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ORIGINAL ARTICLE

Hepatocellular carcinoma as predominant cancer subgroup accounting for sex differences in post-hepatectomy liver failure, morbidity and mortality

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Abstract

Background: Experimental evidence suggests sex dependent differences in liver regeneration. Limited evidence is available examining sex differences in post-hepatectomy liver failure (PHLF) and post-operative outcomes. Our aim was to assess the influence of sex on the outcomes after liver resection.

Methods: The hepatectomy targeted National Surgical Quality Improvement Program (NSQIP) database was assessed for associations between sex and outcomes.

Results: A total of 13,401 patients underwent elective hepatic resection between 2014-2017. PHLF was highest among male patients with hepatocellular carcinoma (HCC) (OR = 2.81,95%CI:1.40–5.62). Male sex was independently associated with increased PHLF (OR = 1.47,95%CI:1.15–1.88), major complications (OR = 1.25,95%CI:1.08–1.45), mortality (OR = 1.61,95%CI:1.03–2.50), and if only major resections were assessed (OR = 1.38,95%CI:1.03–1.84). Diagnosis specific subgroup analyses revealed that effects of sex were predominantly HCC associated.

Conclusions: This is the largest series investigating the effects of gender on outcomes after hepatic resection. We documented that women undergoing liver resection have significantly lower risk of PHLF. This difference seemed influenced by the striking increase of PHLF in male HCC patients. These hypothesis suggest that sex might play a role in preoperative risk stratification.

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Introduction

Liver resection remains standard of care and a potential curative treatment option for several neoplastic entities of the liver.[1,2] While long term survival after liver resection for primary and secondary liver cancer is improving,[3,4] perioperative morbidity and mortality remain a critical issue with 30-day mortality ranging around 2%.[5]

A multitude of prognostic factors and scores have been developed to risk stratify patients undergoing hepatic resection.[5] Several preoperative factors such as age and comorbidities have been shown to predict post-hepatectomy complications. Among these, chronic liver disease, chronic obstructive pulmonary disease (COPD), chronic renal failure, and chronic heart disease appear in multiple studies.[2,6] Factors such as extent of resection

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and actual tumor size contribute as well.[2,4,6,7] In this context, small series have demonstrated that, after adjusting for potential confounders, male sex was associated with increased mortality after liver resection.[8,9]

It is important to note that the ability of the liver remnant to regenerate is one of the most relevant factors determining postoperative outcomes after partial hepatectomy.[10] Interestingly, sex specific differences in liver regeneration have been described quite extensively in rodent models. In particular, estradiol administration after liver resection has been demonstrated to accelerate liver regeneration in mice.[10,11] In the experimental setting, this has led to fully excluding female mice from regenerative models by most research groups, given the interference of their hormonal cycle with liver regeneration. In humans, estrogens have been reported to exhibit a protective role in chronic liver disease.[12] In line with these results, male and female HCC patients have been found to differ in long term postoperative survival.[13]

We recently documented in a retrospective analysis of more than 1000 patients from Austria that, despite significant differences in patient risk factors, no specific disparity in outcomes between male and female patients could be detected. However, given the limited sample size, particularly in subgroups, potential sex differences might not have been identified. In this study, we examined a much larger cohort derived from the hepatectomy targeted National Surgical Quality Improvement Program (NSQIP) database in order to assess sex differences in patients undergoing liver resection.

Material and methods

The NSQIP procedure targeted database on liver resection contains prospectively collected information of patients undergoing liver resections within the United States. Baseline characteristics, pre-operative laboratory values, and pre-operative comorbidities are routinely documented.

All patients who underwent liver resection between January 1, 2014 and December, 31 2017 were identified within the procedure targeted NSQIP database on liver resection using current procedural terminology (CPT) codes: partial hepatectomy (CPT: 47,120, as minor hepatectomy), trisegmentectomy (CPT: 47,122), left lobectomy (CPT: 47,125), and right lobectomy (CPT: 47,130, major hepatectomy). Patients younger than 18 years old and trauma were excluded from final analyses. Patients were further grouped according to their different characteristics as follows: underlying neoplastic entity, patients with only major resection and patients with high Aspartate Aminotransferase (IU/L)/platelet ratio index (x 10^3/mm^3) (APRI) plus Albumin-Bilirubin (ALBI) score (APRI/ALBI), with a value less negative than −2.46 (previously defined cut-off to identify decreased liver function).[5] The APRI score was calculated with the equation: [(AST/upper limit of the normal AST range) x 100]/Platelet Count, while the ALBI score was calculated with the equation: ($\log_{10}$ bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.0852), based on preoperative blood parameters. The addition of APRI and ALBI resulted in the APRI/ALBI score as previously defined.[5]

Definition and classification of outcome parameters

Morbidity was assessed within 30 days after surgery and divided into major and minor complications. Minor complications constituted of superficial surgical site infection (SSI) and urinary tract infections. Deep incisional SSI, organ space SSI, wound disruption, sepsis, progressive renal insufficiency, deep vein thrombosis or thrombophlebitis, pulmonary embolism, cardiac arrest requiring cardiopulmonary resuscitation, myocardial infarction, stroke/cerebrovascular accident with neurological deficit, unplanned intubation, ventilator >48 h, pneumonia, acute renal failure, and return to operating room were defined as major complications. Importantly, the procedure targeted NSQIP database on liver resection contains detailed prospectively collected data on postoperative outcomes in terms of post-hepatectomy liver failure (PHLF) and mortality. In particular, the severity of PHLF was further classified according to the International Study Group of Liver Surgery (ISGLS) criteria: grade A, abnormality in laboratory parameters not requiring a change in clinical management; grade B, deviation from clinical management without invasive treatment; and grade C, deviation from clinical management requiring invasive treatment.[14] Postoperative observation period was 30 days as per NSQIP database.

Statistical analysis

Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as mean (standard deviation, SD) or median (interquartile range), according to its distribution, which was assessed with histogram for skewness and kurtosis. For univariate analysis, we used the Chi-square test for categorical variables, and Student's T test for continuous variables. To determine the strength of the association between study variables and outcomes (PHLF, mortality and major complications), we obtained the Odds Ratio (OR) with a 95% confidence interval using the logistic regression for crude and multivariable models. The latter was performed with all available parameters to account for all potentially confounding factors, even if no univariate association was observed. Given the potential of multicollinearity of included variables by this approach, we performed variance inflation factor (VIF) assessment. This revealed a VIF of less than 2 in all assessed variables documenting a lack of multicollinearity (supplementary table 1). We further performed logistic regression analysis of subgroups of interest. In the APRI/ALBI score subgroup, variables included in this score were omitted as pre-operative AST, platelets, albumin and bilirubin. A P-value <0.05 was considered statistically significant for all the tests. Statistical analyses were performed using SPSS Version 23 (IBM Corp., Armonk, NY, USA).

