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ORIGINAL ARTICLE

Clinical Factors and Postoperative Impact of Bile Leak After Liver Resection

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Abstract

Background Despite technical advances, bile leak remains a significant complication after hepatectomy. The current study uses a targeted multi-institutional dataset to characterize perioperative factors that are associated with bile leakage after hepatectomy to better understand the impact of bile leak on morbidity and mortality.

Methods Adult patients in the 2014–2015 ACS NSQIP targeted hepatectomy dataset were linked to the ACS NSQIP PUF dataset. Bivariable and multivariable regression analyses were used to assess the associations between clinical factors and post-hepatectomy bile leak.

Results Of 6859 patients, 530 (7.7%) had a postoperative bile leak. Proportion of bile leaks was significantly greater in patients after major compared to minor hepatectomy (12.6 vs. 5.1%, $p < 0.001$). The proportion of patients with bile leak was significantly greater in patients after major hepatectomy who had concomitant enterohepatic reconstruction (31.8 vs. 10.1%, $p < 0.001$). Postoperative mortality was significantly greater in patients with bile leaks (6.0 vs. 1.7%, $p < 0.001$). After adjusting for significant covariates, bile leak was independently associated with increased risk of postoperative morbidity (OR = 4.55; 95% CI 3.72–5.56; $p < 0.001$). After adjusting for significant effects of postoperative complications, liver failure, and reoperation (all $p<0.001$), bile leak was not independently associated with increased risk of postoperative mortality ($p = 0.262$).

Conclusion Major hepatectomy and enterohepatic biliary reconstruction are associated with significantly greater rates of bile leak after liver resection. Bile leak is independently associated with significant postoperative morbidity. Mitigation of bile leak is critical in reducing morbidity and mortality after liver resection.

Keywords Bile leak · Hepatectomy · Liver resection · Major hepatectomy · Biliary complication · Drain · Morbidity and mortality

Introduction

Despite significant improvements in perioperative mortality, morbidity after liver resection remains > 20%[1–4].Among complications, bile leakage remains a technical challenge which has the potential to be improved with surgical technique. Single-institution studies suggest various bile leak mitigation strategies with reported bile leak rates as low as 1%[5]. Recent multi-institutional American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) collaborative studies reported bile leak rates approximating 7%[6, 7];however, factors associated with a considerably higher proportion of bile leaks are largely unexplored.

Extent of resection, operative approach, parenchymal transection strategies, post-resection cholangiograms, and use of postoperative drains have all been suggested as factors associated with higher or lower risk of bile leak[8–10]. Associations between bile leak and other clinical factors, such as reoperative surgery, long operating time, and bleeding requiring blood transfusion, have also been described[11–13]. While the impact of this complication at centers with very low rates of

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bile leak is difficult to define, bile leak remains a morbid complication across the majority of hepatobiliary centers.

ACS NSQIP has been recently expanded to include procedure-specific targeted modules for clinically relevant data collection. The current hepatectomy module includes procedure-specific definitions of complications including bile leak, use of drains, and liver failure among others. We aimed to evaluate the impact of clinically relevant factors on post-hepatectomy bile leak and to estimate the associations between post-hepatectomy bile leak and morbidity and mortality.

Methods

Variable Selection and Outcome Definitions

ACS NSQIP is a Health Insurance Portability and Accountability Act (HIPAA) compliant dataset that includes patient-level, aggregated data from participating hospitals nationwide. It is considered a public data set and has been designated exempt by the University of Virginia Institutional Review Board (UVA IRB) for Health Sciences Research (HSR). The targeted hepatectomy module became available starting in 2014. All adult patients ≥ 18 years of age in the 2014 and 2015 ACS NSQIP hepatectomy targeted datasets were linked to the 2014 and 2015 ACS NSQIP Public Use File (PUF) datasets for this retrospective cohort study.

Demographic and clinical variables were abstracted from the linked ACS NSQIP PUF and targeted hepatectomy datasets. Demographic variables included age, sex, race, ethnicity, body mass index (BMI), diabetes, and tobacco and/or alcohol use. Clinical variables included presence of bile leak, operative diagnosis (categorized as benign or malignant), extent of resection, operative approach (minimally invasive or open), length of stay, concomitant bile duct resection and enterohepatic reconstruction, and occurrence of postoperative morbidity and mortality. Extent of resection was categorized based on procedure type according to the index operation using current procedural terminology (CPT) codes: minor hepatectomy (47120) and major hepatectomy (47,122, 47,125, and 47,130). Final pathology report summarized in the ACS NSQIP using the International Classification of Diseases, 9th revision (ICD-9) codes was used to categorize each case as benign or malignant. Malignant tumors include both primary hepatobiliary cancers and secondary, or metastatic, tumors. Benign tumors include hepatic adenomas, abscesses, focal nodular hyperplasia, hemangioma, and other benign indications for liver resection. Fifty-nine patients had missing bile leak variable in the linked data set and were excluded from the study. In addition, seven patients with an unknown or missing final pathologic diagnosis and/or those with an ICD-9 code indicating "neoplasm of uncertain behavior" were also excluded from the analysis.

