original article

Morbidity, mortality and predictors of outcome following hepatectomy at a Saudi tertiary care center

Faisal Al-alem,[a]* Rafif Essam Mattar,[a]* Ola Abdelmonem Fadl,[b] Abdulsalam Alsharabi,[a] Faisal Al-Saif,[a] Mazen Hassanain[ac]

From the [a]Department of General Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [b]Department of Liver Disease, Research Center, King Saud University, Riyadh, Saudi Arabia; [c]Department of Oncology, McGill University, Montreal, Quebec, Canada

Correspondence: Dr. Mazen Hassanain · Department of General Surgery, College of Medicine, King Saud University, Riyadh 11466, Saudi Arabia; Department of Oncology, McGill University, Montreal, Quebec, Canada · mhassanain@ksu.edu.sa · ORCID: http://orcid.org/0000-0002-2441-5142

Ann Saudi Med 2016; 36(6): 414-421

DOI: 10.5144/0256-4947.2016.414

These authors contributed equally to this study.

BACKGROUND: Hepatic resection is a major surgical procedure. Data on outcomes of hepatectomy in Saudi Arabia are scarce.
OBJECTIVE: To measure morbidity and mortality and assess predictors of outcome after hepatectomy.
DESIGN: Descriptive study.
SETTING: Tertiary care center in Saudi Arabia with well-established hepatobiliary surgery unit.
PATIENTS AND METHODS: All patients undergoing liver resection in our institute during 2006-2014. Data were analyzed by Kaplan-Meier survival analysis.
MAIN OUTCOMES MEASURE(S): Postoperative morbidity and 90-day mortality. Secondary outcomes were risk factors associated with increased morbidity and mortality.
RESULTS: Data on 77 resections were collected; 56 patients (72.7%) had a malignant etiology, mainly colorectal liver metastases and hepatocellular carcinoma (45.5% and 14.3% respectively). Complications developed following 30 resections (39.0%), with the majority being Clavien grades I–III. In the univariate analysis, predicting factors were the total bilirubin level preoperatively, operative time, extent of resection (i.e., major resection), use of epidural anesthesia, and postoperative liver dysfunction. In the multivariate analysis, the Schindl liver dysfunction score showed the strongest correlation with the development of complications (P=.006). The 90-day postoperative mortality was 5.2% (4/77 patients); 3 patients fulfilled the 50:50 liver dysfunction criteria. Significant predictors were concurrent intra-abdominal surgery, postoperative liver dysfunction, and multiple complications.
CONCLUSION: Factors that predicted development of complications were elevated total bilirubin level preoperatively, operative time, extent of the resection, use of epidural anesthesia and a postoperative need for blood transfusion. Liver resection is a safe and feasible option at our center.
LIMITATIONS: The small number of indications for resection and consequent reduction in variety of risk factors limited ability to make inferences. Additionally, only a handful of cases were performed laparoscopically.

Hepatic resection is a widely used surgical procedure for both oncologic and non-oncologic diseases[1,2] such as tumors, intrahepatic duct calculi, hydatid disease, and abscesses. Benign neoplasms include hepatocellular adenoma, hepatic hemangioma, and focal nodular hyperplasia. Resection is a curative option for various malignancies, both primary hepatocellular carcinoma[3,4] and metastatic hepatic tumors.[5] Specifically, those arising from colorectal cancer are the most amenable to surgical resection.

According to Höhn's classification,[6] liver resection is considered major abdominal surgery. This procedure has improved significantly over time, and its outcomes have significantly improved over the last few years.[7] This can be attributed to multiple factors, including proper patient selection,[8] focused perioperative management,[9] the use of portal vein embolization to ensure an adequate future liver remnant,[10] a decreased duration of preoperative chemotherapy,[11,12] optimized surgical techniques,[13] tailored multidisciplinary care,[14-17] and improved management plans in the event of complications.[7] Additionally, more of these procedures are being performed at tertiary centers by specially trained hepatobiliary surgeons who have a higher level of expertise.[7] Laparoscopy has also been widely used to decrease the invasiveness of the procedure.[18-21]