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Results

Univariate description and sex differences

13,401 patients underwent elective liver resection between 2014 and 2017. Main characteristics of the population is presented in Table 1. Sex was equally distributed (male vs. female, 50.4% vs. 49.6, respectively). Mean age was 58.52 years (SD: 13.52). Mean body mass index was 28.5 kg/m^2 (SD: 6.29). The majority of patients were Non-Hispanic whites (77.9%), followed by African Americans (10.2%). The most common comorbidities were diabetes (17.3%), COPD (3.5%), and congestive heart failure (0.3%). Preoperative albumin (mean = 4.0 mg/DL, SD: 0.48), bilirubin (mean = 0.66 mg/dL, SD: 0.71), glutamate oxaloacetate transaminase (GOT) (mean = 34.77 IU/L, SD: 35.20) and platelets count (mean = 231.63 × 10^3/mm^3, SD: 87.25) were on average normal. Mean American Society of Anesthesiologists (ASA) classification was 2.77 (SD: 0.59) and the mean of operative time was 236.88 minutes (SD: 117.14). Furthermore, the most frequent diagnoses were colorectal cancer liver metastases (CRCLM) (42.6%) and HCC (17.6%). Less than half of patients underwent major resection (38.1%). The 30-day major complication rate was 15.1%. PHLF occurred in 4.6%. 30-day mortality was 1.6%. From the total of 619 patients with PHLF, 266 (42.9%) had grade A, 204 (33.0%), grade B, and 149 (24.1%), grade C. In line with existing literature, bivariate analyses comparing male and female patients demonstrated that comorbidities (diabetes, COPD, CHF, bleeding disorders), CRCLM and HCC were more frequent in male patients, however, benign lesions were more frequent in female population (all $p < 0.001$). Age, ASA classification, total operative time were also higher in men (all $p < 0.001$). In terms of outcomes, men had increased rates of PHLF, major complications and mortality ($p < 0.001$) (Table 1).

Subgroups according to indication for liver resection

Regardless of diagnosis, rates of PHLF were higher in men than in women: HCC (6.9% vs. 3.9%, $p < 0.01$), cholangiocarcinoma (CCC) (6.2% vs. 2.8%, $p < 0.01$), benign (2.9% vs. 0.4%, $p < 0.01$). Mortality was also higher in men with CRCLM (1.1%% vs. 0.4%, $p < 0.01$), CCC (3.6% vs. 1.3%, $p < 0.01$), and other diagnoses (2.0% vs. 0.5%, $p = 0.012$). Major morbidity was also more frequent among men with CRCLM (12.8% vs. 9.6%, $p < 0.01$), HCC (16.0 vs 11.8%, $p = 0.013$), CCC (19.1% vs. 14.2%, $p = 0.026$), benign tumors (12.9% vs. 6.9%, $p < 0.01$), and other diagnoses (11.8% vs. 7.5%, $p = 0.014$)(supplementary Fig 1).

Multivariable model – PHLF

Multivariable regression analysis (Table 2) revealed that male sex (OR: 1.47, 95% CI: 1.15–1.88), bleeding disorders (OR: 1.82, 95% CI: 1.13–2.93), GOT (OR: 1.003, 95% CI: 1.000–1.005), international normalized ratio (INR) (OR: 1.47, 95% CI: 1.12–1.93), operative time (OR: 1.002, 95% CI: 1.002–1.003), cholangiocarcinoma diagnosis (OR: 1.74, 95% CI: 1.28–2.37), and major resections (OR: 3.29, 95% CI: 2.57–4.21) were associated with increased odds of PHLF. In contrast, albumin (OR: 0.74, 95% CI: 0.59–0.93), platelets (OR: 0.998, 95% CI: 0.997–0.999), and benign diagnosis (OR: 0.47, 95% CI: 0.24–0.96) decreased the odds of PHLF.

Multivariable model – mortality

Factors predictive of mortality were male sex (OR: 1.61, 95% CI: 1.03–2.50), older age (OR: 1.05, 95% CI: 1.03–1.08), Asian race (OR: 2.05, 95% CI: 1.06–3.98), steroid use (OR: 2.97, 95% CI: 1.42–6.19), GOT (OR: 1.005, 95% CI: 1.002–1.008), INR (OR: 1.65, 95% CI: 1.14–2.40), ASA classification (OR: 1.66, 95% CI: 1.10–2.52), operative time (OR: 1.003, 95% CI: 1.002–1.005), CCC diagnosis (OR: 2.71, 95% CI: 1.57–4.68), and major resections (OR: 2.93, 95% CI: 1.88–4.57). Two factors were protective against mortality: higher values of pre-operative albumin (OR: 0.55, 95% CI: 0.37–0.80) and platelets (OR: 0.997, 95% CI: 0.995–0.999) (Table 2).

Multivariable model – major morbidity

Male sex (OR: 1.25, 95% CI: 1.08–1.45), age (OR: 1.01, 95% CI: 1.004–1.016), smoking (OR: 1.21, 95% CI: 1.01–1.45), COPD (OR: 1.87, 95% CI: 1.40–2.51), CHF (OR: 3.09, 95% CI: 1.41–6.78), GOT (OR: 1.003, 95% CI: 1.001–1.005), platelets (OR: 1.001, 95% CI: 1.000–1.002), creatinine (OR: 1.23, 95% CI: 1.08–1.40), operative time (OR: 1.004, 95% CI: 1.003–1.004), CCC diagnosis (OR: 1.74, 95% CI: 1.43–2.12), infectious diagnosis (OR: 2.25, 95% CI: 1.34–3.78) and major resections (OR: 1.52, 95% CI: 1.32–1.75) were associated with increased odds of major complications. Albumin (OR: 0.71, 95% CI: 0.62–0.81) was associated with decreased odds of major morbidity (Table 2).

Multivariable model – PHLF – cancer and resection subgroups

Subgroup analysis of patients separated by diagnosis (Table 3) demonstrated that after controlling for confounders, the association of male sex and higher odds of PHLF was predominantly present in HCC patients (OR: 2.81, 95% CI: 1.40–5.62), while male patients with CRLCM (OR: 1.14, 95%CI: 0.74–1.77) and CCC (OR: 1.43, 95% CI: 0.66–3.11) did not show a significant increase in PHLF upon multivariable analyses.

Examining only patients who underwent major liver resection, we found male sex (OR: 1.38, 95% CI: 1.03–1.84), diabetes mellitus (OR: 1.46, 95% CI: 1.05–2.03) operative time (OR: 1.002, 95% CI: 1.001–1.003), and CCC diagnosis (OR: 1.78, 95% CI: 1.23–2.57) were predictive of PHLF, while albumin (OR: 0.76, 95% CI: 0.58–0.99) and benign diagnoses (OR: 0.30, 95% CI: 0.11–0.85) were protective against PHLF (Table 4).