The primary outcome was postoperative bile leak, defined according to the International Study Group of Liver Surgery (ISGLS) definitions[14],which are used by the ACS NSQIP targeted module. In summary, bile leaks are defined clinically as drain bile levels three times the upper limit of the normal serum total bilirubin level or as persistent drainage requiring continuation of an intraoperatively placed drain after postoperative day three or placement of a new drain. Grade A leaks do not require additional intervention. Grade B leaks require therapeutic intervention such as endobiliary decompression and/or percutaneous drainage. Grade C leaks require management with reoperation and include life-threatening biliary peritonitis or multi-organ failure[14] .Secondary outcomes included mortality, readmission, and reoperation and were defined using standard NSQIP definitions of 30-day occurrences. Liver failure (defined using ISGLS definition), presence of preoperative biliary stent, and presence of surgical drain were included from targeted module data abstraction. Composite all-cause 30-day morbidity was defined as the occurrence of one or more of the following NSQIP-defined complications: pneumonia, reintubation, failure to wean off the ventilator, renal insufficiency, renal failure, cardiac arrest, myocardial infarction, stroke, sepsis, septic shock, fascial dehiscence, organ space infection, or venous thromboembolism (deep vein thrombosis and/or pulmonary embolism).

Data Analysis

Categorical variables were compared using chi-square or Fisher's exact test, as appropriate. Continuous variables are reported as medians with interquartile range and were compared using Wilcoxon rank sum test. Bivariable comparisons were performed to assess the associations between clinical factors and occurrence of post-hepatectomy bile leak in the entire cohort and among patients who had major hepatectomy. Two separate multivariable models were developed to estimate the independent effect of bile leak on morbidity and mortality after liver resection. Clinical variables included in the bivariable logistic regression for both morbidity and mortality model were selected a priori; variables with significant effects ($p < 0.10$) were included in the multivariable analyses. The threshold for statistical significance was set at an alpha level of 0.05. The Stata version 14.2 (StataCorp LP, College Station, TX) software was used for data management and statistical analysis.

Results

Patient Demographics

A total of 6859 patients, median age 60 (interquartile range [IQR] 50–68), were included in the study. More patients were female ($n = 3546$, 51.7%), most were White ($n = 4426$, 64.5%), and median BMI was 27.3 (IQR 23.9–31.4). The majority of patients had minor hepatectomy (4430, 64.6%) for a malignant indication ($n = 5226$, 76.2%) and had an American Society of Anesthesiologists (ASA) class of 3 ($n = 4484$, 65.4%). Most patients were non-smokers ($n = 5833$, 85.0%) and non-diabetic ($n = 5743$, 83.7%).

Postoperative Bile Leak

Of 6859 patients, 530 (7.7%) patients had a postoperative bile leak. Demographic and clinical covariates stratified by presence of bile leak are summarized in Table 1. Grade A leaks were the most common ($n = 278$, 52.5%), followed by grade B ($n = 204$, 38.5%) and grade C leaks ($n = 48$, 9.1%). Demographic covariates did not differ between the two groups. There was no difference in rates of severe, grade C, bile leaks between patients who had major versus minor hepatectomy (9.8 vs. 8.0%, $p = 0.359$). Major hepatectomy, malignant indication for resection, neoadjuvant therapy, longer operative time, concomitant enterohepatic reconstruction, preoperative biliary stent, and presence of surgical drain were all associated with postoperative bile leak (all $p \leq 0.006$). Within the entire study cohort, patients who had minimally invasive resection were less likely to have a bile leak compared to patients who had open resection (3.9 vs. 8.9%, $p < 0.001$). All measured postoperative complications including liver failure (20.2 vs. 4.1%), reoperation (12.1 vs. 2.2%), readmission (35.7 vs. 8.5%), sepsis or septic shock (28.3 vs. 4.8%), and death (6.0 vs. 1.7%) were associated with postoperative bile leak (all $p < 0.001$, Table 1).

