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ORIGINAL ARTICLE

Outcome of bile leakage following liver resection with hepaticojejunostomy for liver cancer

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Abstract

We aimed to investigate contemporary management and outcomes of bile leakage in patients who underwent hepatectomy with hepaticojejunostomy for liver malignancy. The NSQIP database was used to study clinical data of patients who underwent a hepatectomy with hepaticojejunostomy for a primary hepatobiliary cancer and developed bile leakage between 1/2014 and 12/2017. Multivariate regression analysis was performed to investigate outcomes. Five hundred patients underwent a hepatectomy with hepaticojejunostomy for a malignant primary hepatobiliary cancer (41% intrahepatic cholangiocarcinoma, 38.2% hilar cholangiocarcinoma, 9.8% hepatocellular carcinoma, 6% gallbladder cancer, and 5% others). The rate of bile leakage was 33.4%. Most patients (90.4%) did not require re-exploration. In 77 of 157 patients (49.1%), bile leakages were contained with intraoperatively placed drain(s) and no additional surgical intervention was required. A total of 71 patients (42.5%)—including 64 patients with intraoperative drains—required interventional radiology (IR)-guided drainage, with a 88.7% success rate. A total of 16 patients (9.6%) required re-exploration to control the leakage, with 8 of them having undergone failed IR-drainage. When running multivariate analysis, post-hepatectomy liver failure (AOR: 158.26, $P<0.01$), preoperative sepsis (AOR: 36.24, $P=0.03$), and smoking (AOR: 14.07, $P=0.03$) were significantly associated with mortality of patients. Biliary leakage is relatively common following hepatectomy with hepaticojejunostomy for liver malignancy (33.4%), but most patients (90.4%) do not require re-exploration. Intraoperatively placed drains successfully controlled 46.7% of bile leakages. IR-guided drain placement had a 88.7% success rate for adequate leak control.

Keywords Bile leakage · Anastomosis leakage · Hepatectomy

Introduction

Bile leakage is one of the leading causes of morbidity in hepatobiliary procedures [1–4]. Management of bile leaks requires an interdisciplinary approach involving endoscopic, interventional, and operative therapies [3]. Although many factors predictive of biliary leaks have been described in literature, most factors are not easily controllable, and there is no clear consensus on their influence on formation of bile leaks [5].

Multiple strategies have been introduced to decrease the risk of bile leakage [3, 6–9]. Even with the development of specialized centers for liver resection and technical advances, the rate of biliary leaks are still high (21–50%) [1, 5, 10, 11]. The mortality rate associated with reoperation for bile leaks following hepatic resection has been reported as high as 37.5% [12].

Multidisciplinary approaches to anastomosis leakage with preventive strategies from reoperation could decrease mortality of patient who developed the complication to 6.5% [3, 13]. Non-operative management has been reported successful in 69–94% of patients; [3] however, there are limited data surrounding this topic. This study aims to investigate outcomes of biliary leaks in patients who underwent hepatectomy with hepaticojejunostomy.

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Methods

We carried out a retrospective study of patients who underwent hepatectomy using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. The data were analyzed using the Participant Use Data Files (PUF) and the target liver resection files. Patients who underwent hepatectomy and were submitted to the ACS NSQIP during the study period (between Jan. 1 2014 and December 31, 2017) were included. The NSQIP database is a comprehensive surgical database that includes 150 preoperative and intraoperative variables, in addition to the 30-day postoperative morbidity and mortality of patients. Data are collected from 650 participating hospitals of varying sizes and academic affiliations [14]. Informed consents were obtained from individual patients within each hospital, and conducted studies from the database are exempt from IRB approval [14].

This study investigated bile leakage after hemi hepatectomies [right (Segment 5–8) or left (Segment 2–4) including or not Segment 1] and trisectionectomies [right (Segment 5–8 + Segment 4) or left (Segment 2–4 + Segment 5,8) including or not Segment 1] based on the current procedural terminology (CPT) codes of the American Medical Association of 47122, 47125, and 47130 during 2014–2017. Our study only included patients with a primary hepatobiliary cancer (gallbladder cancer, hepatocellular carcinoma, hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, and other primary hepatobiliary malignancies). Patients without a final pathology of primary hepatobiliary cancer were excluded from the study. Biliary leakage was diagnosed with confirmation of high bilirubin levels of abdominal drains, high bilirubin levels of abdominal collection percutaneously drained, high bilirubin levels of spontaneous wound drainage, or operative findings [14].

