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Association of Viral Hepatitis Status and Post-hepatectomy Outcomes in the Era of Direct-Acting Antivirals

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ABSTRACT

Background. The role of viral hepatitis status in post-hepatectomy outcomes has yet to be delineated. This large, multicentred contemporary study aimed to evaluate the effect of viral hepatitis status on 30-day post-hepatectomy complications in patients treated for hepatocellular carcinoma (HCC).

Methods. Patients from the National Surgical Quality Improvement Program (NSQIP) database with known viral hepatitis status, who underwent hepatectomy for HCC between 2014 and 2018, were included. Patients were classified as HBV-only, HCV-only, HBV and HCV co-infection (HBV/HCV), or no viral hepatitis (NV). Multivariable models were used to assess outcomes of interest. The primary outcome was any 30-day post-hepatectomy complication. The secondary outcomes were major complications and post-hepatectomy liver failure (PHLF). Subgroup analyses were performed for cirrhotic and non-cirrhotic patients.

Results. A total of 3234 patients were included. The 30-day complication rate was 207/663 (31.2%) HBV, 356/1077 (33.1%) HCV, 29/81 (35.8%) HBV/HCV, and 534/1413 (37.8%) NV (p = 0.01). On adjusted analysis, viral hepatitis status was not associated with occurrence of any 30-day post-hepatectomy complications (ref: NV, HBV odds ratio (OR) 0.89 [95% confidence interval (CI): 0.71–1.12]; HCV OR 0.91 [95% CI: 0.75–1.10]; HBV/HCV OR 1.17 [95% CI: 0.71–1.93]). Similar results were found in cirrhotic and noncirrhotic subgroups, and for secondary outcomes: occurrence of any major complications and PHLF.

Conclusions. In patients with HCC managed with resection, viral hepatitis status is not associated with 30-day post-hepatectomy complications, major complications, or PHLF compared with NV. This suggests that clinical decisions and prognostication of 30-day outcomes in this population likely should not be made based on viral hepatitis status.

Disclaimer: The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in this program are the sources of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are two of the most important risk factors in the development of hepatocellular carcinoma (HCC) worldwide.[1–3] Hepatectomy is an effective curative strategy for

patients with resectable HCC.[4] Improvements in patient selection, surgical techniques, and perioperative care have led to improvements in post-hepatectomy outcomes.[5,6]

Conflicting evidence exists for the effect of viral hepatitis status on post-hepatectomy outcomes for patients with HCC. Some studies have demonstrated worse post-hepatectomy outcomes in the NV group, secondary to delayed HCC diagnosis, older age, or more advanced disease at time of resection.[7,8] Additionally, studies have demonstrated differences in long-term post-hepatectomy outcomes for HCC between patients with HBV and HCV co-infection (HBV/HCV), compared with HBV-only[9], and those with HCV-only compared with HBV-only.[10,11] Furthermore, many of these existing studies included populations before 2014.[7–14] Since this time, the advent of direct-acting antivirals (DAAs) has shifted the treatment landscape, particularly for the prominent subgroup of HCV HCC patients.[15] Treatment of HCV HCC patients in the post-DAA era (after 2014) has been previously demonstrated to improve overall survival, as well as survival after liver transplantation, compared with the pre-DAA era, with these outcomes becoming more comparable to those of NV HCC and HBV HCC patients.[16,17] However, the overall role of viral hepatitis status in post-hepatectomy outcomes within the current era remains to be delineated.

This large, multicentered contemporary study aimed to evaluate the effect of viral hepatitis status on 30-day complications in patients who underwent hepatectomy for HCC. The primary objective of this study is to compare the occurrence of any 30-day post-hepatectomy complication in patients with and without underlying viral hepatitis. The secondary objectives are to compare the rates of major complications and post-hepatectomy liver failure (PHLF) between these populations. We hypothesized that viral hepatitis status would significantly impact the occurrence of 30-day post-hepatectomy complications.

METHODS

This study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies.[18]

Study Design, Data Source, and Participants

A retrospective cohort study was conducted using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database.[19] The Targeted Hepatectomy Participant Use Files representing hepatectomies performed from 2014 to 2018 were merged with the general NSQIP database based on linkages of patient identifiers. The database was then queried to identify all adult patients aged 18 years or older who underwent hepatectomy between 2014 and 2018 with histological diagnosis of HCC, based on the final surgical pathology report. Viral hepatitis status was retrieved directly from the NSQIP Target Hepatectomy database, collected by trained hospital clinical reviewers. This database captured presence of preoperative viral hepatitis (infection with hepatitis B and/or C, none, unknown, or other, which includes hepatitis A infection). This definition was based on documentation of viral hepatitis in the history or operative note, or based on laboratory values. It included infections that may have occurred many years even prior to the operation. There was no information captured on whether this represented an active viral infection, or the current serologic status.