The proportion of bile leaks was significantly higher in patients after major hepatectomy compared to minor hepatectomy (12.6 vs. 5.1%, $p < 0.001$). Factors associated with bile leaks after major hepatectomy are summarized in Table 2. Among patients who had major hepatectomy ($n = 2429$), malignant diagnosis, concomitant enterohepatic reconstruction, and presence of surgical drain were associated with diagnosis of bile leak (all $p \leq 0.007$). Excluding patients with Grade A leaks, presence of surgical drain was associated with both Grade B and Grade C bile leaks (both $p < 0.001$). There was no difference in Grade B or Grade C bile leaks in patients who had or did not have a surgical drain stratified by extent of hepatectomy (both $p \geq 0.092$).

Proportion of bile leak after enterohepatic reconstruction varied from 29.1% in the entire cohort to 31.8% among patients who had concomitant major hepatectomy. Proportions of bile leak in patients who had minimally invasive and open major hepatectomy were similar (9.2 vs. 12.7%, $p = 0.081$). Excluding patients who had enterohepatic reconstruction, proportions of bile leak after minimally invasive and open hepatectomy were also not significantly different (6.9 vs. 9.9%, $p < 0.117$). Preoperative biliary stenting was highly correlated with enterohepatic reconstruction. Among 34% of patients who had preoperative biliary stent, but did not have enterohepatic reconstruction, presence of preoperative biliary stent was associated with postoperative bile leak (16.5 vs. 5.9%, $p < 0.001$). Similar to the entire cohort, patients with a bile leak after major hepatectomy were significantly more likely to have other postoperative complications, including reoperation, readmission, septic shock or sepsis, and death (all $p < 0.001$).

Multivariable Analysis

Two separate logistic regression models tested the effects of clinically relevant covariates on morbidity and mortality after liver resection. Bile leak, perioperative blood transfusion, longer operative time, major hepatectomy and enterohepatic reconstruction were all significantly associated with morbidity after hepatectomy (all $p < 0.001$), Table 3. Bile leak remained a statistically significant factor (OR = 4.55; 95% CI 3.72–5.56; $p < 0.001$) associated with post-hepatectomy morbidity after adjusting for covariates, model C-statistic 0.73. Bile leak, liver failure, reoperation, and composite NSQIP complications were associated with mortality after hepatectomy (all $p < 0.001$), Table 4. After adjusting for independent effects of liver failure, reoperation, and composite NSQIP complications (all $p < 0.001$), bile leak was not an independent factor associated with post-hepatectomy mortality (OR = 0.77; 95% CI 0.48–1.22; $p = 0.262$), model C-statistic 0.90.

Discussion

In this multi-institutional, independent data collection analysis of patients who had liver resection in 2014 and 2015, nearly 8% of patients developed bile leak after hepatectomy. Proportion of bile leak after major hepatectomy is greater than 12%, which is significantly higher than the proportion of bile leak after minor liver resection; the proportion of bile leaks after hepatectomy with bile duct reconstruction exceeds 29%. These statistics are important. Bile leak is associated with every clinically important complication after liver resection including sepsis, organ space infection, prolonged length of hospitalization, readmission, reoperation, liver failure, and composite NSQIP-defined complication.

Previously established clinically important factors such as concomitant bile duct reconstruction, blood transfusion, and extent of resection were associated with postoperative

Table 1 Characteristics among patients with and without bile leak ($n = 6859$)