The analyzed data include: demographics, comorbidities, perioperative laboratory data, hospitalization length, admission type, primary diagnosis, operative factors (such as operative length, use of a drain, and procedure type), presence of biliary leakage, treatment method of biliary leakage, reoperation, and other related complications (including sepsis, septic shock, and mortality). The primary endpoints were rate, outcomes, and treatment of bile leakage after hepatectomy with hepaticojejunostomy. All variables' definition is accessible on the NSQIP website [14]. The grade of bile leakage was defined per guideline of the International Study Group of Liver Surgery (ISGLS) for severity of bile leakage after hepatobiliary surgery with: grade A being a bile leakage causing no change in patients' clinical management; grade B requiring active therapeutic intervention, but manageable without re-laparotomy; grade C bile leakage re-laparotomy is required [2].

Statistical analysis

All data analyses and management were performed using the Statistical Package for Social Sciences (SPSS) software, Version 22 (SPSS Inc., Chicago, IL). A univariate analysis was performed for all variables of the study to determine the difference in proportions for dichotomous and categorical variables between study groups using Pearson's χ^2 test (Table 1). A multivariable logistic regression model was created to identify independent risk factors for primary adverse outcome (mortality). Another multivariable logistic regression model was created to investigate associations between perioperative variables and development of bile leakage. All investigated variables in the study were included in the logistic regression models. The one-way analysis of variance was used to assess the differences in mean for continuous variables. The estimated adjusted odds ratio (AOR) was calculated for each correlation, with a 95% confidence interval. A P value of $P < 0.05$ was considered statistically significant.

Results

Five hundred patients who underwent hepatectomy with hepaticojejunostomy for a primary hepatobiliary cancer during 2014–2017 were selected from within the NSQIP database. Our study population includes 41% intrahepatic cholangiocarcinoma, 38.2% hilar cholangiocarcinoma, 9.8% hepatocellular carcinoma, 6% gallbladder cancer, and 5% other malignant primary hepatobiliary cancers.

Overall, 94.6% of procedures were performed with open approach. Of the patients included, 24.4% underwent left lobectomy, 27.8% underwent right lobectomy, and 47.8% underwent trisegmentectomy. A biliary drain was placed in 92.2% of cases. Intraoperative ablation and Pringle maneuver were performed in 1.2 and 27.6% of patients, respectively. Bile leak within 30 days postoperatively was reported in 167 patients (33.4%). The descriptive statistics, patient demographics, and clinical characteristics of the study populations by presence of bile leak are summarized in Table 1.

Among patients who developed a confirmed biliary leakage with a biliary drain placed intraoperatively (157 patients), bilirubin levels in the drain were equal or higher than 3 in 80.9% of patients. The bile leak was contained with the current drain in 49.1% of patients and no intervention was required to control the leakage (grade A).

A total of 71 patients (42.5%) required interventional radiology (IR)-guided drainage, with an 88.7% success rate (ISGLS grade B). This includes 64 patients with intraoperative drains. Sixteen patients (9.6%) required re-exploration to control the leakage, 8 of which underwent failed IR-drainage procedures (ISGLS grade C).

Table 1 Demographics and clinical characteristics of patients underwent hepatectomy with hepaticojejunostomy by bile leakage

