Rückert et al., J Liver Disease Transplant 2016, 5:2
DOI: 10.4172/2325-9612.1000136

Journal of Liver: Disease & Transplantation

Research Article

A SCITECHNOL JOURNAL

Predictors of Postoperative Morbidity after Minor and Major Liver Resections in a Single German Centre

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Abstract

Background: Hepatic resections are classically subdivided into major and minor resections. These definitions are important for the perioperative management as major resections are associated with a higher incidence of complications like liver failure or bile leakage. However, other perioperative factors might also influence patient outcome. The present study aims to evaluate the significance of major and minor hepatic resection as well as other factors on the postoperative course. For this purpose we analysed data retrospectively from our centre.

Patients and methods: The study was based on a prospective database of all liver resections performed at the University Hospital Mannheim between January 1998 and December 2010 (a total of 627 consecutive liver resections). In these patients 135 major hepatectomies, and 192 minor resections were performed. Wedge resections were excluded from analysis. Variables independently associated with the occurrence of complications were identified using a binary regression analysis model.

Results: 186 (56.9%) of the patients were male, the mean age of all patients was 61.9 years (SD 11.5). The rate of patients with postoperative liver failure was 3.4% and 30-day mortality was 5.5%. Mean length of stay was 15.6 days. Surgical and non-specific complications were significantly more frequent in major hepatectomies. However, we found that the performed procedure was no independent risk factor for the incidence of specific complications, liver failure and mortality. Multivariate analysis could reveal different other independent risk factors for the incidence of complications and mortality. Among these were ASA classification, low preoperative serum albumin and elevated preoperative levels of ALAT.

Conclusion: Our data suggests that quality and quantity of complications does not only depend on the extent of the performed procedure. Our analysis identified additional independent risk factors. These risk factors, as well as the performed procedure, should be considered in the perioperative management.

Keywords

Hepatic resections; Serum albumin; Valvular defects

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Received: February 28, 2016 **Accepted:** April 04, 2016 **Published:** April 11, 2016

Introduction

During the last century, different important discoveries like Pringles´ manoeuvre or the description of the liver segments by Couinaud enabled surgeons to perform safe hepatic resections [1,2]. These and other improvements in surgical treatment resulted in morbidity that now ranges from 22% to 45% and mortality that ranges from 2.5% to 8.4% [3-7]. Besides the advances in operative techniques, the improved outcomes are due to optimized perioperative management of hepatic surgery. Clinical pathways bundle and standardize many items of the perioperative management like assessment of patients, preoperative diagnostic and postoperative care of patients [8,9]. In our department, clinical pathways for hepatectomies were introduced in 2011. Because the extent of the resection strongly correlates with quantity and quality of complications we implemented specific clinical pathways for minor and major hepatectomies to meet the different requirements in perioperative management [3,4]. However, there might be additional factors that influence the postoperative outcome of patients. The present retrospective study aims to validate the significance of the extent of resection on the postoperative course and to possibly identify further predictors associated with morbidity. New predictors might help to identify patient that are in high risk of complications. The implementation of these predictors into the clinical pathways might optimize patients' outcome.

Patients and Methods

Patients and data collection

Patients undergoing liver resection have been prospectively entered into an institutional database in the Department of Surgery, University Medical Centre Mannheim. For the purpose of this retrospective study we only included patients that were operated between 1998 and 2010. In this period, 627 consecutive patients were treated for benign and malignant hepatic lesions. We included patient with minor or major liver resection. Biopsies, wedge resections, traumatic lesions or liver resections in context of other operations were excluded from the analysis. This resulted in 327 patients (Figure 1). We used the database to identify those patients. Missing Data were complemented by physicians' and surgeons' office notes. Demographic characteristics are summarized in Table 1. Missing data never exceeded 10 percent.

Outcome variables and definitions

For our outcome analysis (univariate and multivariate) we classified pre-existing conditions as cardiac disease (congestive heart failure, myocardial infarction, atrial fibrillation, coronary heart disease, insufficiency and valvular defects), pulmonary disease (COPD, emphysema), renal failure, and diabetes mellitus. Other independent variables were the extent of the performed procedure, experience of the surgeon, age, sex, ASA classification, Child-Pugh score and preoperative laboratory values (haemoglobin level, platelets, INR, ASAT, total bilirubin, albumin, cholinesterase). We further analysed intra-operative parameters (Pringles manoeuvre, blood loss, transfusion of packed red cells) on the outcome.

