (RS ≥8); McNemar's Test for matched pairs. (B) Activity, (C) consciousness, and (D) total RSs in FL and matched controls on PACU arrival; Wilcoxon test.

majority of CYP enzyme activity.[24-28] Furthermore, NAFLD has been shown to specifically affect biliary anatomy and flow in zone 3.[29] Overall, these zonal changes may explain the association of FL with drug metabolism. However, despite these mechanistic findings, no study to date assessed their clinical implications.

Although the association of FL with delayed recovery is plausible given the changes in drug metabolism,

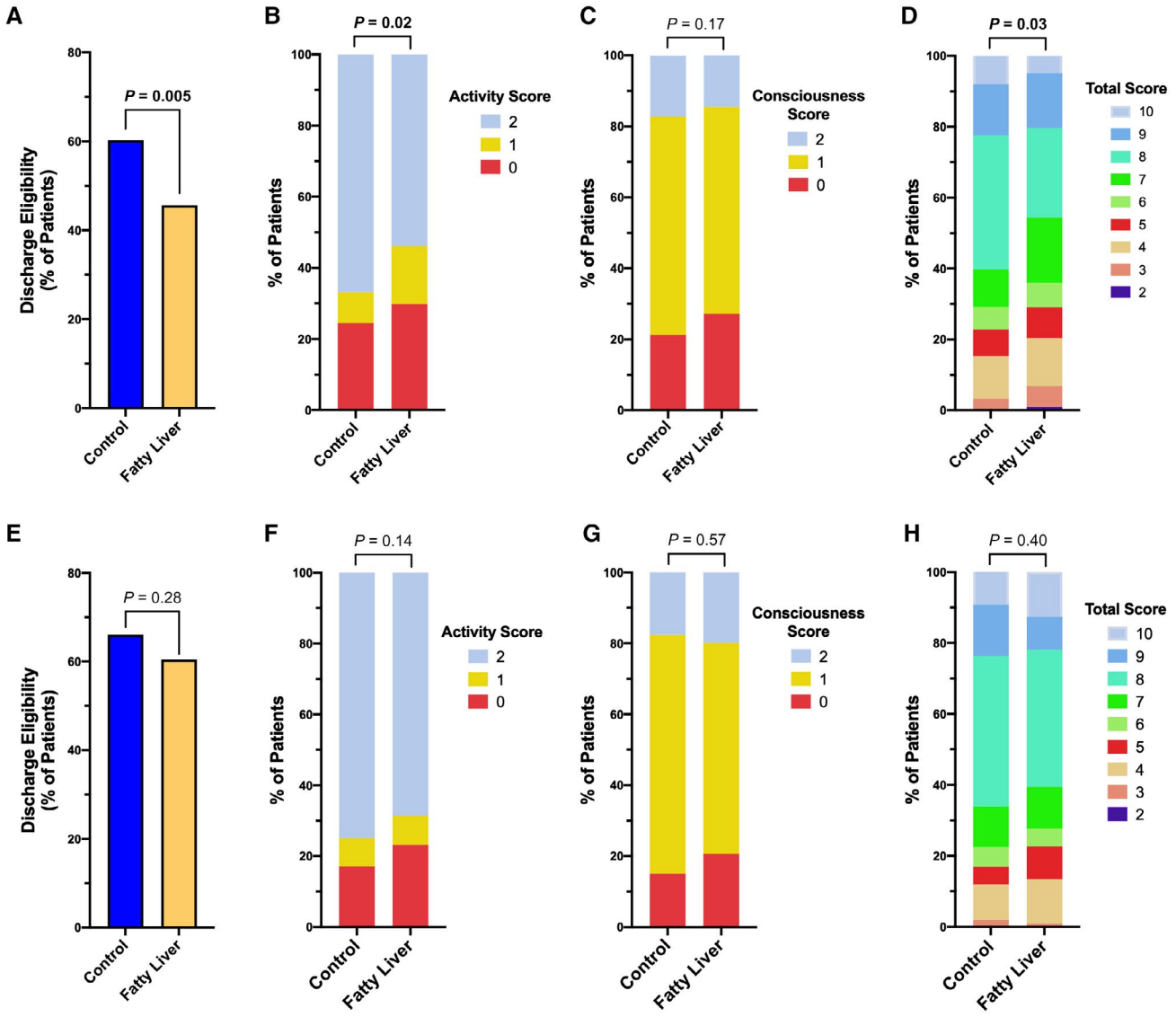

FIG. 4. Association of FL and postanesthesia recovery grouped by BMI. (A) Discharge eligibility, (B) activity, (C) consciousness, and (D) total RSs on PACU arrival in patients with BMI <30 kg/m^2. (E) Discharge eligibility, (F) activity, (G) consciousness, and (H) total RSs on PACU arrival in patients with BMI ≥30 kg/m^2; Fisher's exact test and Mann-Whitney U test.