Before 1980, liver resection was associated with a mortality risk above 10%;[7] however, this rate has decreased dramatically, and it is reported to be <2.5% and even <1% at specialized centers.[22-24] Despite favorable outcomes, hepatic resection remains a complex procedure associated with significant morbidity.[25] A number of postoperative complications may occur that should always be anticipated, including hemorrhage, pleural effusion, and sub-phrenic infection, biliary tract injury, liver dysfunction, and biliary tract hemorrhage. The most feared life-threatening complication is post-hepatectomy liver failure (PHLF)[26,27] which occurs following about 10% of resections.[28,29] PHLF is defined by the International Study Group of Liver Surgery as an increased international normalized ratio and hyperbilirubinemia on or after the fifth postoperative day, thus indicating the inability of the liver to perform its synthetic, excretory, and detoxifying tasks.[30] PHLF accompanied by acute renal failure (ARF) may lead to hepatorenal syndrome. ARF is a complication that is usually reversible, mainly by means of dehydration and diuretics.[31] Bile leakage is another feared complication that occurs in 4–17% of cases.[32] Coagulation disorders can also develop.[33,34] Infections are predicted following most procedures, with surgical site infections being common. However, intra-abdominal abscesses, postoperative pneumonia and urinary tract infection are also seen, more so in the elderly.[35,36]

Our teaching institution, King Saud University Medical City, has a specialized hepato-pancreatico-biliary (HPB) unit that was established in 2006. Our unit consists of three reputable surgeons trained in advanced HPB and transplant procedures, with a focus on hepatobiliary and oncological diseases. We report our rates of morbidity and mortality following hepatectomy, and our analysis of predicting factors.

PATIENTS AND METHODS

Data were collected from our HPB unit's database for all hepatectomy cases performed at King Saud University Medical City from 2006–2014. Data were collected from hospital medical records, operative records, pathology reports, radiology software, and outpatient clinics. Variables collected were divided into general demographics, preoperative, intraoperative, and postoperative variables, and outcomes. Liver dysfunction was calculated via two common scores: the Schindl score[37] (which is based on total serum bilirubin and lactate, in addition to prothrombin time and encephalopathy), and the 50:50 score[38] (which is based on total serum bilirubin and prothrombin time). Primary outcomes were postoperative morbidity (according to the Clavien-Dindo surgical complication score)[39] and 90-day mortality. Secondary outcomes were all risk factors associated with postoperative morbidity and mortality. A univatiate analysis was done using chi square for nominal variables and the *t* test or Mann–Whitney U test for continuous variables not normally distributed. Significant variables were then used in a multivariate analysis.

Survival curves were generated to determine disease-specific mortality rates using Kaplan-Meier curves. The log-rank test was used to analyze all collected variables to determine significant risk factors for morbidity after resection and 90-day mortality. Statistical analyses were performed using JMP 11.2.0 software (SAS Institute, Cary, NC).

RESULTS

Indications

Ninety-six liver resections were screened; 19 were excluded due to missing data. Seventy-seven resections were included for further analysis; 56 patients (72.72%) had a malignant etiology, mainly colorectal liver metastases, in 35 patients, and hepatocellular carcinoma in 11 patients (45.45% and 14.29% respectively) (**Table 1**). Four patients had a second resection for recurrences. All patients underwent preoperative assessment of liver volume, and possibility of portal hypertension as clinically indicated.

Baseline characteristics

The mean (standard deviation) age of the 77 patients was 49.1 (15.5) years. Our youngest patient was 14 years, whereas the eldest was 74 years. The percentage of our male patients was slightly higher than that of our female patients (53.3% vs. 46.8%). The mean American Society of Anesthesiologists classification was 2. The median preoperative hospitalization period was 4 days (range: 0–25 days, IQR: 2–8 days). The remaining baseline characteristics and preoperative lab values are in **Table 2**. Fifty-six resections were performed for malignant indications. Thirty-seven were

Table 1. Indications for liver resection (n=77).

Indication for liver resection	Frequency	Percentage
Malignant indications (n=56, 72.7%)		
Colorectal cancer liver metastasis	35	45.5
Hepatocellular carcinoma	11	14.3
Cholangiocarcinoma	2	2.6
Neuroendocrine tumor	2	2.6
Other malignancies*	6	6.5
Benign indications (n=21, 27.3%)		
Hemangioma(s)	7	6.5
Focal nodular hyperplasia	4	5.2
Hydatid cyst	3	3.9
Simple cyst	3	1.3
Hepatocellular adenoma	1	1.3
Traumatic liver injury	1	1.3
Focal steatosis	2	9.1
Total	**77**	**100**

*One resection for each of the following was performed: (1) direct invasion of colorectal cancer into the liver, (2) breast cancer liver metastasis, (3) monophasic synovial sarcoma liver metastasis, (4) hepatoblastoma (5) sarcomatoid tumor and (6) part of extended cholecystectomy for gallbladder cancer.