HCC subgroup

Given the remarkable increase in risk of PHLF in male patients within the HCC subgroup, we aimed to explore this subgroup

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Table 1 Univariate analysis and bivariate analysis by sex

Variables	Total	Sex		P value
	N = 13,401 N (%)	Female N = 6652 N (%)	Male N = 6749 N (%)	
Age (age) – mean (SD)	58.52 (13.52)	56.28 (14.84)	60.72 (12.11)	**< 0.001***
BMI (mg/kg^2)– mean (SD)	28.54 (6.29)	28.56 (6.99)	28.51 (5.50)	**< 0.001***
Race				
Non-Hispanic White	8395 (77.9)	4273 (78.8)	4122 (77.0)	**< 0.001†**
American Indian	50 (0.5)	23 (0.4)	27 (0.5)	
Asian	871 (8.1)	348 (6.4)	523 (9.8)	
Black or AA	1367 (10.2)	572 (10.5)	528 (9.9)	
Hispanic White	359 (3.3)	206 (3.8)	153 (3.3)	
Diabetes	2320 (17.3)	900 (13.5)	1420 (21.0)	**< 0.001†**
Smoking	2086 (15.6)	907 (13.6)	1179 (17.5)	**< 0.001†**
COPD	474 (3.5)	190 (2.9)	284 (4.2)	**< 0.001†**
CHF	46 (0.3)	12 (0.02)	34 (0.5)	**0.001†**
Steroids	407 (3.0)	212 (3.2)	195 (2.9)	0.32†
Weight loss	494 (3.7)	234 (3.5)	260 (3.9)	0.30†
Bleeding disorder	405 (3.0)	152 (2.3)	253 (3.7)	**< 0.001†**
Albumin (mg/dL) – mean (SD)	4.00 (0.48)	4.00 (0.49)	3.99 (0.48)	0.21*
Bilirubin (mg/dL)– mean (SD)	0.66 (0.71)	0.57 (0.59)	0.74 (0.80)	**< 0.001***
GOT (IU/L)– mean (SD)	34.77 (35.20)	32.18 (34.75)	37.30 (35.45)	**< 0.001***
Platelets (x 10^3/mm^3)– mean (SD)	231.63 (87.25)	251.36 (88.47)	212.34 (81.55)	**< 0.001***
INR – mean (SD)	1.04 (0.22)	1.02 (0.24)	1.05 (0.21)	**< 0.001***
Creatinine (mg/dL) – mean (SD)	0.89 (0.42)	0.78 (0.29)	0.99 (0.49)	**< 0.001***
ASA Classification – mean (SD)	2.77 (0.59)	2.69 (0.60)	2.85 (0.57)	**< 0.001***
Operative Time (min) – mean (SD)	236.88 (117.14)	224.75 (112.49)	248.84 (120.36)	**< 0.001***
Diagnosis				**< 0.001†**
CRCLM	5631 (42.6)	2505 (38.4)	3126 (46.8)	
HCC	2324 (17.6)	649 (9.9)	1675 (25.1)	
CCC	1716 (13.0)	947 (14.5)	769 (11.5)	
Benign	1297 (9.8)	1073 (16.4)	224 (3.4)	
Infectious	156 (1.2)	77 (1.2)	79 (1.2)	
Other	1392 (10.5)	919 (14.1)	473 (7.1)	
Other metastases	687 (5.2)	355 (5.4)	332 (5.0)	
Major Resections	5111 (38.1)	2529 (38.0)	2582 (38.3)	0.78†
Biliary stent	613 (4.6)	303 (4.6)	310 (4.6)	0.89†
Neoadjuvant therapy	4034 (30.1)	1970 (29.6)	2064 (30.6)	0.22†
Viral hepatitis	1675 (13.7)	847 (13.9)	828 (13.5)	0.48†
Ablation	1842 (13.7)	919 (13.8)	923 (13.7)	0.82†
Pringle maneuver	3255 (24.3)	1593 (23.9)	1662 (24.6)	0.36†
PHLF	619 (4.6)	216 (3.2)	403 (6.0)	**< 0.001†**

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Table 1 (*continued*)

Variables	Total	Sex		P value
	N = 13,401 N (%)	Female N = 6652 N (%)	Male N = 6749 N (%)	
Major complications	2027 (15.1)	820 (12.3)	1207 (17.9)	< 0.001†
Death at 30 days	219 (1.6)	63 (0.9)	156 (2.3)	< 0.001†

BMI: body mass index. SD: standard deviation. IU: international units. AA: African American. COPD: chronic obstructive pulmonary disease. CHF: congestive heart failure. GOT: Glutamate Oxaloacetate Transaminase. INR: International Normalized Ratio. ASA: American Society of Anesthesiologists. CRCLM: colorectal cancer liver metastases. HCC: hepatocellular carcinoma. CCC: cholangiocellular carcinoma. PHLF: post-hepatectomy liver failure.
* P-value was calculated using Student's T test.
† P-value was calculated using Chi-square test.

further. Subgroup analysis of patients with HCC found that diabetes, ASA classification, operative time, PHLF, and major complications were significantly higher in men ($p < 0.05$) (Supplementary table 2). Compared to women, men with HCC had greater frequency of superficial infection, organ SSI, pneumonia, unplanned re-intubation, pulmonary embolism, failure to wean, renal insufficiency, postoperative renal failure, cardiac arrest, myocardial infarction, DVT, sepsis/septic shock, and reoperation (Supplementary fig 2).

Multivariable model – PHLF – reduced liver function subgroup

To assess sex differences in patients with altered liver function we assessed patients with reduced liver function according to their APRI/ALBI score. A previously defined cut-off was defined to classify patients in high and low risk groups.[5,15,16] From a total of 5124 patients who had an APRI/ALBI higher than −2.46, 2987 were men and 2137 were women. Subgroup analysis of patients with preoperative underlying liver disease as quantified by APRI/ALBI higher than −2.46, found that also in patients with reduced liver function, men had higher odds of PHLF (OR: 1.43, 95% CI: 1.05–1.94) (Table 5).

Illustrations of ORs with associated CIs obtained by multivariable analyses for several subgroups and outcomes, demonstrating worse outcomes for male sex in the general population (PHLF, major morbidity and mortality), patients who underwent major liver resections (PHLF) and had an APRI/ALBI score > -2.46 (PHLF) is depicted in Fig. 1. Of note, the strongest effect was observed in patients with HCC.

Discussion

In this large cohort of >13,000 patients, we were able to provide a robust assessment of sex differences in terms of PHLF, morbidity and 30-day mortality after hepatic resection, even after adjusting for potential confounders,. Importantly, when assessing subgroups, we were able to demonstrate that this increased risk of PHLF in male patients was predominantly mediated by an almost 3 times increased risk in HCC patients.

Liver regeneration represents an important determinant of postoperative outcome after hepatic resection. Sex has been implicated to affect liver regeneration in rodent models.[10,11] Here we assessed sex differences in a population of patients who underwent elective hepatic resection to explore the in human relevance of these findings. Accordingly, we found that men were at significantly higher risk to develop PHLF or suffer from major complication or 30-day mortality. This association prevailed upon multivariable and multiple subgroup analyses. However, we observed that the negative effect of male sex on outcomes was particularly high in patients undergoing resection for HCC. Accordingly, the almost 3 times higher risk of PHLF in men suffering from HCC should be considered when developing multidisciplinary treatment strategies (including portal vein embolization), particularly if major liver resection is planned. Integrating sex into clinical decision making might therefore ultimately improve patient care.