potential confounders should be considered. Obesity, known to be associated with delayed recovery from anesthesia,[16] is a potential confounder of the association we found with FL. Obesity can delay recovery through various mechanisms, such as altered metabolism of CYP450 substrates[30,31] or prolongation of the effects of agents with a high volume of distribution.[32] Furthermore, beyond its effect on drug metabolism, obesity is a well-established consideration for anesthetic dosing and perianesthetic monitoring.[33-35] As a visible phenotype, obesity could lead to differential treatment of subjects with FL, who are more likely to be obese, and could potentially introduce bias. To control for possible confounding by obesity, we applied several approaches. First, we adjusted for BMI in multivariate regressions; second, we matched for it in matched-pair analyses; and third, we analyzed the effects of FL in subjects without obesity. The association of FL with delayed recovery persisted after adjustment or matching, confirming its independence of obesity. In addition, even when limiting the analysis to subjects with BMI <30 kg/m^2,

patients with FL continued to demonstrate decreased recovery compared to controls. The association of FL with delayed postanesthetic recovery, therefore, cannot be attributed solely to confounding by obesity.

Another potential confounder is alcohol, which is known to induce drug-metabolizing enzymes[14] and to promote FL. There were no significant differences in recorded alcohol consumption between patients with FL and the control group, suggesting alcohol is unlikely to be playing a role in the observed differences in recovery. Diabetes has also been shown to influence drug-metabolizing enzymes[36] and recovery from anesthesia,[37] but the association of FL with delayed recovery was independent of its presence. Cirrhosis and hepatitis C were previously shown to affect hepatic drug-metabolizing enzymes.[38-40] However, the findings held even after exclusion of subjects with these diagnoses, confirming an independent association with FL.

Our study has several strengths. First, this is the first study to assess the impact of FL on recovery from anesthesia and to demonstrate a potential clinical implication of prior mechanistic findings. Second, it includes a large cohort with 5 years of clinical data, all collected in a standard manner. Third, we were able to control for several important confounders by using multivariate analyses as well as case-control matching. Fourth, we used Aldrete's RS, a well-established clinically meaningful outcome measure that is less susceptible to bias than duration of time in the PACU, which can be influenced by availability of transportation, patient load, and physician availability to enter orders.[41,42]

Our study has several important limitations. First, our study is retrospective, and although we aimed to carefully control for potential confounders, it still faces the inherent limitations of such studies. Second, we do not have data on anesthetic drug dosing and serum drug levels and hence cannot confirm that the association is indeed due to altered metabolism. Third, due to the limitations of a retrospective analysis using deidentified data, the diagnosis of FL was based on radiologic reports and not on imaging review. The prevalence of FL in this study is 11.6%, which is lower than what has been reported in the United States and in our own center.[43] Similarly, the prevalence of FL within diabetics in our study cohort is lower than expected. Therefore, it is plausible that FL was underreported and that a proportion of the control group may actually have had FL, representing potential differential misclassification.[44] To account for this, we compared patients with FL to controls with radiologically confirmed absence of FL, finding that the difference between confirmed controls and subjects with NAFLD was even greater and retained statistical significance. This suggests that the results of the main analysis would have been even more robust if not for underreporting of FL and inclusion of these subjects as control and that the bias leads to underestimation of the effect. Fourth, our study is focused on the immediate postprocedural period and is not aimed at assessing long-term recovery or surgical complications, which are less likely to be related to anesthetic drug metabolism. Finally, our data are from a single center and require confirmation before they can be generalized with confidence.

In summary, we demonstrate that FL is associated with significantly reduced RSs and a delay in discharge eligibility in the immediate postanesthesia period. Our findings suggest that patients with FL may have slower recovery from anesthesia through impaired metabolism of anesthetic agents. Future studies should look to confirm these results at other institutions and correlate recovery with drug-metabolizing enzyme activity.