Table 2. Baseline characteristics (n=77).

Age, years (median, range)	49 (14–74)
Sex	
Male	41 (53.3)
Female	36 (46.8)
Body Mass Index (mean, range)	25.9 (17.7–51.7)
ASA Class	
Class 1	7 (9.1)
Class 2	32 (41.6)
Class 3	12 (15.6)
Class 4	1 (1.3)
Class 5 or 6	0 (0)
Smokers	5 (6.49)
Bronchial asthma	4 (5.19)
Diabetes mellitus	15 (19.48)
Hypertension	15 (19.48)
History of stroke	3 (3.9)
Bleeding disorder	1 (0.13)
Hepatitis B or C	7 (9.09)
Ascites on CT	5 (6.49)
Preoperative transfusion	3 (3.9)
Previous operation within 30 days	7 (9.09)
Preoperative hospitalization, days (median, range)	4 (0–25)
Preoperative radiation	5 (6.49)
White blood cell count, $\times 10^9$/L , (median, range)	6.9 (1.5–20.8)
Hematocrit level, % (median, range)	35 (21.9–47.4)
Platelet count, $\times 10^3$/µL, (median, range)	247 (53–728)
International normalized ratio, (median, range)	1.1 (0.9–1.76)
Partial thromboplastin time, s, (median, range)	36.1 (29–90.2)
Blood urea nitrogen level, mmol/L, (median, range)	4 (0.8–8.7)
Creatinine level, µmol/L, (median, range)	70 (34–182)
Total bilirubin level, µmol/L, (median, range)	9 (3–70)
Albumin level, g/L, (median, range)	32 (17–43)
Alkaline phosphatase level, U/L, (median, range)	101 (54–533)
Aspartate Aminotransferase Level, U/L, (median, range)	35 (8–596)
Alanine Aminotransferase Level, U/L – median (range)	60.5 (25–512)

Values are numbers (percentages), unless indicated otherwise. ASA, American Society of Anesthesiologists; CT, computed tomography

Table 3. Postoperative outcomes (n=77).

Overall complications	30 (39.0)
Pneumonia	1 (1.3)
Acute renal insufficiency/failure	5 (6.5)
Sepsis/septic shock	15 (19.5)
Surgical site infection	2 (2.6)
Organ space infection	8 (10.4)
Transfusion	10 (13.0)
Venous thromboembolism	2 (2.6)
Respiratory failure	5 (6.5)
Return to operation room	3 (3.9)
Reintubation	6 (7.8)
Ventilator dependence/failure to wean >48h	4 (5.2)
Cardiac arrest	3 (3.9)
Coma	2 (2.6)
Other	16 (20.8)
Liver dysfunction (50:50 rule)	12 (15.6)
Liver dysfunction (Schindl score)	
All liver dysfunction (Schindl score ≥ 1)	38 (49.4)
0 (none)	0 (0)
1-2 (mild dysfunction)	16 (20.8)
3-4 (moderate dysfunction)	18 (23.4)
≥5 (severe dysfunction)	4 (5.2)
Missing values	39
Length of stay, days (median, range)	12 (4-80)
90-day mortality	4 (5.2)
Clavian-Dindo Complication Classification	
All complications (Clavian-Dindo score ≥ 1)	30 (39.0)
0 (no complications)	35 (45.5)
1	6 (7.8)
2	10 (13.0)
3	6 (7.8)
4	4 (5.2)
5	4 (5.2)
Missing values	12

All values are number (percent) unless otherwise indicated.

for metastatic lesions (most commonly colorectal liver metastasis, 35 cases), the primary tumor had been resected previously in 29 cases. Extrahepatic synchronous metastasis was documented in 7 patients; 4 of which had pulmonary lesions, the remainders were in peritoneum and colon. Other indications for resection for malignant disease were 11 hepatocellular carcinomas, 2 cases of cholangiocarcinomas, 2 neuroendocrine masses, 1 hepatoblastoma, 1 as part of en bloc resection for colorectal cancer and 1 for a rare hepatic sarcoma. In patients with colorectal liver metastasis (35), 60% received chemotherapy before liver resections (21 cases), with an average of 10 cycles. The median time from the end of chemotherapy to the time of resection was 4.47 months (IQR: 2.53–13.9, range: 1.03–24.2 months). Right portal vein embolization was performed in 6 resections, aiming to improve the future liver residual.