Previous reports have documented sex differences in outcomes after liver surgery, as we found in our investigation. Contemporary outcome analyses from Norway indicated male sex to be an independent risk factor for worse postoperative outcome after liver resection.[17] Similarly, Bachellier et al. found male sex as an independent risk factor for PHLF in patients who underwent major hepatectomy with combined portal vein resection probably due to a different pathophysiologic response to hepatic stress in men, influenced by sex hormones and their role in immune and cardiovascular regulation.[18] In a large cohort of HCC patients in China, men had a higher incidence of mortality after hepatic resection.[9] In line with these results, clinical models developed specifically for HCC include male sex as a risk factor for worse clinical outcomes.[19] However, some conflicting results have been published suggesting only minor effects of sex on outcomes after liver resection.[20] Certainly, limited power of respective analyses might explain these differences, particularly as our results indicate that the observed effect is predominantly associated with HCC patients. To our knowledge, this is yet the largest analysis assessing the relevance of sex for postoperative outcome in patients undergoing liver resection, by which we

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Table 2 Univariate and multivariate logistic regression analysis between study variables, post-hepatectomy liver failure, mortality, and only major complications in general population

Variables	Post-hepatectomy liver failure						Mortality						Major complications					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	CI 95%	P value	OR	CI 95%	P value	OR	CI 95%	P value	OR	CI 95%	P value	OR	CI 95%	P value	OR	CI 95%	P value
Male Sex	**1.89**	**1.60–2.24**	**< 0.001**	**1.47**	**1.15–1.88**	**0.002**	**2.48**	**1.84–3.32**	**< 0.001**	**1.61**	**1.03–2.50**	**0.036**	**1.55**	**1.41–1.71**	**< 0.001**	**1.25**	**1.08–1.45**	**0.003**
Age (age) – mean (SD)	**1.016**	**1.01–0.02**	**< 0.001**	1.01	0.99–1.02	0.16	**1.07**	**1.05–1.08**	**< 0.001**	**1.05**	**1.03–1.08**	**< 0.001**	**1.02**	**1.01–1.02**	**< 0.001**	**1.01**	**1.004–1.016**	**0.001**
BMI (mg/kg^2)– mean (SD)	0.99	0.98–1.01	0.26	0.99	0.98–1.02	0.83	1.009	0.988–1.03	0.42	1.03	0.99–1.07	0.08	1.002	0.994–1.009	0.63	1.004	0.993–1.015	0.48
Race																		
Non-Hispanic White	1.00			1.00			1.00			1.00			1.00			1.00		
American Indian	0.47	0.07–3.41	0.45	0.63	0.08–4.75	0.65	–	–	–	–	–	–	0.25	0.06–1.05	0.06	0.31	0.07–1.33	0.12
Asian	1.17	0.84–1.62	0.36	1.17	0.79–1.74	0.44	1.17	0.68–2.01	0.57	**2.05**	**1.06–3.98**	**0.034**	0.83	0.67–1.03	0.08	0.87	0.66–1.15	0.33
Black or AA	0.73	0.51–1.05	0.09	0.86	0.58–1.29	0.47	0.92	0.54–1.58	0.77	0.89	0.44–1.79	0.75	1.06	0.89–1.27	0.51	1.13	0.91–1.41	0.26
Hispanic White	0.93	0.54–1.61	0.80	1.35	0.74–2.46	0.33	0.75	0.28–2.05	0.58	1.15	0.35–3.81	0.82	0.97	0.71–1.31	0.82	1.25	0.85–1.82	0.26
Diabetes	**1.51**	**1.24–1.82**	**< 0.001**	1.23	0.93–1.62	0.14	**2.70**	**2.04–3.57**	**< 0.001**	1.42	0.92–2.19	0.12	**1.38**	**1.22–1.55**	**< 0.001**	1.07	0.89–1.27	0.48
Smoking	1.09	0.88–1.35	0.45	0.85	0.62–1.17	0.31	1.067	0.75–1.53	0.72	1.42	0.83–2.41	0.20	**1.27**	**1.12–1.44**	**< 0.001**	**1.21**	**1.01–1.45**	**0.042**
COPD	1.57	1.01–2.13	0.044	1.13	0.67–1.93	0.65	1.17	0.60–2.30	0.64	0.71	0.27–1.84	0.48	**1.98**	**1.60–2.45**	**< 0.001**	**1.87**	**1.40–2.51**	**< 0.001**
CHF	1.44	0.47–4.66	0.54	0.56	0.07–4.29	0.58	**4.24**	**1.31–13.79**	**0.016**	2.52	0.55–11.65	0.24	**3.31**	**1.82–6.03**	**< 0.001**	**3.09**	**1.41–6.78**	**0.005**
Steroids	0.95	0.59–1.54	0.85	1.17	0.65–2.10	0.61	**2.40**	**1.41–4.09**	**0.001**	**2.97**	**1.42–6.19**	**0.004**	1.17	0.90–1.52	0.24	1.14	0.79–1.64	0.49
Weight loss	**2.44**	**1.80–3.31**	**< 0.001**	1.48	0.97–2.24	0.07	**2.69**	**1.69–4.31**	**< 0.001**	1.32	0.64–2.73	0.45	**1.94**	**1.57–2.39**	**< 0.001**	1.25	0.93–1.68	0.14