Patients with "unknown" (n = 140, 4%) or "other" (n = 34, 1%) viral hepatitis status were excluded for nonspecific categorization. The remainder of the patients were classified based on listed coding as either HBV-only (HBV), HCV-only (HCV), HBV and HCV co-infection (HBV/HCV), or no viral hepatitis (NV), which included all other etiologies of liver disease (i.e., alcoholic, cryptogenic, nonalcoholic steatohepatitis) (Fig. 1). For subgroup analysis, patients in the database with coding "cirrhotic" liver texture were grouped as patients with cirrhosis. In contrast, those with other coding for liver texture ("normal," "fibrotic," and "fatty") were grouped as patients without cirrhosis.

Outcome

The primary outcome was defined as occurrence of any 30-day post-hepatectomy complication (binary outcome). Post-hepatectomy complications were subcategorized as minor complications, defined as outcomes meeting Clavien–Dindo (CD) classification I–II, major complications, defined as outcomes meeting CD classification III–V, or "other" for complications that did not fit into the CD classification.[20] These subcategorizations for minor and major complications were made according to previously published methodology for ACS-NSQIP.[21–23] Minor complications included the following collected binary-level complications: superficial surgical site infection (SSI), deep incisional SSI, organ space SSI, wound disruption, bleeding requiring transfusion, pneumonia, urinary tract infection (UTI), deep vein thrombosis (DVT), pulmonary embolism (PE), and bile leak (requiring no intervention).[21–24] Major complications included the following collected binary-level complications: sepsis, septic shock, bile leak (requiring intervention), stroke/cerebrovascular accident (CVA), unplanned intubation, ventilator > 48 h, acute renal failure, myocardial infarction, cardiac arrest requiring cardiopulmonary resuscitation (CPR), return to

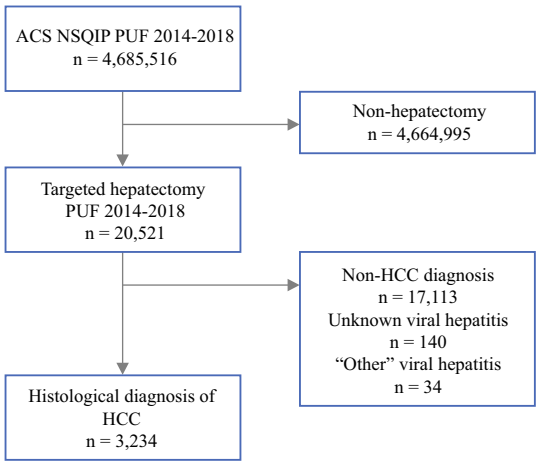

FIG. 1 Flow diagram for cohort selection from the ACS NSQIP database with Participant Use Data Files (PUF)

the operating room, PHLF, as defined by the International Study Group of Liver Surgery (ISGLS),[25] and 30-day mortality.[21–24] Other complications included hospitalization > 30 days (binary) and within 30-day readmission (binary).[24] The secondary outcomes were defined as occurrence of a major complication (binary outcome) and occurrence of PHLF (binary outcome).

Exposures and Covariates

Viral hepatitis status (HBV, HCV, HBV/HCV, or NV) was the main exposure variable. Covariates considered as potential confounders in the risk adjustments were selected based on clinical importance and literature review.[3,25–28] These included: age (continuous), sex (binary), body mass index (BMI) [kg/m^2] (continuous), American Society of Anesthesiologist (ASA) score [I–IV], presence of ascites (binary), presence of cirrhosis on pathology (binary), hepatectomy type [partial, left, right, or trisegmentectomy], operative approach [minimally invasive surgery, or open], neoadjuvant chemotherapy (binary), operation time [min] (continuous), and use of Pringle maneuver (binary).[3,25–28]