Intraoperative variables

Of the 77 resections, about two-thirds (45/77, 58.4%) were major (i.e., ≥3 segments). Concurrent intra-abdominal surgery was performed in 8 cases, all for either the colon or rectum, and one patient had a breast mass that was excised simultaneously. Epidural anesthesia was used in slightly less than half of the procedures (34/77, 44.2%). A transfusion was needed intraoperatively for 29 patients (37.7%). Our mean total operative time was 5.3 hours (range: 1.7–10.3 hours).

Outcomes

Histologically, the average number of resected lesions was 2 (range: 0–20). The median length of total hospital stay was 12 days, although it ranged from 4–80 days. Complications developed following 30 resections (39.0%), with the majority being Clavien grades I–III. The most frequent complications were sepsis (15/77, 19.5%), blood transfusion (10/77, 3.0%), and organ space infection (8/77, 10.4%) (**Table 3**). Almost half the patients (38/77, 49.4%) exhibited an element of hepatic impairment postoperatively, mostly mild or moderate based on the Schindl liver dysfunction score.[37] Interestingly, when calculating liver dysfunction using the 50:50 criteria, only 12/77 patients (15.6%) had liver dysfunction.

Factors associated with morbidity in a univariate analysis were only the total bilirubin level preoperatively, operative time, extent of the resection (i.e. major resection), use of epidural anesthesia, and postoperative liver dysfunction (calculated by both the Schindl liver dysfunction score and 50:50 criteria). In a multivariate analysis, the Schindl liver dysfunction

Table 4. Univariate analysis for variables correlating with morbidity following liver resection (statistically significant factors shown, *P*<.05).

Factors	*P*
Baseline factors	
Total bilirubin	.0272
Intraoperative factors	
Operative time	.0043
Extent of resection (major)	.0487
Epidural anaesthesia	.0208
Schindl liver dysfunction score postoperatively	.0261
50:50 liver dysfunction criteria postoperatively	.0022

Statistically nonsignificant factors shown in Appendix 1.

Table 5. Univariate analysis for variables correlating with 90-day postoperative mortality following liver resection (statistically significant factors shown, *P*<.05).

Factors	*P*
Intraoperative factors	
Concurrent intra-abdominal surgery	.0082
Postoperative factors	
Schindl liver dysfunction score	.0002
50:50 liver dysfunction criteria	<.0001
Postoperative transfusion	<.0001
Bleeding transfusion (>4 units of blood within 72h after surgery)	.0030
Acute renal insufficiency/failure	< .0001
Respiratory failure	.0001
Return to OR	<.0001
Reintubation	<.0001
Ventilator dependence	<.0001
Cardiac arrest	<.0001
Coma	.0023
Venous thromboembolism	.0021
Sepsis	.0013

Statistically nonsignificant factors shown in Appendix 2.

score showed the strongest correlation (*P*=.006) with postoperative morbidity. Details of the outcomes and factors that correlated with morbidity and 90-day postoperative mortality are illustrated in **Tables 4 and 5,** respectively (All factors shown as **Appendices 1 and 2**). Factors such as age, gender, body mass index, white blood cell count, hematocrit and several others were not significantly associated with morbidity. The 90-day postoperative mortality was 5.2% (4/77 patients); 3 fulfilled the 50:50 liver dysfunction criteria. Significant predictors were concurrent intra-abdominal surgery, postoperative liver dysfunction, and the development of multiple complications listed in **Table 5**. Notably, following the 55 resections performed for malignant indications, histology showed a positive margin in 5 patients (9.1%).

Overall survival and disease-free survival Patients were followed for a median of 13 months (IQR: 1.49–22.67, range: 0–56.7 months). Recurrence/progression of the disease was documented after 29/77 resections (37.7%); these were mostly intrahepatic (22/77). Seven recurrences developed in the lung, and 10 in other distant locations. The median time to recurrence/progression was 5.8 months (IQR: 2.0–10.8, range: 0.33–49.07 months). The overall median survival was 13.23 months (IQR: 0.77–22.48, range: 0.13–49.5 months). Overall and disease-free survival curves are shown in **Figures 1 and 2**.

DISCUSSION

Liver resection is a major surgical intervention that is the cornerstone of managing various benign and malignant diseases. In Saudi Arabia, data on the indications and outcomes of this procedure are scarce. Therefore, we performed this study to benchmark our experi-ence and identify predictors of morbidity and mortality at our center. We aimed to optimize our patient care in light of our results. As this paper is a retrospective study it suffers all the limitations that apply to this type of study, including missing data, which is apparent in our paper. However from the collected data, the mor-bidity and mortality rates reached 39.0% and 5.2% re-spectively. Compared with data reported by Aloia et al[8] in the National Surgical Quality Improvement Project (NSQIP), our rates are within an acceptably close range.[40] However, the relatively small sample size of our study limits such a comparison, and ongoing prospec-tive data collection is being carried out for future com-parisons and quality improvement.