Acknowledgment: We thank Drs. Andrew Mannes, Julian Hercun, Anusha Vittal, and Spencer Bigelow for helpful advice, Dr. Dolores Njoku for study inspiration and L.D. for support.

REFERENCES

1) Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 2013;10:686-690.
2) Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40:1387-1395.
3) Kanwal F, Kramer JR, Duan Z, Yu X, White D, El-Serag HB. Trends in the burden of nonalcoholic fatty liver disease in a United States cohort of veterans. Clin Gastroenterol Hepatol 2016;14:301-308.e1-e2.
4) Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol 2011;9:524-530.e1.
5) Bellentani S. The epidemiology of non-alcoholic fatty liver disease. Liver Int 2017;37(Suppl. 1):81-84.
6) Wong T, Dang K, Ladhani S, Singal AK, Wong RJ. Prevalence of alcoholic fatty liver disease among adults in the United States, 2001-2016. JAMA 2019;321:1723-1725.
7) Merrell MD, Cherrington NJ. Drug metabolism alterations in nonalcoholic fatty liver disease. Drug Metab Rev 2011;43:317-334.
8) Kolwankar D, Vuppalanchi R, Ethell B, Jones DR, Wrighton SA, Hall SD, et al. Association between nonalcoholic hepatic steatosis

and hepatic cytochrome P-450 3A activity. Clin Gastroenterol Hepatol 2007;5:388-393.
9) Woolsey SJ, Mansell SE, Kim RB, Tirona RG, Beaton MD. CYP3A activity and expression in nonalcoholic fatty liver disease. Drug Metab Dispos 2015;43:1484-1490.
10) Cobbina E, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. Drug Metab Rev 2017;49:197-211.
11) Jamwal R, Barlock BJ. Nonalcoholic fatty liver disease (NAFLD) and hepatic cytochrome P450 (CYP) enzymes. Pharmaceuticals (Basel) 2020;13:222.
12) Weltman MD, Farrell GC, Hall P, Ingelman-Sundberg M, Liddle C. Hepatic cytochrome P450 2E1 is increased in patients with nonalcoholic steatohepatitis. Hepatology 1998;27:128-133.
13) Dietrich CG, Rau M, Jahn D, Geier A. Changes in drug transport and metabolism and their clinical implications in nonalcoholic fatty liver disease. Expert Opin Drug Metab Toxicol 2017;13:625-640.
14) Ogu CC, Maxa JL. Drug interactions due to cytochrome P450. Proc (Bayl Univ Med Cent) 2000;13:421-423.
15) Manikandan P, Nagini S. Cytochrome P450 structure, function and clinical significance: a review. Curr Drug Targets 2018;19:38-54.
16) Gabriel RA, Waterman RS, Kim J, Ohno-Machado L. A predictive model for extended postanesthesia care unit length of stay in outpatient surgeries. Anesth Analg 2017;124:1529-1536.
17) Pavlin DJ, Rapp SE, Polissar NL, Malmgren JA, Koerschgen M, Keyes H. Factors affecting discharge time in adult outpatients. Anesth Analg 1998;87:816-826.
18) Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg 1970;49:924-934.
19) Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995;7:89-91.
20) Ead H. From Aldrete to PADSS: reviewing discharge criteria after ambulatory surgery. J Perianesth Nurs 2006;21:259-267. Erratum in: J Perianesth Nurs 2007;22:154.
21) Wells MM, Li Z, Addeman B, McKenzie CA, Mujoomdar A, Beaton M, et al. Computed tomography measurement of hepatic steatosis: prevalence of hepatic steatosis in a Canadian population. Can J Gastroenterol Hepatol 2016;2016:4930987.
22) Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008;372:139-144.
23) Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, et al. Size and distribution of the global volume of surgery in 2012. Bull World Health Organ 2016;94:201-209F.
24) Enzan H, Toi M, Hayashi Y, Hamauzu T, Kuroda N, Hiroi M. Zone 3 predominance of histopathological features in nonalcoholic steatohepatitis. In: Okita K, ed. NASH and Nutritional Therapy. Tokyo, Japan: Springer Tokyo; 2005:50-57.