Statistical Analysis

Two sample *t*-test was used to compare differences between groups for normally distributed data. Mann–Whitney *U* test was used for non-normally distributed data. Continuous data are summarized using mean and standard deviation (SD). Count data are summarized as proportions and analyzed using chi-square or Fisher's exact test. Dunn's test with Bonferroni correction was used for non-parametric pairwise multiple comparisons. Multivariable logistic regression analyses were conducted for any 30-day post-hepatectomy complications, major complications, and PHLF. All effect estimates were reported as odds ratios (OR) with 95% confidence intervals (CI). Covariates for constructing the multivariable logistic regression models were chosen a priori based on clinical relevance to post-hepatectomy complications and relevant literature,[3,25–28] and were performed as complete-case analyses. Subgroup analysis was conducted by repeating the above analyses for cirrhotic versus noncirrhotic patients. Statistical significance was defined as a probability of less than 0.05 α, and two-sided tests were conducted. For age (continuous), those coded "90+" were reclassified as missing (n = 8, 0.2%) as they could not be measured on a continuous scale. Missing data among covariates included in the model were managed using multiple imputation (rms 2.1.1 package in R).[29] Ten multiply imputed datasets were created using predictive mean matching.[30] Effect estimates were calculated within each imputed dataset, and then combined using Rubin's rules.[31] All analyses were performed using SAS University Edition v9.4 software (SAS Institute, NC) and R version 4.0.5.[32]

RESULTS

Patient Characteristics

A total of 3234 patients who underwent hepatectomy for HCC were included in the study. We found that 663 (20.5%) had a diagnosis of HBV-only, 1077 (33.3%) HCV-only, 81 (2.5%) HBV/HCV, and 1413 (43.7%) NV. There was a statistically significant difference between groups based on age, sex, BMI, ASA score, and presence of ascites and cirrhosis (Table 1). Patients within the viral hepatitis groups (HBV, HCV, and HBV/HCV) were more likely to be younger, male, have lower BMI, and have cirrhosis compared with the NV group. There was a significant difference also in the operative approach, operation time, and tumor (T) stage of disease between the groups. Patients in the HCV-only group were more likely to undergo partial hepatectomy ($p < 0.001$) and a minimally invasive approach to surgery ($p = 0.01$), while a smaller proportion of patients had node-positive disease on pathology ($p = 0.002$), compared with the NV group. Both HCV and HCV/HBV had shorter operation time compared with NV. HBV/HCV had significantly greater proportion of patients with early T stage (T0–T2), while HBV-only and HCV-only groups had lower proportion of patients with nodal disease (N1–2 stage), compared with the NV group.

TABLE 1 Characteristics comparing patients with no viral hepatitis, with patients with hepatitis B virus, hepatitis C virus, or hepatitis B and C virus co-infection