We found that significant predictors of morbidity were the total bilirubin level preoperatively, operative time, extent of resection, use of epidural anesthesia, and postoperative Schindl score for liver dysfunction. In the literature, it is well established that the opera-

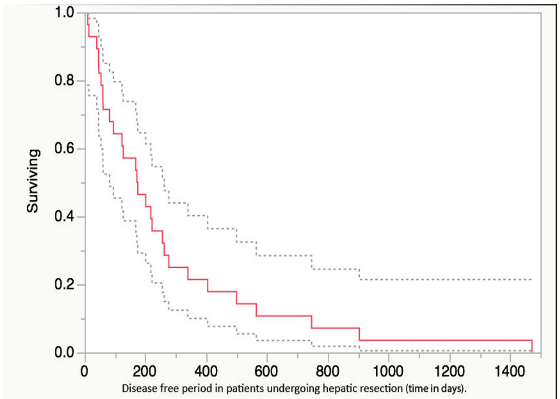

Figure 1. Kaplan-Meier disease-free survival.

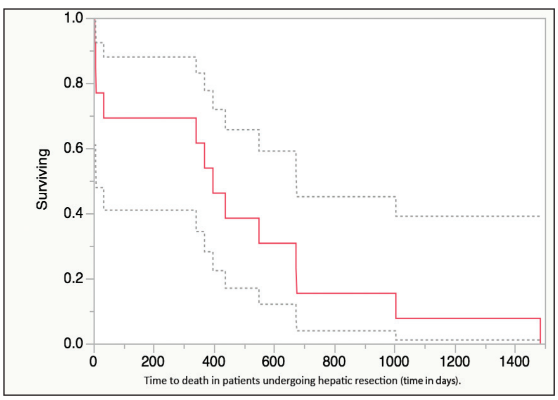

Figure 2. Kaplan-Meier overall survival.

tive time and blood loss influence morbidity, whereas epidural anesthesia has a protective role.[41-43] We think the discrepancies in our data were mainly because of the effect of epidural anesthesia on the operative time, which included within it the anesthesia time.

Significant predictors of 90-day mortality were concurrent intra-abdominal surgery, the postoperative Schindl score for liver dysfunction, the 50:50 liver dysfunction criteria, postoperative blood transfusion, and the development of complications. These data correlate with reported findings,[30] as liver failure is the most commonly reported cause of postoperative mortality following major liver resection. The majority of our liver resections were performed for an oncological indication, which may explain the significant rate of postoperative liver dysfunction.[27] Most of our patients underwent a major liver resection (45 patients, 58.4%), defined as resection of three segments or more. Taking this into consideration when comparing our results to NSQIP data, our morbidity (38.96%) and mortality rates (5.19%) lie in close proximity to their rates for extended resections (31.9% and 5.2% respectively). In our cohort liver dysfunction (49.35%) was the most common complications followed by sepsis (14.98%), and organ space infection (10.39%). In NSQIP data, both organ space collection (4.5-10.9%) and sepsis (5.7-9.6%) were also the most common complications.

In conclusion, liver resection is a safe and feasible option at our center. We attained acceptable preliminary results. However, further care should be taken to note the operative time and postoperative liver failure. Laparoscopic liver surgery is a new emerging modality that has a promising future, and it can be utilized at our institution. Factors that predicted development of complications were elevated total bilirubin level preoperatively, operative time, extent of the resection (i.e. major resection), use of epidural anesthesia and a postoperative need for blood transfusion. The development of postoperative liver dysfunction correlated with 90-day mortality in our sample ($P<.0001$). The relatively small number of indications for resection, which decreases the variety of risk factors and our inability to derive statistical inferences is a major limitation of the study. Additionally, only a handful of cases were performed laparoscopically, which limits the statistical analysis of that form of surgery.

Acknowledgments

We thank Weam Hussain and Maram AlKhammash of the Liver Disease Research Center at King Saud University for their help and contributions during data collection.