	Bile leak ($n = 530$)	No leak ($n = 6329$)	p value
Age, median (IQR)	60 (50–69)	60 (50–68)	0.285
Female sex, n (%)	260 (49.1)	3286 (51.9)	0.205
BMI, median (IQR)	27.6 (23.7–31.1)	27.3 (23.9–31.5)	0.800
Race/ethnicity, n (%)			0.907
White	350 (77.3)	4076 (76.9)	
Black	43 (9.5)	489 (9.2)	
Asian	29 (6.4)	323 (6.1)	
Hispanic	31 (6.8)	411 (7.8)	
Diabetes, n (%)	82 (15.5)	1034 (16.3)	0.604
Smoking, n (%)	68 (12.8)	958 (15.1)	0.153
Preoperative biliary stent, n (%)	99 (18.7%)	255 (4.1%)	< 0.001
Major hepatectomy, n (%)	305 (57.6)	2124 (33.6)	< 0.001
Surgical approach, n (%)			< 0.001
Open	464 (87.6)	4725 (74.7)	
Minimally invasive	65 (12.3)	1595 (25.2)	
Perioperative transfusion, n (%)	193 (36.4)	1051 (16.6)	< 0.001
Malignant diagnosis, n (%)	434 (81.9)	4792 (75.7)	0.002
Neoadjuvant chemotherapy, n (%)	190 (36.1)	1907 (30.3)	0.006
Operative time ≥ 225 min (median time), n (%)	387 (73.0)	3056 (48.3)	< 0.001
Enterohepatic reconstruction, n (%)	134 (25.6)	326 (5.2)	< 0.001
Surgical drain, n (%)	443 (84.1)	2593 (41.1)	< 0.001
Any complication, n (%)	305 (57.6)	1051 (16.6)	< 0.001
Post-hepatectomy liver failure, n (%)	107 (20.2)	257 (4.1)	< 0.001
Reoperation, n (%)	64 (12.1)	142 (2.2)	< 0.001
Readmission, n (%)	189 (35.7)	534 (8.5)	< 0.001
Death, n (%)	32 (6.0)	106 (1.7)	< 0.001
Length of stay, median (IQR)	9 (6–15)	5 (4–7)	< 0.001
Sepsis or septic shock, n (%)	150 (28.3)	304 (4.8)	< 0.001
Deep/organ space SSI, n (%)	202 (38.1)	303 (4.8)	< 0.001

IQR interquartile range, *BMI* body mass index, *HCT* hematocrit

morbidity in the present study. Importantly, bile leak was an independent variable significantly associated with postoperative morbidity after adjusting for other covariates. However, after adjusting for clinically relevant effects of liver

Table 2 Bile leaks among patients after major hepatectomy ($n = 2429$)

	Bile leak ($n = 305$)	No leak ($n = 2124$)	p value
Surgical approach, n (%)			0.081
Open	277 (90.8)	1852 (87.3)	
Minimally invasive	28 (9.2)	269 (12.7)	
Diagnosis, n (%)			0.007
Benign	42 (13.8)	430 (20.3)	
Malignant	263 (86.2)	1692 (79.7)	
Enterohepatic reconstruction, n (%)	104 (34.1)	223 (10.5)	< 0.001
Surgical drain, n (%)	258 (84.6)	1084 (51.2)	< 0.001
Neoadjuvant chemotherapy, n (%)	120 (39.3)	794 (37.6)	0.504
Operative time ≥ 225 min (median time), n (%)	256 (83.9)	1476 (69.5)	< 0.001
Perioperative transfusion, n (%)	125 (41.0)	545 (25.7)	< 0.001

Table 3 Logistic regression model for perioperative morbidity after hepatectomy

Variable	Odds ratio	95% CI min	95% CI max	*p* value
Univariate				
Bile leak	6.81	5.66	8.19	< 0.001
Perioperative transfusion	3.51	3.07	4.02	< 0.001
Operative time	1.005	1.004	1.005	< 0.001
Major hepatectomy	2.07	1.84	2.34	< 0.001
Enterohepatic reconstruction	6.35	5.22	7.72	< 0.001
Multivariable				
Bile leak	4.55	3.72	5.56	< 0.001
Perioperative transfusion	2.29	1.96	2.67	< 0.001
Operative time	1.002	1.0017	1.0029	< 0.001
Major hepatectomy	1.19	1.03	1.37	0.015
Enterohepatic reconstruction	2.81	2.23	3.53	< 0.001

C-statistic for model is 0.73

failure, reoperation, and composite NSQIP complications, bile leak did not have an independent association with post-hepatectomy mortality.

Higher morbidity and mortality of concomitant major hepatectomy with bile duct resection and reconstruction has been described previously. Patients resected for perihilar cholangiocarcinoma are in a particularly high-risk group with risk of perioperative mortality exceeding 8–10% at experienced centers[15, 16].A single-institution study evaluating effects of clinical covariates on bile leak identified both extent of liver resection and bile duct resection and reconstruction as independent covariates associated with bile leak after hepatectomy[11]. Additive negative effects of major hepatectomy and malignant diagnosis have also been described. A recent ACS NSQIP study using data collected prior to the targeted hepatectomy dataset demonstrated the highest morbidity and mortality among patients who had major hepatectomy for primary liver malignancy including hepatocellular carcinoma and intrahepatic cholangiocarcinoma[17].