Bleeding disorder	**2.01**	**1.41–2.87**	**< 0.001**	**1.82**	**1.13–2.93**	**0.013**	1.72	0.93–3.17	0.09	1.29	0.53–3.13	0.57	**1.31**	**1.01–1.69**	**0.038**	0.94	0.64–1.38	0.75
Albumin (mg/dL) – mean (SD)	**0.56**	**0.48–0.66**	**< 0.001**	**0.74**	**0.59–0.93**	**0.009**	**0.35**	**0.28–0.45**	**< 0.001**	**0.55**	**0.37–0.80**	**0.002**	**0.52**	**0.47–0.58**	**< 0.001**	**0.71**	**0.62–0.81**	**< 0.001**
Bilirubin (mg/dL)– mean (SD)	**1.27**	**1.19–1.35**	**< 0.001**	0.96	0.86–1.08	0.49	**1.31**	**1.21–1.42**	**< 0.001**	0.84	0.67–1.05	0.13	**1.37**	**1.29–1.46**	**< 0.001**	1.05	0.97–1.14	0.20
GOT (IU/L)– mean (SD)	**1.005**	**1.003–1.006**	**< 0.001**	**1.003**	**1.000–1.005**	**0.037**	**1.006**	**1.004–1.007**	**< 0.001**	**1.005**	**1.002–1.008**	**0.004**	**1.006**	**1.005–1.007**	**< 0.001**	**1.003**	**1.001–1.005**	**0.002**
Platelets (x 10^3/mm^3)– mean (SD)	**0.99**	**0.997–0.999**	**0.003**	**0.998**	**0.997–0.999**	**0.003**	**0.998**	**0.996–1.000**	**0.017**	**0.997**	**0.995–0.999**	**0.017**	**1.001**	**1.001–1.002**	**< 0.001**	**1.001**	**1.000–1.001**	**0.044**
INR – mean (SD)	**1.37**	**1.10–1.69**	**0.005**	**1.47**	**1.12–1.93**	**0.006**	**1.51**	**1.19–1.92**	**0.001**	**1.65**	**1.14–2.40**	**0.008**	**1.23**	**1.03–1.49**	**0.026**	1.03	0.75–1.41	0.88
Creatinine (mg/dL) – mean (SD)	1.12	0.98–1.29	0.11	1.07	0.82–1.38	0.63	**1.30**	**1.13–1.50**	**< 0.001**	1.23	0.92–1.64	0.16	**1.24**	**1.13–1.36**	**< 0.001**	**1.23**	**1.08–1.40**	**0.002**
ASA Classification – mean (SD)	**1.52**	**1.32–1.75**	**< 0.001**	1.10	0.88–1.37	0.42	**3.26**	**2.55–4.17**	**< 0.001**	**1.66**	**1.10–2.52**	**0.017**	**1.56**	**1.43–1.69**	**< 0.001**	1.07	0.93–1.23	0.33
Operative Time (min) – mean (SD)	**1.005**	**1.004–1.005**	**< 0.001**	**1.002**	**1.002–1.003**	**< 0.001**	**1.005**	**1.005–1.006**	**< 0.001**	**1.003**	**1.002–1.005**	**< 0.001**	**1.005**	**1.005–1.005**	**< 0.001**	**1.004**	**1.003–1.004**	**< 0.001**
Diagnosis																		
CRCLM	1.00			1.00			1.00			1.00			1.00			1.00		
HCC	**1.74**	**1.41–2.15**	**< 0.001**	1.28	0.94–1.74	0.12	**2.33**	**1.611–3.38**	**< 0.001**	1.18	0.65–2.13	0.59	**1.25**	**1.09–1.43**	**0.001**	1.04	0.85–1.27	0.74
CCC	**2.39**	**1.93–2.95**	**< 0.001**	**1.74**	**1.28–2.37**	**< 0.001**	**4.58**	**3.24–6.46**	**< 0.001**	**2.71**	**1.57–4.68**	**< 0.001**	**2.31**	**2.03–2.64**	**< 0.001**	**1.74**	**1.43–2.12**	**< 0.001**
Benign	**0.27**	**0.15–0.46**	**< 0.001**	**0.47**	**0.24–0.96**	**0.037**	-	-	-	-	-	-	**0.59**	**0.48–0.73**	**< 0.001**	1.03	0.77–1.39	0.83
Infectious	0.98	0.43–2.23	0.95	0.70	0.21–2.29	0.55	0.62	0.09–4.50	0.64	0.98	0.12–7.84	0.98	**1.77**	**1.20–2.61**	**0.004**	**2.25**	**1.34–3.78**	**0.002**
Other	**0.61**	**0.42–0.88**	**0.008**	0.73	0.45–1.18	0.19	1.19	0.69–2.05	0.54	1.52	0.71–3.25	0.28	0.84	0.70–1.00	0.053	1.13	0.89–1.45	0.32
Other metastases	0.62	0.38–1.02	0.059	0.70	0.35–1.41	0.32	1.42	0.72–2.79	0.31	2.42	0.97–6.02	0.06	1.02	0.81–1.28	0.87	1.25	0.91–1.73	0.17
Major resections	**4.45**	**3.72–5.32**	**< 0.001**	**3.29**	**2.57–4.21**	**< 0.001**	**3.05**	**2.31–4.03**	**< 0.001**	**2.93**	**1.88–4.57**	**< 0.001**	**1.99**	**1.81–2.19**	**< 0.001**	**1.52**	**1.32–1.75**	**< 0.001**
Biliary stent	1.02	0.70–1.50	0.92	0.91	0.52–1.59	0.74	1.10	0.60–2.03	0.76	0.85	0.30–2.38	0.76	1.01	0.80–1.26	0.96	1.01	0.73–1.40	0.97
Neoadjuvant therapy	1.03	0.87–1.23	0.74	0.94	0.74–1.20	0.62	0.74	0.54–1.01	0.056	0.79	0.50–1.25	0.32	0.95	0.85–1.05	0.29	0.93	0.80–1.08	0.33
Viral hepatitis	0.93	0.72–1.19	0.56	1.05	0.76–1.46	0.77	0.97	0.64–1.45	0.86	1.25	0.71–2.19	0.44	0.94	0.81–1.09	0.42	0.93	0.76–1.14	0.48
Ablation	1.03	0.81–1.30	0.82	1.005	0.73–1.38	0.98	0.96	0.65–1.42	0.83	0.92	0.51–1.65	0.77	1.08	0.95–1.24	0.25	1.17	0.97–1.14	0.10
Pringle maneuver	0.92	0.76–1.12	0.42	1.02	0.80–1.31	0.86	0.92	0.67–1.27	0.61	0.91	0.58–1.43	0.69	0.99	0.88–1.10	0.81	1.01	0.67–1.18	0.86