	NV (Ref*)	HBV	*p**	HCV	*p**	HBV/HCV	*p**	Overall *p*
Patients, *n*	1413	663		1077		81		
Age, years, mean (SD)	66.5 (12.8)	60.4 (11.5)	< 0.001	64.1 (6.5)	< 0.001	63.3 (7.0)	< 0.001	< 0.001
Male, *n* (%)	907 (64.2)	532 (80.2)	< 0.001	885 (82.2)	< 0.001	68 (84.0)	< 0.001	< 0.001
BMI, kg/m^2, mean (SD)	29.8 (6.2)	25.8 (4.4)	< 0.001	28.1 (5.7)	< 0.001	26.8 (4.6)	< 0.001	< 0.001
ASA score III–IV, *n* (%)	1167 (82.6)	448 (67.8)	< 0.001	943 (87.6)	0.01	65 (80.2)	NS	< 0.001
Ascites, *n* (%)	16 (1.1)	2 (0.3)	NS	17 (1.6)	NS	3 (3.7)	NS	0.02
CHF, *n* (%)	7 (0.5)	0 (0.0)	NS	10 (0.9)	NS	1 (1.2)	NS	0.07
Cirrhosis, *n* (%)	334 (23.6)	289 (43.6)	< 0.001	604 (56.1)	< 0.001	43 (53.1)	< 0.001	< 0.001
COPD, severe, *n* (%)	94 (6.7)	11 (1.7)	< 0.001	106 (9.8)	0.01	13 (16.0)	0.01	< 0.001
Current smoker, *n* (%)	218 (15.4)	112 (16.9)	NS	443 (41.1)	< 0.001	35 (43.2)	< 0.001	< 0.001
Diabetes, *n* (%)	547 (38.7)	126 (19.0)	< 0.001	241 (22.4)	< 0.001	18 (22.2)	0.01	< 0.001
Dyspnea, *n* (%)	138 (9.8)	50 (7.5)	NS	91 (8.4)	NS	10 (12.3)	NS	0.24
Hypertension, *n* (%)	943 (66.7)	295 (44.5)	< 0.001	667 (61.9)	NS	47 (58.0)	NS	< 0.001
Preoperative transfusion, *n* (%)	8 (0.6)	3 (0.5)	NS	6 (0.6)	NS	0 (0.0)	NS	0.90
Hepatectomy type, *n* (%)			NS		< 0.001		NS	< 0.001
Partial hepatectomy	888 (62.8)	423 (63.8)		811 (75.3)		60 (74.1)		
Left hepatectomy	153 (10.8)	61 (9.2)		67 (6.2)		9 (11.1)		
Right hepatectomy	262 (18.5)	139 (21.0)		155 (14.4)		9 (11.1)		
Trisegmentectomy	110 (7.8)	40 (6.0)		44 (4.1)		3 (3.7)		
Operative approach, MIS *n* (%)	335 (23.7)	186 (28.1)	NS	319 (29.6)	0.01	23 (28.4)	NS	0.01
Neoadjuvant chemotherapy, *n* (%)	156 (11.0)	51 (7.7)	NS	106 (9.8)	NS	6 (7.4)	NS	0.46
Portal vein embolization, *n* (%)	62 (4.4)	26 (3.9)	NS	46 (4.3)	NS	4 (4.9)	NS	0.95
Operation time, min, mean (SD)	223.25 (108.82)	211.29 (97.17)	NS	210.98 (99.85)	0.04	189.91 (90.55)	0.02	0.001
Pringle maneuver, *n* (%)	363 (25.7)	182 (27.5)	NS	251 (23.3)	NS	16 (19.8)	NS	0.15
Biliary reconstruction, *n* (%)	49 (3.5)	18 (2.8)	NS	13 (1.2)	0.002	3 (3.8)	NS	0.005
Intraoperative ablation, *n* (%)	133 (9.5)	40 (6.1)	NS	128 (11.9)	NS	7 (8.8)	NS	0.001
Intraoperative drains, *n* (%)	713 (50.6)	296 (44.6)	NS	507 (47.3)	NS	34 (42.5)	NS	0.05
T stage (pathological), *n* (%)			NS		NS		0.004	0.03
T0–T2	1035 (73.2)	516 (77.8)		851 (79.0)		66 (81.5)		
T3–T4	261 (18.5)	103 (15.5)		160 (14.9)		11 (13.6)		
T*x*	117 (8.3)	44 (6.6)		66 (6.1)		4 (4.9)		
N1–2 stage (pathological), *n* (%)	32 (2.3)	4 (0.6)	0.01	6 (0.6)	0.002	2 (2.5)	NS	0.001

*p-values reported in comparison with NV group (ref)

ASA American Society of Anesthesiologist, *BMI* body mass index, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HBV/HCV* hepatitis B and C co-infection, *MIS* minimally invasive surgery, *NS* no significance, *NV* no viral hepatitis, *SD* standard deviation

Primary Outcome: 30-Day Post-hepatectomy Complications

There were statistically significant differences in overall 30-day post-hepatectomy complication across the groups: 207/663 (31.2%) HBV, 356/1077 (33.1%) HCV, 29/81 (35.8%) HBV/HCV, 534/1413 (37.8%) NV (p = 0.01). Significant difference was seen across the groups in the proportion of minor complications (p = 0.03), major complications (p = 0.04), and within 30-day readmissions (p = 0.02) (Table 2). HBV and HCV groups had fewer patients with bleeding requiring blood transfusions compared with the NV group. The HBV group had fewer major complications (p = 0.03) and fewer within 30-day readmissions (p = 0.01) compared with the NV group.

On multivariable logistic regression analysis using a priori selected variables, relative to NV, viral hepatitis status was not associated with development of any 30-day post-hepatectomy complication in patients undergoing hepatectomy for HCC (ref: NV, HBV OR 0.89 [95% CI 0.71–1.12], p = 0.31; HCV OR 0.91 [95% CI 0.75–1.10], p = 0.32; HBV/HCV OR 1.17 [95% CI 0.71–1.93], p = 0.54) (Fig. 2). This association was not affected by the presence of cirrhosis (1270 cirrhotic patients: ref: NV, HBV OR 0.84 [95% CI 0.57–1.25], p = 0.40; HCV OR 0.80 [95% CI 0.59–1.08], p = 0.15; HBV/HCV OR 0.87 [95% CI 0.42–1.81], p = 0.71; 1964 noncirrhotic patients: ref: NV, HBV OR 0.88 [95% CI 0.66–1.18], p = 0.39; HCV OR 0.99 [95% CI 0.77–1.28], p = 0.96; HBV/HCV OR 1.45 [95% CI 0.72–2.94], p = 0.30).