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APPENDIX MATERIAL FOR: Morbidity, mortality and predictors of outcome following hepatectomy at a Saudi tertiary care center

Al-alem F, Mattar RE, Fadl OA, Alsharabi A, Al-Saif F, Hassanain M. Morbidity, mortality and predictors of outcome at a Saudi tertiary care center. Ann Saudi Med 2016; 36(6): 414-421. DOI: 10.5144/0256-4947.2016.414

Appendix 1. Univariate analysis for correlation with morbidity following liver resection.

Factor	*P* value
Indication (Benign vs. Malignant)	.0650
Indication (Type of Malignancy)	.4203
Age	.9909
Gender	.5354
Body Mass Index	.2218
White Blood Cell Count	.1552
Haematocrit	.6881
Platelets	.1158
International Normalized Ratio	.3221
Partial Thromboplastin Time	.7562
Blood Urea Nitrogen	.4374
Creatinine	.0816
Total Bilirubin	.0272
Albumin	.2622
Alkaline Phosphatase	.8425
Aspartate Aminotransferase	.1534
Alanine Aminotransferase	.4200
American Society of Anesthesiologists Physical Status Class	.5083
Smoking Status	.2553
Bronchial Asthma	.2180
Diabetes Mellitus	.6902
Hypertension	.7174
Stroke History	.1145
Bleeding Disorder	.2682
Previous Coronary Stent	.3589
Previous Cardiac Surgery	.3589
Sepsis	.2597
Preoperative Transfusion	.4466
Operative Procedure within 30-days	.8581
Number of Hospitalization Days Preoperatively	.0915
Radiotherapy	.4868

Chemotherapy	.4064
Number of Chemotherapy Cycles Preoperatively	.7695
Primary disease not resected	.9484
Operative Time	.0043
Extent of Resection (major)	.0487
Epidural Anaesthesia	.0208
Concurrent Intra-abdominal Surgery	.8498
Intraoperative Transfusion	.4665
Fong Score	.2692
Number of Resected Lesions	.5887
Schindl Liver Dysfunction Score Postoperatively	.0261
50:50 Liver Dysfunction Criteria Postoperatively^a^	.0022

[a]Intra-operative factor; *P*>.05.

Appendix 2. Univariate analysis for variables correlation with 90-day postoperative mortality.

Baseline Factor	***P* value**
Indication (Benign vs. Malignant)	.7957
Indication (Type of Malignancy)	.9941
Age	.3614
Gender	.9326
Portal Vein Embolization	.1924
Body Mass Index	.2494
White Blood Cell Count	.8543
Haematocrit	.3349
Platelets	.6055
International Normalized Ratio	.2299
Partial Thromboplastin Time	.7926
Blood Urea Nitrogen	.0854
Creatinine	.1393
Total Bilirubin	.3084
Albumin	.3978
Alkaline Phosphatase	.7664
Aspartate Aminotransferase	.2535
Alanine Aminotransferase	.3012
American Society of Anesthesiologists Physical Status Class	.8813
Smoking Status	.5990
Bronchial Asthma	.6469
Diabetes Mellitus	.6659

Hypertension	.6417
Stroke History	.6965
Bleeding Disorder	.8231
Previous Coronary Stent	.8231
Previous Cardiac Surgery	.7520
Sepsis	.6469
Presence of Ascites on CT	.5646
Preoperative Transfusion	.6940
Operative Procedure within 30-days	.2095
Number of Hospitalization Days Preoperatively	.3418
Radiotherapy	.5990
Chemotherapy	.9234
Number of Chemotherapy Cycles Preoperatively	.6627
Time Between Chemotherapy and Resection	.4750
Primary disease not resected	.2042
Intraoperative Factors	
Operative Time	.2336
Extent of Resection (major vs. minor)	.0832
Epidural Anaesthesia	.0956
Concurrent Intra-abdominal Surgery	**.0082***
Intraoperative Transfusion	.4963
Postoperative Factors	
Schindl Liver Dysfunction Score	**.0002**
50:50 Liver Dysfunction Criteria	**<.0001**
Postoperative Transfusion	**<.0001**
Bleeding Transfusion (>4 units of blood within 72h after surgery)	**.0030**
Acute Renal Insufficiency/Failure	**<.0001**
Respiratory Failure	**.0001**
Return to OR	**<.0001**
Reintubation	**<.0001**
Ventilator Dependence	**<.0001**
Cardiac Arrest	**<.0001**
Coma	**.0023**
Venous Thromboembolism	**.0021**
Pneumonia	.8231
Sepsis	**.0013**
Surgical Site Infection	.7500
Organ Space Infection	.2637
Length of Stay	.8066