OR: odds ratio. CI: confidence interval. BMI: body mass index. AA: African American. COPD: chronic obstructive pulmonary disease. CHF: congestive heart failure. GOT: Glutamate Oxaloacetate Transaminase. INR: International Normalized Ratio. ASA: American Society of Anesthesiologists. CRCLM: colorectal cancer liver metastases. HCC: hepatocellular carcinoma. CCC: cholangiocellular carcinoma.

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Table 3 Univariate and multivariate logistic regression analysis between study variables, post-hepatectomy liver failure according to diagnoses

Variables	CRCLM						CCC						HCC					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	CI 95%	P value	OR	CI 95%	P value	OR	CI 95%	CI 95%	OR	CI 95%	P value	OR	CI 95%	P value	OR	CI 95%	P value
Male Sex	1.24	0.90–1.72	0.19	1.14	0.74–1.77	0.55	**2.34**	**1.31–4.19**	**0.004**	1.43	0.66–3.11	0.37	**1.80**	**1.15–2.83**	**0.011**	**2.81**	**1.40–5.62**	**0.004**
Age (age) – mean (SD)	1.003	0.99–1.02	0.64	0.99	0.97–1.01	0.21	1.02	0.99–1.05	0.20	1.01	0.97–1.05	0.67	1.01	0.99–1.02	0.44	0.99	0.97–1.02	0.51
BMI (mg/kg^2)– mean (SD)	1.00	0.97–1.03	0.97	1.00	0.97–1.03	0.96	0.99	0.95–1.04	0.66	**0.93**	**0.87–0.99**	**0.044**	0.99	0.96–1.02	0.53	0.98	0.94–1.03	0.42
Race																		
Non-Hispanic White	1.00			1.00			1.00			1.00			1.00			1.00		
American Indian	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Asian	0.77	0.28–2.13	0.62	0.97	0.33–2.80	0.95	0.85	0.20–3.66	0.83	0.57	0.07–4.66	0.60	0.86	0.50–1.48	0.58	0.75	0.39–1.46	0.41
Black or AA	0.98	0.51–1.89	0.95	1.12	0.55–2.28	0.76	0.60	0.18–1.99	0.40	0.75	0.19–2.92	0.67	0.86	0.45–1.62	0.63	0.57	0.26–1.25	0.16
Hispanic White	0.32	0.04–2.31	0.26	0.54	0.07–4.00	0.54	0.60	0.08–4.54	0.63	1.08	0.13–9.17	0.94	2.04	0.89–4.66	0.09	1.87	0.71–4.92	0.20
Diabetes	1.21	0.79–1.86	0.38	1.13	0.63–2.04	0.68	**2.11**	**1.17–3.79**	**0.013**	**2.56**	**1.08–6.08**	**0.034**	1.15	0.79–1.67	0.48	1.10	0.64–1.91	0.72
Smoking	0.65	0.36–1.15	0.14	0.70	0.35–1.42	0.33	0.73	0.31–1.74	0.48	0.47	0.14–1.52	0.21	0.98	0.66–1.48	0.94	1.02	0.58–1.79	0.94
COPD	1.90	0.87–4.15	0.11	**2.65**	**1.04–6.74**	**0.04**	0.93	0.28–3.06	0.90	1.26	0.27–5.94	0.77	0.88	0.42–1.84	0.74	0.67	0.23–1.98	0.47
CHF	-	-	-	–	–	–	-	-	-	–	–	–	**5.24**	**1.40–19.60**	**0.014**	2.63	0.28–24.69	0.40
Steroids	0.64	0.20–2.02	0.44	0.67	0.16–2.84	0.59	0.84	0.11–6.30	0.86	1.32	0.15–11.45	0.80	1.24	0.49–3.12	0.66	1.61	0.54–4.80	0.39
Weight loss	1.34	0.58–3.09	0.49	0.99	0.37–2.63	0.98	1.66	0.50–5.54	0.41	1.34	0.25–7.04	0.73	1.94	0.95–3.97	0.07	1.61	0.62–4.22	0.33
Bleeding disorder	1.60	0.77–3.31	0.21	1.17	0.44–3.12	0.75	0.78	0.10–5.84	0.81	0.42	0.04–5.08	0.50	**2.09**	**1.09–4.02**	**0.027**	**2.63**	**1.07–6.45**	**0.035**
Albumin (mg/dL) – mean (SD)	**0.60**	**0.42–0.85**	**0.004**	0.71	0.44–1.13	0.15	0.63	0.37–1.07	0.09	0.65	0.32–1.32	0.23	**0.58**	**0.41–0.81**	**0.002**	**0.51**	**0.32–0.83**	**0.006**
Bilirubin (mg/dL)– mean (SD)	**1.42**	**1.08–1.88**	**0.013**	**1.54**	**1.02–2.32**	**0.04**	1.06	0.81–1.40	0.66	0.69	0.36–1.32	0.26	**1.33**	**1.01–1.74**	**0.039**	0.98	0.60–1.58	0.93
GOT (IU/L)– mean (SD)	**1.006**	**1.002–1.010**	**0.001**	1.00	0.99–1.01	0.17	1.004	0.998–1.01	0.18	1.01	0.99–1.02	0.12	1.002	0.999–1.005	0.18	0.99	0.994–1.005	0.84
Platelets (x 10^3/mm^3)– mean (SD)	**0.997**	**0.995–0.999**	**0.014**	0.998	0.995–1.001	0.11	**0.995**	**0.991–0.999**	**0.008**	0.995	0.99–1.00	0.07	0.99	0.999–1.001	0.425	0.998	0.995–1.001	0.15
INR – mean (SD)	1.31	0.87–1.97	0.19	1.27	0.79–2.05	0.33	1.35	0.89–2.04	0.16	**3.28**	**1.29–8.38**	**0.013**	1.22	0.78–1.91	0.37	1.30	0.76–2.22	0.33
Creatinine (mg/dL) – mean (SD)	1.12	0.85–1.47	0.43	1.28	0.88–1.87	0.20	1.14	0.81–1.60	0.46	1.38	0.68–2.82	0.38	1.06	0.73–1.53	0.77	0.75	0.30–1.83	0.52
ASA Classification – mean (SD)	1.29	0.94–1.76	0.12	1.01	0.66–1.56	0.96	**2.37**	**1.39–4.06**	**0.002**	1.27	0.62–2.60	0.51	1.17	0.85–1.63	0.34	0.83	0.52–1.31	0.43
Operative Time (min) – mean (SD)	**1.004**	**1.003–1.005**	**< 0.001**	1.002	1.000–1.004	0.089	**1.003**	**1.001–1.005**	**0.001**	1.00	0.997–1.004	0.89	**1.004**	**1.002–1.005**	**< 0.001**	1.001	0.998–1.003	0.55
Biliary stent	1.14	0.55–2.35	0.73	0.77	0.27–2.20	0.63	1.46	0.44–4.88	0.54	2.20	0.55–8.82	0.27	1.01	0.43–2.34	0.99	1.28	0.43–3.81	0.66
Major Resections	**4.50**	**3.15–6.43**	**< 0.001**	**3.72**	**2.36–5.86**	**< 0.001**	**4.11**	**2.24–7.55**	**< 0.001**	**3.29**	**1.53–7.08**	**0.002**	**2.84**	**1.99–4.06**	**< 0.001**	**3.37**	**1.99–5.69**	**< 0.001**
Neoadjuvant therapy	1.05	0.74–1.48	0.79	0.79	0.50–1.26	0.33	0.94	0.50–1.77	0.85	0.76	0.32–1.84	0.55	1.19	0.82–1.71	0.36	1.46	0.8–2.42	0.14
Viral hepatitis	0.63	0.36–1.13	0.12	0.60	0.29–1.22	0.16	1.07	0.47–2.44	0.87	0.97	0.34–2.80	0.97	0.95	0.54–1.69	0.86	1.28	0.62–2.65	0.51
Ablation	1.34	0.88–2.04	0.18	1.38	0.81–2.35	0.24	0.76	0.32–1.82	0.54	0.36	0.09–1.49	0.16	0.81	0.47–1.38	0.44	0.65	0.29–1.41	0.27
Pringle maneuver	0.76	0.51–1.14	0.18	0.83	0.51–1.36	0.45	1.45	0.79–2.67	0.23	1.65	0.76–3.61	0.21	0.90	0.59–1.36	0.61	1.27	0.75–2.15	0.38

OR: odds ratio. CI: confidence interval. BMI: body mass index. AA: African American. COPD: chronic obstructive pulmonary disease. CHF: congestive heart failure. GOT: Glutamate Oxaloacetate Transaminase. INR: International Normalized Ratio. ASA: American Society of Anesthesiologists. CRCLM: colorectal cancer liver metastases. HCC: hepatocellular carcinoma. CCC: cholangiocellular carcinoma.

were able to document that the effects of sex might be particularly important in HCC patients.

In our study, men had more comorbidities than women, such as diabetes, smoking, COPD, CHF, and bleeding disorders. Multimorbidity has been shown to predict worse outcomes following hepatic resection.[21–23] However, in our study, multivariable analyses were adjusted for race, reported comorbidities, laboratory findings, ASA classification, and underlying liver pathology, suggesting that male sex was independent of those factors. While there is certainly the possibility that there are additional non-documented confounders that were not recorded in the dataset, the majority of previously documented confounders for postoperative outcome were included in our analyses.