Secondary Outcomes

Thirty-Day Major Complications There were statistically significant differences in the occurrence of any major complication (CD III–V) within the first 30 days post hepatectomy across the groups: 77/663 (11.6%) HBV, 159/1077 (14.8%) HCV, 14/81 (17.3%) HBV/HCV, 231/1413 (16.3%) NV (p = 0.040) (Table 2). There were no significant differences in 30-day post-hepatectomy mortality between the groups (p = 0.33). On multivariable logistic regression analysis, relative to NV, viral hepatitis status was associated with similar odds of 30-day major complications (n = 3234, 487 events), ref: NV, HBV OR 0.76 [0.56–1.04], p = 0.09; HCV 0.95 [0.74–1.21], p = 0.66; HBV/HCV 1.28 [0.68–2.40], p = 0.45) (Table 3).

Thirty-Day Post-hepatectomy Liver Failure There were no statistically significant differences between the groups with regards to rate of PHLF (p = 0.85) (Table 2). On multivariable logistic regression analysis, relative to NV, viral hepatitis status was associated with similar odds of PHLF (n = 3234, 219 events), ref: NV, HBV OR 0.86 [0.56–1.32], p = 0.48; HCV 0.97 [0.68–1.39], p = 0.86; HBV/HCV 0.96 [0.36–2.55], p = 0.93) (Table 3).

DISCUSSION

In this study, we found that viral hepatitis status was not associated with increased odds of occurrence of any 30-day post-hepatectomy complication, major complication, or PHLF, relative to NV. A greater proportion of patients with viral hepatitis had cirrhosis, compared with those without viral hepatitis. However, viral hepatitis status in the presence or absence of cirrhosis was not associated with worse 30-day post-hepatectomy outcomes. This suggests that viral hepatitis status likely should not contribute to clinical decision-making and prognostication of outcomes for patients undergoing hepatectomy for HCC. To our knowledge, this is the first multicenter national registry study with the inclusion of patients undergoing hepatectomy for HCC to assess the effect of viral hepatitis status on 30-day post-hepatectomy complications.

One single-center retrospective study by Kabir et al. highlighted HBV as a factor predictive of developing 30-day post-hepatectomy complications (Clavien–Dindo classification II–V) in patients who underwent hepatectomy for HCC from 2001 to 2016 (p = 0.04).[12] Another single-center study showed similar rates of post-hepatectomy complications between those with and without HBV in patients who underwent hepatectomy for HCC between 2008 and 2012.[14] Despite this, the HBV population had higher rates of post-hepatectomy infection and PHLF within the first 2 years.[14] However, these studies are limited by small sample size and single-center data.[12,14]

Furthermore, many existing studies investigating the effect of viral hepatitis status on post-hepatectomy outcomes do not include all prevalent viral hepatitis groups (HBV, HCV, HBV/HCV, NV).[9,14,33] Since the introduction of DAAs in 2014, some studies have shown significant reduction in risk of death and improved survival and post-transplant outcomes, specifically for patients with HCV-related HCC, compared with patients from the pre-DAA era (before 2014).[16,17,34] Additionally, in the pre-DAA era, survival outcomes were significantly worse in the HCV HCC population compared with HBV or NV, but these outcomes have been shown to be comparable in the post-DAA era.[16,17] Our large, multi-institutional population study compared these prevalent viral groups in the current, post-DAA era and did not demonstrate an association between viral hepatitis status and occurrence of any 30-day post-hepatectomy complication.