Variables	Patients with bile leakage (167)	Patients without bile leakage (333)	*P* value
Age			
Age > 70 years	53(31.7%)	84(25.2%)	0.12
Sex			
Female	64(38.3%)	153(45.9%)	0.10
Race			
White	122(88.4%)	217(81.9%)	0.17
Black or African American	8(4.8%)	15(5.7%)	0.10
Asian	8(4.8%)	30(11.3%)	0.06
Other	0(0%)	3(1.1%)	0.17
Comorbidity			
Hypertension	72(43.1%)	142(42.6%)	0.92
Diabetes mellitus	27(16.2%)	60(18%)	0.60
Weight loss	25(15%)	58(17.4%)	0.48
History of severe chronic obstructive pulmonary disease	9(5.4%)	9(2.7%)	0.12
Obesity	43(25.9%)	69(21%)	0.21
Preoperative sepsis/SIRS	6(3.6%)	13(3.9%)	0.63
Bleeding disorders	3(2.3%)	9(3.5%)	0.54
Congestive heart failure	0(0%)	1(0.3%)	0.47
Smoking within one year	26(15.6%)	63(18.9%)	0.35
Cirrhotic liver	14(8.4%)	40(12%)	0.17
Dyspnea	8(4.8%)	24(7.2%)	0.29
Chronic steroid use	2(1.2%)	10(3%)	0.21
Diagnosis			
Gallbladder cancer	8(4.8%)	22(6.6%)	0.42
Hepatocellular carcinoma	13(7.8%)	36(10.8%)	0.28
Hilar cholangiocarcinoma	60(35.9%)	131(39.3%)	0.45
Intrahepatic cholangiocarcinoma	75(44.9%)	130(39%)	0.20
Other primary hepatobiliary malignancies	11(6.6%)	14(4.2%)	0.24
Laboratory variables			
Serum albumin less than 3 g/dL	28(17.8%)	45(14.4%)	0.32
Leukocytosis	29(18%)	64(19.3%)	0.72
Type of procedure			
Left lobectomy	34(20.4%)	88(26.4%)	0.13
Right lobectomy	48(28.7%)	91(27.3%)	0.73
Trisegmentectomy	85(50.9%)	154(46.2%)	0.32
Other factors			
Presence of a biliary drain	157(94%)	304(91.3%)	0.28
Presence of biliary stent	103(61.7%)	210(63.1%)	0.95
Neoadjuvant therapy	38(22.8%)	63(18.9%)	0.52
Post-haepatectomy liver failure	63(37.7%)	58(17.4%)	< 0.01
ASA **score more than two	127(76.5%)	262(78.7%)	0.58
Pringle	53(31.7%)	85(25.2%)	0.14

**American Society of Anesthesiologists

During the four years our study examined, no significant decrease in the rate of bile leakage occurred (34.5% in 2014 and 39.2% in 2017). However, we observed a steady decrease in the rate of reoperation for patients who underwent hepatectomy with hepaticojejunostomy and developed bile leakage (from 12.8% in 2014 to 6.1% in 2017) (Fig. 1).

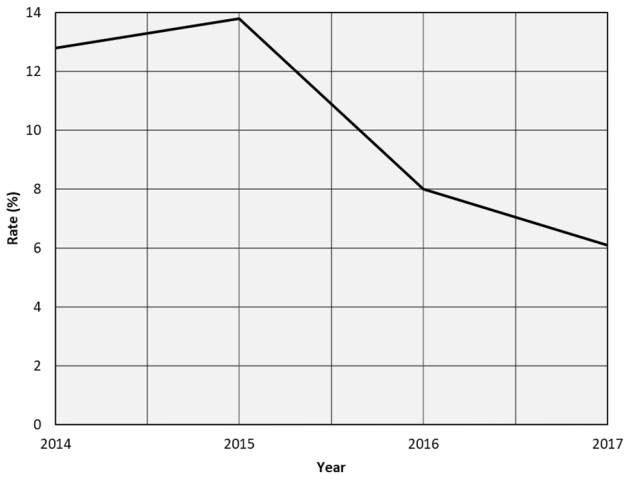

Fig. 1 Rate of reoperation for patients who underwent hepatectomy with hepaticojejunostomy and developed biliary leakage by year

Among patients who underwent hepatectomy, 167 (33.4%) developed bile leakage within 30 days postoperatively. Bile leakage significantly increased hospitalization length (median 15 vs. 9 days, $P<0.01$). Also, the rate of 30-day-unplanned readmissions for patients with bile leakage was 29.3%; the most common reason was intra-abdominal infection/abscess (38.8%).

Multivariate analysis was used to investigate mortality predictors of patients who underwent hepatectomy. All variables of the study were considered as covariant. When running multivariate analysis, post-hepatectomy liver failure (AOR: 158.26, $P<0.01$), preoperative sepsis (AOR: 36.24, $P=0.03$), and smoking (AOR: 14.07, $P=0.03$) were significantly associated with mortality of the patients, however, were not associated with bile leakage (AOR: 1.02, $P=0.98$) (Table 2).

Perioperative factors of patients with or without bile leakage were compared using a univariate analysis (Table 1). Patients who developed post-hepatectomy liver failure had significantly higher risk of bile leakage. Other perioperative factors were not significantly different between patients with and without bile leakage. When running multivariate analysis with all preoperative variables of the study included as covariables, post-hepatectomy liver failure (AOR: 16.52, $P<0.01$) was the only factor significantly associated with development of bile leakage (Table 3).