25) Takahashi Y, Fukusato T. Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol 2014;20:15539-15548.
26) Ahn J, Ahn JH, Yoon S, Nam YS, Son MY, Oh JH. Human three-dimensional in vitro model of hepatic zonation to predict zonal hepatotoxicity. J Biol Eng 2019;13:22.
27) Soto-Gutierrez A, Gough A, Vernetti LA, Taylor DL, Monga SP. Pre-clinical and clinical investigations of metabolic zonation in liver diseases: the potential of microphysiology systems. Exp Biol Med (Maywood) 2017;242:1605-1616.
28) Lindros KO. Zonation of cytochrome P450 expression, drug metabolism and toxicity in liver. Gen Pharmacol 1997;28:191-196.
29) Segovia-Miranda F, Morales-Navarrete H, Kücken M, Moser V, Seifert S, Repnik U, et al. Three-dimensional spatially resolved geometrical and functional models of human liver tissue reveal new aspects of NAFLD progression. Nat Med 2019;25:1885-1893.
30) Brill MJE, Diepstraten J, van Rongen A, van Kralingen S, van den Anker JN, Knibbe CAJ. Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 2012;51:277-304.
31) Kotlyar M, Carson SW. Effects of obesity on the cytochrome P450 enzyme system. Int J Clin Pharmacol Ther 1999;37:8-19.
32) Casati A, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. J Clin Anesth 2005;17:134-145.
33) Chau EHL, Mokhlesi B, Chung F. Obesity hypoventilation syndrome and anesthesia. Sleep Med Clin 2013;8:135-147.
34) Passannante AN, Rock P. Anesthetic management of patients with obesity and sleep apnea. Anesthesiol Clin North Am 2005;23:479-491.
35) Huschak G, Busch T, Kaisers UX. Obesity in anesthesia and intensive care. Best Pract Res Clin Endocrinol Metab 2013;27:247-260.
36) Jamwal R, de la Monte SM, Ogasawara K, Adusumalli S, Barlock BB, Akhlaghi F. Nonalcoholic fatty liver disease and diabetes are associated with decreased CYP3A4 protein expression and activity in human liver. Mol Pharm 2018;15:2621-2632.
37) Wang J, Chen K, Li X, Jin X, An P, Fang YI, et al. Postoperative adverse events in patients with diabetes undergoing orthopedic and general surgery. Medicine (Baltimore) 2019;98:e15089.
38) Nakai K, Tanaka H, Hanada K, Ogata H, Suzuki F, Kumada H, et al. Decreased expression of cytochromes P450 1A2, 2E1, and 3A4 and drug transporters Na+-taurocholate-cotransporting polypeptide, organic cation transporter 1, and organic anion-transporting peptide-C correlates with the progression of liver fibrosis in chronic hepatitis C patients. Drug Metab Dispos 2008;36:1786-1793.
39) Becquemont L, Chazouilleres O, Serfaty L, Poirier JM, Broly F, Jaillon P, et al. Effect of interferon alpha-ribavirin bitherapy on cytochrome P450 1A2 and 2D6 and N-acetyltransferase-2 activities in patients with chronic active hepatitis C. Clin Pharmacol Ther 2002;71:488-495.
40) Chalasani N, Gorski JC, Patel NH, Hall SD, Galinsky RE. Hepatic and intestinal cytochrome P450 3A activity in cirrhosis: effects of transjugular intrahepatic portosystemic shunts. Hepatology 2001;34:1103-1108.
41) Cowie B, Corcoran P. Postanesthesia care unit discharge delay for nonclinical reasons. J Perianesth Nurs 2012;27:393-398. https://doi.org/10.1016/j.jopan.2012.05.013.
42) Tessler MJ, Mitmaker L, Wahba RM, Covert CR. Patient flow in the post anesthesia care unit: an observational study. Can J Anaesth 1999;46:348-351.
43) Takyar V, Nath A, Beri A, Gharib AM, Rotman Y. How healthy are the "healthy volunteers"? Penetrance of NAFLD in the biomedical research volunteer pool. Hepatology 2017;66:825-833.
44) Rothman KJ, Greenland S. Basic Concepts. In: Ahrens W, Pigeot I, eds. Handbook of Epidemiology. New York, NY: Springer New York; 2014:75-122.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1772/suppinfo.