TABLE 2 Thirty-day post-hepatectomy complications comparing patients with no viral hepatitis, against patient groups with hepatitis B virus, hepatitis C virus, or hepatitis B and C virus co-infection

	NV (Ref*) (n = 1413)	HBV (n = 663)	p*	HCV (n = 1077)	p*	HBV/HCV (n = 81)	p*	Overall p
Minor complication (CD I–II)	428 (30.3)	169 (25.5)	NS	275 (25.5)	NS	24 (29.6)	NS	0.03
Superficial SSI, n (%)	38 (2.7)	19 (2.9)	NS	42 (3.9)	NS	3 (3.7)	NS	0.36
Deep incisional SSI, n (%)	8 (0.6)	1 (0.2)	NS	6 (0.6)	NS	1 (1.2)	NS	0.44
Organ space SSI, n (%)	92 (6.5)	37 (5.6)	NS	50 (4.6)	NS	1 (1.2)	NS	0.07
Wound disruption, n (%)	9 (0.6)	1 (0.2)	NS	7 (0.6)	0.40	1 (1.2)	NS	0.40
Bleeding requiring transfusion, n (%)	290 (20.5)	102 (15.4)	0.02	154 (14.3)	< 0.001	14 (17.3)	NS	< 0.001
Pneumonia, n (%)	54 (3.8)	37 (5.6)	NS	63 (5.8)	NS	6 (7.4)	NS	0.06
Urinary tract infection, n (%)	31 (2.2)	10 (1.5)	NS	18 (1.7)	NS	0 (0.0)	NS	0.38
DVT, n (%)	28 (2.0)	8 (1.2)	NS	22 (2.0)	NS	2 (2.5)	NS	0.57
Pulmonary embolism, n (%)	14 (1.0)	12 (1.8)	NS	10 (0.9)	NS	1 (1.2)	NS	0.34
Bile leak, no intervention	24 (1.7)	1 (0.2)	0.003	4 (0.4)	0.003	0 (0.0)	NS	<0.001
Major complication (CD III–V)	231 (16.3)	77 (11.6)	0.03	159 (14.8)	NS	14 (17.3)	NS	0.04
Sepsis, n (%)	44 (3.1)	16 (2.4)	NS	28 (2.6)	NS	1 (1.2)	NS	0.62
Septic shock, n (%)	27 (1.9)	14 (2.1)	NS	23 (2.1)	NS	0 (0.0)	NS	0.60
Bile leak requiring intervention	44 (3.2)	9 (1.4)	NS	21 (2.0)	NS	0 (0.0)	NS	0.03
Stroke/CVA	5 (0.4)	1 (0.2)	NS	2 (0.2)	NS	0 (0.0)	NS	0.74
Unplanned intubation	55 (3.9)	16 (2.4)	NS	36 (3.3)	NS	4 (4.9)	NS	0.31
Ventilator > 48 h, n (%)	45 (3.2)	16 (2.4)	NS	34 (3.2)	NS	2 (2.5)	NS	0.77
Acute renal failure, n (%)	22 (1.6)	7 (1.1)	NS	21 (1.9)	NS	2 (2.5)	NS	0.48
Myocardial infarction, n (%)	31 (2.2)	8 (1.2)	NS	9 (0.8)	0.04	2 (2.5)	NS	0.04
Cardiac arrest requiring CPR, n (%)	20 (1.4)	5 (0.8)	NS	13 (1.2)	NS	1 (1.2)	NS	0.65
Return to OR, n (%)	35 (2.5)	11 (1.7)	NS	39 (3.6)	NS	5 (6.2)	NS	0.02
Post-hepatectomy liver failure, n (%)	99 (7.0)	40 (6.0)	NS	75 (7.0)	NS	5 (6.2)	NS	0.85
30-day mortality, n (%)	44 (3.1)	12 (1.8)	NS	27 (2.5)	NS	3 (3.7)	NS	0.33
Other			NS		NS		NS	
Hospitalization > 30 days, n (%)	16 (1.1)	5 (0.8)	NS	11 (1.0)	NS	0 (0.0)	NS	0.69
Within 30-day readmission, n (%)	152 (10.8)	43 (6.5)	0.01	99 (9.2)	NS	9 (11.1)	NS	0.02

*p-values reported in comparison with NV group (ref)

CD Clavien–Dindo, *CPR* cardiopulmonary resuscitation, *CVA* cerebrovascular accident, *DVT* deep vein thrombosis, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HBV/HCV* hepatitis B and C co-infection, *MIS* minimally invasive surgery, *NS* no significance, *SD* standard deviation, *SSI* surgical site infection