Discussion

Our study results show one-third of patients who underwent hepatectomy with hepaticojejunostomy develop bile leakage. This rate is consistent with previous reports in literature (21–50%) [1, 5, 10, 11]. The wide variation in range is partially related to the lack of a uniform definition for bile leakage, as well as the extent of liver resection and biliary reconstructions in different studies [11, 15]. Similar to a recently published study, we could not find any significant decrease in the rate of the complication during our study period [3].

Modification of risk factors of bile leakage is important, however, our multivariate analysis only found that post-hepatectomy liver failure was a significant risk factor for bile leakage. Many studies identify a correlation between the extent of liver resection and post-hepatectomy liver failure [11, 16, 17]. Preoperative preventive strategies such as portal vein embolization to enlarge the future liver remnant, or two-staged hepatectomy, might be helpful to decrease the risk of post-hepatectomy liver failure and subsequently bile leakage [16, 17]. Further studies are needed to investigate effectiveness of these methods in decreasing bile leakage after surgery.

Our study shows that bile leakage following hepatectomy is associated with a significant increase in hospitalization length and readmission rate. This is consistent with prior studies [18, 19]. We identified post-hepatectomy liver failure, preoperative sepsis, and smoking as factors significantly associated with mortality of patients, which is in line with previous studies [20–24]. Although patients with bile leakage had higher mortality in our study (15 vs. 8.7%), using multivariate analysis bile leakage did not independently increase mortality of patients. In our population, bile leakage affected morbidity and hospitalization length of patients rather than mortality. This finding may be related to advancements in management of biliary leaks during last decade.

This study result reveals that most of the patients with bile leakage can be managed without re-exploration (90.4%). We also found the rate of re-exploration decreased over time and it reached to 6.1% in 2017 in our study (Fig. 1). This is in line with recent reports of non-operative management of bile leakage in most of patients with the complication in literature [3, 6, 7, 25–28]. This can be the result of advancement in non-operative management of bile leak. The indications for re-exploration after bile leakage are not clear in literature. Factors such as early bile leaks and failure of interventional therapy may affect the surgeon's decision [29]; however, more clinical trials are needed to define the criteria of reoperation in patients who develop bile leakage.

Finally, we found 29.3% unplanned readmissions for patients with bile leakage, with the most common reason being intra-abdominal infection/abscess. Advancement in endoscopic and interventional radiology procedures may decrease the readmission rate in the future.

Table 2 Risk-adjusted analysis of mortality predictors of patients after major hepatectomy

Variable	Adjusted odds ratio	95% confidence interval	*P* value
Age			
Age > 70 years	4.30	0.63–28.98	0.13
Gender			
Female vs. male	2.47	0.27–21.87	0.41
Comorbidity			
Dyspnea	24.35	0.97–607.84	0.05
Chronic steroid use	1	0.98–1.11	0.99
Diabetes	0.46	0.04–4.91	0.52
Cirrhosis	7.49	0.92–60.57	0.05
Obesity	5.45	0.59–49.78	0.13
Weight loss	1.45	0.15–14.06	0.76
Chronic obstructive pulmonary disease	0.89	0.02–40.44	0.95
Bleeding disorders	3.19	0.17–58.97	0.43
Hypertension	0.17	0.02–1.28	0.08
Diagnosis			
Gallbladder cancer	–	Reference	–
Hepatocellular carcinoma	1.01	0.90–1.10	0.33
Hilar cholangiocarcinoma	1	0.99–1.01	0.99
Intrahepatic cholangiocarcinoma	1	0.98–1.02	0.99
Other primary hepatobiliary malignancies	1.01	0.97–1.02	0.99
Type of the procedure			
Left hepatectomy	–	Reference	–
Right hepatectomy	1.01	0.98–1.12	0.99
Trisegmentectomy	0.01	0.001–28.09	0.18
Other factors			
Post-hepatectomy liver failure	158.26	10.93–2290.03	< 0.01
Smoking	14.07	1.26–156.64	0.03
Preoperative sepsis	36.24	1.36–963.14	0.03
ASA* score more than two	10.30	0.66–159.13	0.09
Serum albumin less than 3 g/dL	1.75	0.18–16.33	0.61
MELD score**	0.90	0.45–1.80	0.78
Bile leakage need reoperation	1.02	0.10–9.91	0.98
Preoperative leukocytosis	0.70	0.07–6.69	0.76