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Table 4 Univariate and multivariate logistic regression analysis between study variables, post-hepatectomy liver failure in patients who underwent only major resection

Variables	Univariate analysis			Multivariate analysis		
	OR	CI 95%	P value	OR	CI 95%	P value
Male Sex	**1.74**	**1.43–2.13**	**< 0.001**	**1.38**	**1.03–1.84**	**0.032**
Age (age) – mean (SD)	**1.016**	**1.009–1.024**	**< 0.001**	1.008	0.99–1.02	0.19
BMI (mg/kg^2)– mean (SD)	0.99	0.98–1.01	0.29	0.99	0.96–1.01	0.35
Race						
Non-Hispanic White	1.00			1.00		
American Indian	0.77	0.10–5.86	0.80	1.30	0.16–10.83	0.81
Asian	1.29	0.88–1.90	0.19	1.36	0.85–2.16	0.20
Black or AA	0.77	0.50–1.19	0.25	0.89	0.55–1.44	0.63
Hispanic White	0.98	0.49–1.96	0.96	1.40	0.68–2.92	0.36
Diabetes	**1.66**	**1.32–2.10**	**< 0.001**	**1.46**	**1.05–2.03**	**0.026**
Smoking	1.10	0.86–1.43	0.45	0.92	0.64–1.34	0.67
COPD	1.35	0.83–2.20	0.23	0.85	0.41–1.76	0.67
CHF	1.91	0.42–8.65	0.40	1.03	0.12–8.74	0.98
Steroids	0.91	0.50–1.65	0.76	1.25	0.63–2.49	0.53
Weight loss	**2.06**	**1.47–2.90**	**< 0.001**	1.35	0.84–2.17	0.22
Bleeding disorder	**1.81**	**1.12–2.94**	**0.016**	1.80	1.97–3.34	0.063
Albumin (mg/dL) – mean (SD)	**0.60**	**0.50–0.73**	**< 0.001**	**0.76**	**0.58–0.99**	**0.043**
Bilirubin (mg/dL)– mean (SD)	**1.17**	**1.08–1.26**	**< 0.001**	0.94	0.82–1.07	0.33
GOT (IU/L)– mean (SD)	**1.004**	**1.002–1.006**	**< 0.001**	1.003	1.000–1.005	0.07
Platelets (x 10^3/mm^3)– mean (SD)	0.999	0.998–1.001	0.31	0.999	0.997–1.00	0.12
INR – mean (SD)	**1.83**	**1.14–2.92**	**0.012**	1.55	0.86–2.79	0.15
Creatinine (mg/dL) – mean (SD)	**1.26**	**1.03–1.55**	**0.023**	1.23	0.90–1.70	0.20
ASA Classification – mean (SD)	**1.43**	**1.21–1.69**	**< 0.001**	1.04	0.79–1.36	0.79
Operative Time (min) – mean (SD)	**1.003**	**1.003–1.004**	**< 0.001**	**1.002**	**1.001–1.003**	**0.001**
Diagnosis						
CRCLM	1.00			1.00		
HCC	**1.56**	**1.20–2.04**	**0.001**	1.19	0.82–1.73	0.37
CCC	**2.28**	**1.78–2.94**	**< 0.001**	**1.78**	**0.23–2.57**	**0.002**
Benign	**0.21**	**0.10–0.45**	**< 0.001**	**0.30**	**0.11–0.85**	**0.023**
Infectious	0.82	0.29–2.28	0.70	0.55	0.13–2.38	0.42
Other	0.74	0.49–1.12	0.16	0.84	0.49–1.45	0.54
Other metastases	0.77	0.42–1.42	0.40	0.73	0.31–1.73	0.48
Biliary stent	1.13	0.72–1.77	0.60	0.98	0.51–1.88	0.96
Neoadjuvant therapy	1.10	0.90–1.36	0.36	0.92	0.68–1.23	0.56
Viral hepatitis	0.91	0.67–1.24	0.55	0.99	0.66–1.49	0.97
Ablation	1.02	0.77–1.35	0.88	1.06	0.72–1.56	0.76
Pringle maneuver	0.97	0.77–1.22	0.81	1.11	0.82–1.49	0.50

OR: odds ratio. CI: confidence interval. BMI: body mass index. AA: African American. COPD: chronic obstructive pulmonary disease. CHF: congestive heart failure. GOT: Glutamate Oxaloacetate Transaminase. INR: International Normalized Ratio. ASA: American Society of Anesthesiologists. CRCLM: colorectal cancer liver metastases. HCC: hepatocellular carcinoma. CCC: cholangiocellular carcinoma.

Several mechanisms may explain the sex difference in PHLF following hepatectomy. Preclinical literature suggests that estrogen plays a critical role in liver regeneration. Animal studies have elucidated this hypothesis. Chaturantabut et al.[10] exposed zebrafish to 17β-estradiol and reported increased hepatocytes proliferation in different states of life. Similarly, liver regeneration was

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Table 5 Univariate and multivariate logistic regression analysis between study variables and post-hepatectomy liver failure in patients who had APRI/ALBI > -2.46

Variables	Univariate analysis			Multivariate analysis		
	OR	CI 95%	CI 95%	OR	CI 95%	P value
Male Sex	**1.47**	**1.16–1.85**	**0.001**	**1.43**	**1.05–1.94**	**0.023**
Age (age) – mean (SD)	**1.009**	**1.00–1.02**	**0.047**	**1.01**	**1.001–1.028**	**0.029**
BMI (mg/kg^2)– mean (SD)	0.99	0.97–1.01	0.15	0.99	0.97–1.02	0.46
Race						
Non-Hispanic White	1.00			1.00		
American Indian	0.62	0.08–4.57	0.64	0.87	0.11–6.73	0.90
Asian	1.17	0.76–1.80	0.48	1.19	0.72–1.97	0.49
Black or AA	0.66	0.41–1.05	0.08	0.80	0.48–1.34	0.40
Hispanic White	1.46	0.81–2.63	0.21	**2.12**	**1.12–4.05**	**0.02**
Diabetes	1.19	0.91–1.55	0.20	1.20	0.85–1.70	0.31
Smoking	0.99	0.73–1.33	0.94	1.30	0.89–1.89	0.17
COPD	1.19	0.69–2.03	0.53	0.8.	0.39–1.78	0.64
CHF	1.48	0.34–6.36	0.60	0.88	0.11–6.87	0.90
Steroids	0.96	0.54–1.69	0.88	1.32	0.67–2.63	0.43
Weight loss	**1.96**	**1.35–2.84**	**< 0.001**	1.43	0.89–2.30	0.14
Bleeding disorder	1.54	0.98–2.42	0.06	1.39	0.75–2.55	0.30
INR – mean (SD)	1.33	0.95–1.85	0.10	**1.51**	**1.05–2.17**	**0.028**
Creatinine (mg/dL) – mean (SD)	1.05	0.87–1.26	0.63	1.09	0.82–1.44	0.55
ASA Classification – mean (SD)	1.49	1.21–1.84	<0.001	1.17	0.87–1.56	0.30
Operative Time (min) – mean (SD)	**1.004**	**1.003–1.005**	**< 0.001**	**1.002**	**1.001–1.003**	**< 0.001**
Biliary stent	0.89	0.51–1.55	0.68	0.60	0.26–1.39	0.23
Major Resections	**3.67**	**2.88–4.67**	**< 0.001**	**3.17**	**2.29–4.39**	**< 0.001**
Neoadjuvant therapy	0.96	0.76–1.21	0.72	0.92	0.68–1.26	0.62
Viral hepatitis	0.83	0.58–1.19	0.31	0.74	0.47–1.16	0.19
Ablation	1.07	0.78–1.46	0.68	1.06	0.71–1.59	0.78
Pringle maneuver	0.83	0.64–1.07	0.15	1.01	0.74–1.39	0.96