Our study showed that the HBV, HCV, and HBV/HCV patient groups had a higher proportion of cirrhosis compared with the NV group. This is in keeping with findings from other studies showing a greater prevalence of cirrhosis in patients with HCC and viral hepatitis.[7,35–37] Studies have also highlighted cirrhosis as a risk factor for post-hepatectomy complications.[38,39] One study by Zhang et al. showed a significant association between moderate to severe cirrhosis (Laennec score F4B/ F4C) and post-hepatectomy complications in patients with HBV-related HCC who underwent hepatectomy between 2011 and 2013.[38] Similarly, another study of HCV-related HCC showed worse long-term OS and disease-free survival post-hepatectomy in the patients with cirrhosis compared with those without, although this association was not observed on multivariable analysis.[40]

In our study, multivariable model analyses of the subgroups of patients with and without cirrhosis did not show a significant association between viral hepatitis status and the occurrence of any 30-day post-hepatectomy complication. One single-center study by Hsu et al. assessed the long-term OS post-hepatectomy for patients with HCC between 2008 and 2018 and compared HBV, HCV, HBV/HCV, and no viral or alcoholic hepatitis (NBNC) groups.[35] After further stratification based on presence of cirrhosis, this study showed that, in patients with cirrhosis, the NBNC group had worse OS than each of the viral hepatitis

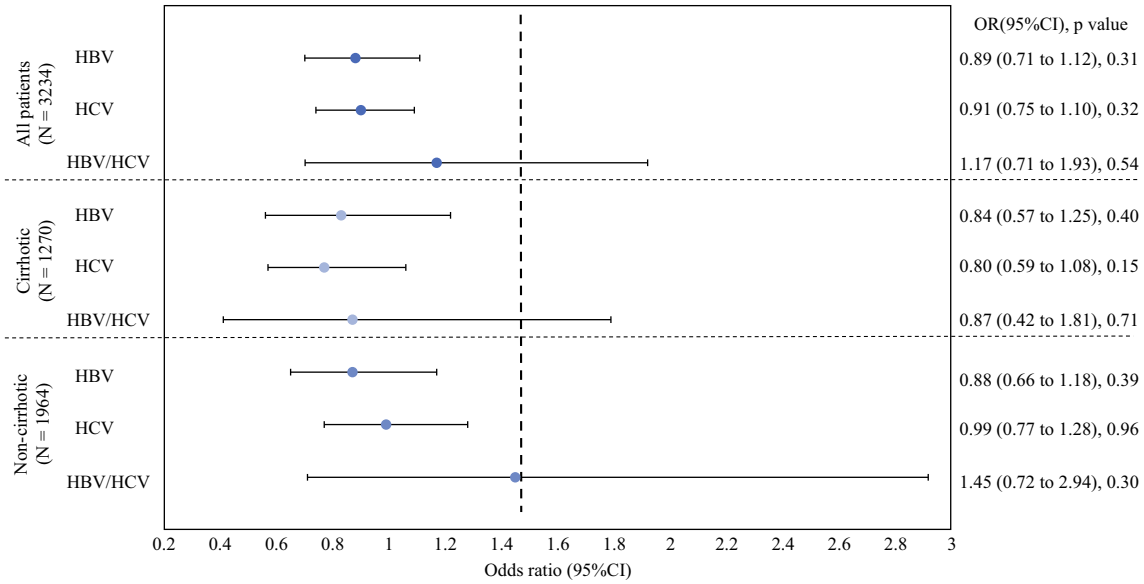

FIG. 2 Forest plot of multivariable logistic regression models using a priori selected variables, for occurrence of any 30-day complication (Clavien–Dindo classification I–V), in all patients, cirrhotic patients only, and noncirrhotic patients only (ref: NV). *Adjusted for age, sex, BMI, ASA score, presence of ascites, presence of cirrhosis, hepatectomy type, operative approach, operation time, use of Pringle maneuver. *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HBV/HCV* hepatitis B and C co-infection, *NV* no viral hepatitis, *OR* odds ratio

TABLE 3 Multivariable logistic regression and a priori selected variables, for occurrence of 30-day major complication (CD III–V) and 30-day post-hepatectomy liver failure (PHLF) in all patients (N=3234)

Characteristic	Major complication (CD III–V) (487 events)		PHLF (219 events)	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Viral hepatitis status				
NV (ref)	–		–	
HBV	0.76 (0.56–1.04)	0.09	0.86 (0.56–1.32)	0.48
HCV	0.95 (0.74–1.21)	0.66	0.97 (0.68–1.39)	0.86
HBV/HCV	1.28 (0.68–2.40)	0.45	0.96 (0.36–2.55)	0.93