Table 4 Logistic regression model for mortality after hepatectomy

Variable	Odds ratio	95% CI min	95% CI max	*p* value
Univariate				
Bile leak	3.77	2.51	5.66	< 0.001
Any complication	29.6	18.0	48.7	< 0.001
Liver failure	22.5	15.8	32.0	< 0.001
Reoperation	17.5	11.8	25.9	< 0.001
Multivariable				
Bile leak	0.77	0.48	1.22	0.262
Any complication	15.2	8.92	25.8	< 0.001
Liver failure	7.05	4.75	10.5	< 0.001
Reoperation	3.59	2.28	5.63	< 0.001

C-statistic for model is 0.90

When evaluating all patients reported in the combined targeted hepatectomy ACS NSQIP PUF dataset, the proportion of bile leaks after minimally invasive liver resection was significantly less than after open resection. However, among patients who underwent major hepatectomy, the proportion of bile leaks between operative approaches did not differ. The proportion of bile leaks after minimally invasive liver resection in this study, nearly 4% in the entire cohort and over 9% after major hepatectomy, is significantly greater than the 1.5% bile leak occurrence reported in a review of nearly 3000 aggregated cases from composite aggregate of the published literature[18].

The relationship between surgical drains and bile leaks is important to discuss. In this study, as in most retrospective analyses, presence of a surgical drain was associated with presence of a leak. The association between operative site drainage and bile leak was recently explored using the ACS NSQIP targeted hepatectomy dataset[6].Using propensity-matched analysis, this study demonstrated similar proportions of major bile leaks that required intervention between patients with and without an operatively placed drain. In contrast, patients with drains had significantly higher likelihood of minor bile leaks that did not require intervention compared to patients without a drain. Despite already having a drain, patients with surgical drains underwent more postoperative interventions compared to patients without an operatively placed drain. However, cautious interpretation of these data is required. While a number of retrospective analyses suggested lack of benefit to drains after pancreaticoduodenectomy[19, 20], a recent multi-institutional randomized controlled trial was stopped prior to study completion by the Data Safety Monitoring Board as a result of increase in mortality from 3% in patients with a drain to 12% in patients without operative site drainage[21].While limited use of drains after liver resection should be considered, further prospective data might help understand and mitigate risk in patients after high-risk operations (such as extended resections and enterohepatic reconstruction). Patients with bile leaks after major hepatectomy and enterohepatic reconstruction are at highest risk for postoperative complications including infections, bleeding, and reoperation[22, 23].

Multiple studies have examined strategies for diagnosis and mitigation of risk of bile leak after hepatectomy[5,10,24–27]. Proposed options for decreasing bile leaks have included operative site drainage, nasobiliary drainage, sealants, and completion cholangiograms. Routine use of both air and contrast cholangiograms have been associated with reduced risk of postoperative bile leaks in multiple studies[5, 27, 28]. Air cholangiograms, in particular, offer an elegant and technically reproducible method for post-hepatectomy bile leak detection without need for contrast injection or use of fluoroscopy[5]. Barriers to routine use of completion cholangiograms are largely unexplored, but are likely related to additional operative time and perceived inconvenience. Given a relatively high rate of bile leaks, routine cholangiography should be considered in patients after major hepatectomy.

Conclusions

Nearly 8% of patients have bile leak after liver resection. Proportion of bile leak is especially high after major hepatectomy and/or enterohepatic reconstruction. Bile leak is independently associated with significant postoperative morbidity. Mitigation of bile leak is imperative to improve postoperative complications in patients after hepatectomy.

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Author Contribution

Category 1

Conception and design of study: Martin, Stukenborg, Zaydfudim.

Acquisition of data: Martin, Narayanan, Turrentine.

Analysis and/or interpretation of data: Martin, Narayanan, Turrentine, Bauer, Adams, Stukenborg, Zaydfudim.

Category 2

Drafting the manuscript: Martin, Narayanan, Turrentine.

Revising the manuscript critically for important intellectual content: Bauer, Adams, Stukenborg, Zaydfudim.

Category 3

Final approval of the version of the manuscript to be published: Martin, Narayanan, Turrentine, Bauer, Adams, Zaydfudim.

G. Stukenborg significantly contributed to the entire project including manuscript composition and revision prior to his sudden and untimely death at the end of Summer 2017.

Category 4

Agreement to be accountable for all aspects of the work: Martin, Narayanan, Turrentine, Bauer, Adams, Stukenborg (posthumously), Zaydfudim.

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Compliance with Ethical Standards

Disclosure Nothing to disclose.

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