Aspartate Aminotransferase/platelet ratio index: APRI. Albumin-Bilirubin score: ALBI. OR: odds ratio. CI: confidence interval. BMI: body mass index. AA: African American. COPD: chronic obstructive pulmonary disease. CHF: congestive heart failure. GOT: Glutamate Oxaloacetate Transaminase. INR: International Normalized Ratio. ASA: American Society of Anesthesiologists.

associated with estrogen receptor (ER) α transcriptome, and cell metabolic function was associated with ERβ transcriptome in mice.[24] Further, estradiol administration has been shown to accelerate liver regeneration in mice through ERα.[25] In a rat 70% partial hepatectomy model with 17β-estradiol injection, Batmunkh et al.[11] reported that ERα was co-expressed with the proliferating cell nuclear antigen, which is a factor in DNA synthesis, polymerase function, and has a role in cell cycle regulation and chromatic cohesion.[21] Similarly, Yokoyama et al. indicated that female hormones promote hepatocyte proliferation, whereas male hormones suppress this mechanism.[26] In spite that the extrapolation of our results are consistent with these experimental results, we cannot assume a causality between estradiol and liver regeneration in humans with our current analyses. Future studies, utilizing translational research, need to explore the presumable association of sex hormones and liver regeneration in humans. In particular, the protective effect of female sex on post-hepatectomy outcomes would be better understood if future studies assess the effect of menopause, serum estradiol levels, exogenous estrogen replacement therapies as well as birth control pills and anti-estrogen drugs.

Another potential explanation of the superior postoperative outcome after liver resection in women may be the relationship between non-alcoholic steatohepatitis (NASH) and better post-operative outcomes in HCC patients. While nonalcoholic fatty liver disease (NAFLD) in women of reproductive age is not as frequent as in men, the prevalence of NAFLD in postmenopausal women is actually greater than that in age-matched males.[27] For example, a large cohort of HCC patients with a median age of 66 years found that NAFLD/NASH was significantly more frequent in women

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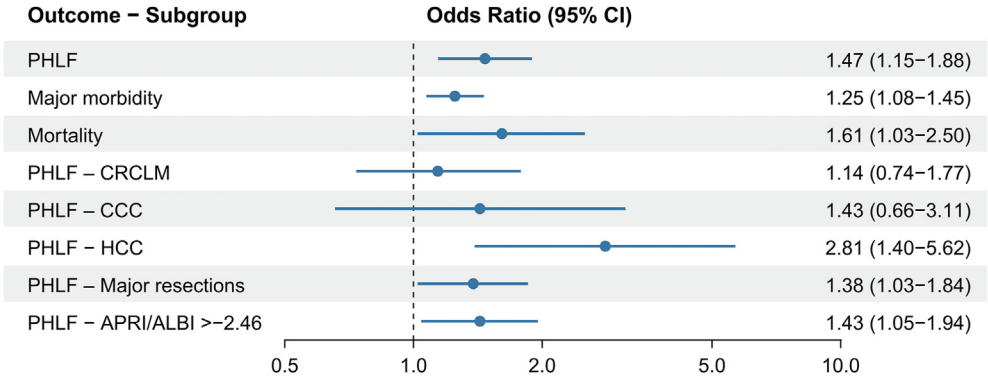


Figure 1 Forest plot of multivariable logistic regression (odds ratios and confidence interval) between male sex and outcomes sorted by groups. PHLF, post hepatectomy liver failure; CRCLM, colorectal cancer liver metastasis; CCC, cholangio-carcinoma; HCC, hepatocellular carcinoma; APRI, aspartate to platelet ratio index; ALBI, albumin-bilirubin grade; CI, confidence interval

(21.5% vs. 7.2% in men).[28] NASH is a common cause of HCC,[29] however, available evidence suggests improved oncologic outcome when compared to other types of liver disease such as alcoholic or viral cirrhosis. Further, a large cohort of HCC patients who underwent hepatic resection showed that patients with diabetes and/or NASH-related HCC had lower risk of postoperative mortality compared to viral or alcoholic hepatitis-related HCC.[30] Accordingly, the HCC predominant association with improved outcome after liver resection in women, might be influenced by an increased prevalence of NASH, which is known to be associated with an improved outcome after liver hepatic resection, as compared to other chronic liver disease types.[31]

Furthermore, recent evidence suggests further sex specific differences in pathophysiologic processes appearing after liver resection. Sex-determining region Y (SRY) mediated sex dimorphism in hepatic ischemia/reperfusion injury has recently been reported and may represent another explanation for the sex-specific differences we observed in outcomes following hepatectomy. Very recent data in mice report on a striking increase in SRY expression following partial hepatectomy, with disparate expression in males. In a subsequent mouse model, they were able to demonstrate that SRY expression directly exacerbated hepatic reperfusion/ischemia injury.[32] Additional translational research is required to further explore if this mechanism does account in part for the worse outcomes observed in men after liver resection.

As a large database study, there are inherent limitations of our analyses, which need to be taken into account when interpreting our results. The known lack of granularity in the NSQIP database limits our analyses and NSQIP data may not be representative of surgical outcomes outside of NSQIP participating sites. Furthermore, outcomes beyond 30 days are not included in the NSQIP data, which limits our results as post hepatectomy liver failure, associated morbidity and mortality are known to occur beyond 30 post-operative days. Specific to our research question, the NSQIP database does also not contain critical information on underlying liver disease such as NASH/NAFLD, fibrosis/cirrhosis or portal hypertension, which limits the power of the database for further analysis and recommendations. Additionally, specific information about the extent of liver resection and future liver remnant are not available. These aspects should certainly be considered in future studies assessing the relevance of sex on clinical outcome after hepatic resection. Accordingly, our results, while intriguing, need to be considered as hypothesis generating and need further prospective validation.

In this study of >13,000 patients, we found that male sex is an independent predictor of PHLF, major morbidity and mortality following hepatectomy. While the exact biologic mechanism for this difference has yet to be elucidated in translational research studies, our observations suggest that sex should be taken into account in patients undergoing hepatic resection, particularly when a major resection is necessary. This seems to be particularly importantly in HCC patients, as we observed the highest increase of risk for PHLF in this subgroup. Utilizing this new evidence in routine clinical decision making might ultimately result in improved patients care and outcomes after hepatic resection. However, further prospective studies and more detailed databases are needed to substantiate the relevance of female sex in patients undergoing hepatic resection.

Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.02.009.

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