*Adjusted for age, sex, BMI, ASA score, presence of ascites, presence of cirrhosis, hepatectomy type, operative approach, operation time, use of Pringle maneuver

groups (HBV $p = 0.001$, HCV $p < 0.001$, HBV/HCV $p = 0.008$).[35] This study also showed that patients in the NBNC group were older, with higher prevalence of metabolic comorbidities, and more advanced stage of cancer at time of diagnosis or treatment.[35] Though our data were limited to 30-day post-hepatectomy outcomes, we did not show significantly worse complications in the NV group, compared with the other viral hepatitis groups. However, the HBV group had significantly lower rates of major complications and within 30-day readmissions compared with the NV group. Additionally, we similarly showed that patients in the viral hepatitis groups were older, with greater medical comorbidities, compared with the NV group. Furthermore, the HBV-only and HCV-only groups were less likely to have advanced nodal (N1–2) disease, compared with NV.

Regarding the analysis of our secondary outcomes, our study did not demonstrate an association between viral hepatitis status and occurrence of any 30-day major complication or PHLF. In contrast, Dhir et al. utilized the 2014–2016 NSQIP hepatectomy database and showed that, on multivariable regression analysis, preoperative diagnosis of HBV and HCV was "predictive" of grade B/C PHLF.[27] However, their study included all patients who underwent hepatectomy and excluded grade A PHLF.[27] Our study was specific to the HCC population within the 2014–2018 NSQIP hepatectomy database. Additionally, we included all grades of PHLF, based on the rationale that all grades of PHLF, including grade A, have been shown to be associated with worse post-hepatectomy outcomes in patients undergoing curative resection for HCC.[41,42]

There are several limitations to this study. This is a retrospective study using a prospectively maintained registry that may not have accounted for all unmeasured and residual confounders. Selection bias may exist as the database only captures those who underwent resection and is missing the denominator of those who are potential resection candidates in the context of viral hepatitis. Furthermore, key oncologic metrics such as tumor size and tumor multifocality are missing, making it difficult to strongly determine how much of a selection bias may be present in our analysis from possible earlier cancer detection or lower tumor burden in the hepatitis group.

The NSQIP database does not provide data beyond the 30-day post-hepatectomy complications, which limits ability to analyze disease recurrence and other long-term outcomes. Procedure-specific complications are not measured in time, but rather as a binary outcome (whether an event occurred). Furthermore, the analysis is limited by the available variables of the dataset and the coding used by the NSQIP library. For instance, the complication "organ space infection" was captured on the basis of occurrence of the event, but the database does not provide details on whether any of these occurrences required intervention or not. This might affect the distribution of minor versus major complication rates, as organ space infection requiring a drain should be classified as a major complication. However, when we perform a sensitivity analysis after reclassifying organ space infections as a major complication, there are no changes in the results. It was unclear whether those coded within the HBV group also included a population with hepatitis D virus co-infection or other co-infections.

There was no clear definition of what constituted partial hepatectomy, and this was presumed to involve a resection less than a formal left or right hepatectomy.[43] Additionally, the definition of cirrhosis was based on the NSQIP coding of "cirrhotic" liver texture, which is vague. It likely does not capture varying degrees of cirrhosis, particularly given the high proportion of patients in our study with viral hepatitis who are classified in the noncirrhotic population. However, the strength of our study lies in its multi-institutional nature and inclusion of a large population of patients with and without viral hepatitis (n = 3234). We characterized most of the 30-day post-hepatectomy complications in patients with HCC and compared them across the prevalent viral hepatitis groups. Additionally, this was a contemporary study, with a population who underwent liver resection for HCC between 2014 and 2018, since the advent of DAAs for the eradication of HCV-related HCC in 2014. Understanding the influence of factors such as viral hepatitis status in the development of 30-day post-hepatectomy complications in the current era may help to anticipate the overall short- and long-term outcomes post-hepatectomy for HCC.[12]

CONCLUSIONS

In patients with HCC managed with surgical resection, viral hepatitis status is not associated with 30-day post-hepatectomy complications, major complications, or PHLF relative to patients without viral hepatitis. This finding was consistent irrespective of cirrhosis status. This suggests that viral hepatitis status likely should not contribute to clinical decision-making and prognostication of outcomes for patients undergoing hepatectomy for HCC. However, clear conclusions on long-term post-hepatectomy oncologic outcomes cannot be drawn due to limitations of the NSQIP database.

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