*The American Society of Anesthesiologists score

**model for end-stage liver disease score

Study limitations

This study is primarily limited by its retrospective nature. We are unable to draw causal conclusions and the reported associations need to be confirmed by clinical trials. In addition, the database used contains little information regarding surgical techniques and intraoperative factors, such as the number and placement of drains, preoperative liver function, size of the liver remnant after resection, and intraoperative evaluation of the biliary anastomosis for leakage. Also, due to the limitation of database, we could not classify bile leakage according to the Strasberg classification [30]. Despite these limitations, this study is one of the largest to report outcomes and contemporary management of patients developing biliary leakage following hepatectomy with biliary reconstruction.

Conclusion

Bile leakage following hepatectomy is associated with a significant increase in hospitalization length and readmission rate. One-third of patients undergoing hepatectomy with hepaticojejunostomy develop a biliary leak, but most patients (90.4%) do not require re-exploration. Re-exploration rates have decreased over time, reaching 6.1% in 2017.

Table 3 Risk-adjusted analysis of predictors of bile leakage after major hepatectomy

Variable	Adjusted odds ratio	95% confidence interval	*P* value
Age			
Age > 70 years	0.62	0.27–1.45	0.27
Gender			
Female vs. male	0.33	0.17–0.1	0.05
Comorbidity			
Dyspnea	1.02	0.22–4.66	0.97
Chronic steroid use	0.42	0.02–6.11	0.52
Diabetes	0.80	0.30–2.13	0.66
Cirrhosis	0.23	0.0.6–0.1.01	0.05
Obesity	0.69	0.28–1.73	0.44
Weight loss	0.94	0.34–2.59	0.90
Chronic obstructive pulmonary disease	16.62	0.91–302.82	0.05
Bleeding disorders	1.01	0.98–1.10	0.99
Hypertension	1.72	0.79–3.76	0.16
Diagnosis			
Gallbladder cancer	–	Reference	–
Hepatocellular carcinoma	0.21	0.009–5.06	0.33
Hilar cholangiocarcinoma	0.54	0.05–5.08	0.59
Intrahepatic cholangiocarcinoma	0.59	0.07–4.47	0.61
Other primary hepatobiliary malignancies	0.99	0.12–7.65	0.99
Type of the procedure			
Left hepatectomy	–	Reference	–
Right hepatectomy	0.32	0.06–1.79	0.19
Trisegmentectomy	0.70	0.22–2.25	0.55
Other factors			
Post-hepatectomy liver failure	3.38	1.39–8.20	< 0.01
Smoking	0.85	0.30–2.41	0.77
Preoperative sepsis	0.65	0.10–4.14	0.65
ASA* score more than two	0.39	0.16–1	0.05
Serum albumin less than 3 g/dL	1.34	0.50–3.59	0.56
MELD score**	0.94	0.71–1.25	0.69
Preoperative leukocytosis	1.59	0.64–3.98	0.33

*The American Society of Anesthesiologists score

**Model for end-stage liver disease score

Endoscopic and IR-guided drain placement have an 88.7% success rate for adequate leak control. Nearly one-third of patients with biliary leakage (29.3%) were readmitted to the hospital within 30 days for intra-abdominal infection/abscess. Post-hepatectomy liver failure, preoperative sepsis, and smoking are significantly associated with mortality of patients after hepatectomy but not bile leakage.

Author contributions MZ: conceived and designed the analysis; collected the data; contributed data or analysis tools; performed the analysis; wrote the paper, approval of final version, accountable for all aspects of the work. RV conceived and designed the analysis, critical revision, co-wrote and edited paper, approval of final version, accountable for all aspects of the work. DL conceived and designed the analysis, critical revision, co-wrote and edited paper, approval of final version, accountable for all aspects of the work. KAF: conceived and designed the analysis; collected the data; contributed data or analysis tools; performed the analysis; wrote the paper, approval of final version, accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no relevant or material financial interests that relate to the research described in this paper.

Research involving human participants and/or animals Conducted studies from the NSQIP database are exempt from IRB approval.

Informed consent Informed consents were obtained from individual patients within each hospital.

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