For the purpose of statistical analysis we categorized variables as

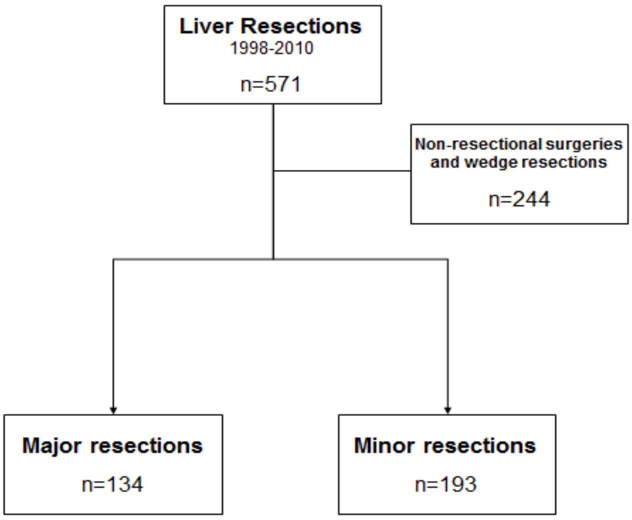

Figure 1: Flow chart of the patient cohort analysed in the present study.

Table 1: Characteristics of our patient cohort. "Procedures" only documents the leading resection (e.g. in case of right hemihepatectomy with wedge resection we only give right hemihepatectomy).

	Patients n=327 n (%)
Age	61.9 (SD 11.5)
Male sex	186 (56.9)
BMI	26.3 (SD 4.5)
Diagnosis	
Benign	37 (11.3)
HCC	48 (14.7)
CCC	15 (4.6)
Klatskin	8 (2.4)
Metastases	219 (66.9)
Child-Pugh Score	
None	293 (89.6)
A	27 (8.3)
B	7 (2.1)
C	0
Co-Morbidities	
Cardiac	87 (26.6)
Pulmonary	39 (11.9)
Renal	25 (7.6)
Diabetic	34 (10.4)
Procedures	
Segmental resection	167 (50.8)
LL segmentectomy	25 (7.6)
Left hemihep	61 (18.7)
Right hemihep	30 (9.2)
Ext left hemihep	18 (5.5)
Ext right hemihep	13 (4.0)
Central resection	13 (4.0)
Number of synchronous liver resections	
Single resection	260 (79.5)
Synchronous resections	67 (20.5))

BMI: Body-Mass-Index; **HCC**: Hepatocellular carcinoma; **CCC**: Cholangiocellular carcinoma; **LL**=Left lateral; **Ext**: Extended; **hemihep**: Hemihepatectomy

follows: extent of intra-operative blood loss (<1500 ml, more than 1500 ml), Child-Pugh score (none versus patients with grade A and B), length of Pringles manoeuvre (<40 min, >40 min), transfusion of red packed cells (0-2, >2), age (<75 years and >75 years), and experience of surgeon (0-30 operations, >30 operations). Lab values were categorized according to corresponding limits of the norm of our laboratory into low, normal or elevated. We distinguished specific (surgical) complications and non-specific complications. Specific complications included postoperative haemorrhage, bile leakage, biliary collection and intra-abdominal abscess. We only considered such biliary collections as complication that needed intervention.

Non-specific complications were wound infection, cardiac complications (myocardial infarction, cardiac failure, and atrial fibrillation), pulmonary complications (pneumonia, acute respiratory insufficiency, and pulmonary embolism), sepsis, and acute renal failure. Operative mortality was defined as any death occurring during the surgical procedure or within the 30th postoperative day.

Bile leakage was defined as bilirubin concentration in the drain fluid at least 3 times the serum bilirubin concentration on or after postoperative day 3 or as the need for radiologic or operative intervention resulting from biliary collections or bile peritonitis in accordance to a recently published definition [10]. Liver failure was characterized by an increased INR (>1.5) and concomitant hyperbilirubinemia (>1.2 mg/dl) on or after postoperative day 5 with the need for invasive management or other deviation from the regular postoperative course [11]. Minor hepatectomy was defined as resection of one or two liver segments [3,4]. Central resection was defined as resection of the segments IV, V, VIII (± segment I).

Statistical analysis

All clinical and pathological characteristics were grouped to build categorical variables (see above). Univariate examination of the relationship between assessed criteria and complications was performed with X^2 test. Factors with $p<0.05$ were retained for multivariate analysis. The factors were multivariate tested to identify independent risk factors for complications using a binary logistic regression model with backward elimination. Factors demonstrating statistical significance in the multivariate analysis were considered verifiable risk factors for the prediction of morbidity. Independent samples with a continuous measurement were tested with the Mann-Whitney Test. To compare normally distributed parameters t-test was used. Statistical significance for all analyses was accepted at $p<0.05$. Data are presented as 95% confidence intervals (95% CI) and standard deviation (SD). Statistical computations were performed using Excel (Microsoft, Redmond, Wash) and PASW Statistics 18.0 for Windows (Chicago, Ill).

Results

Short term results after minor and major hepatectomies

The procedure that was most frequently performed in our patient cohort was segmental resection (n=167; 50.8%), the least frequent procedure performed was central resection (n=13; 4.0%). 248 wedge resections were excluded from our analysis. Short term results were analysed for minor and major hepatectomies. The group of patients receiving major hepatectomies had a significant higher incidence of surgical complications (n=37; 27.4%) compared to patients undergoing minor hepatectomies (n=31; 16.1%) (p=0.019). Baseline characteristics of patients with major and minor hepatectomies are given in the Supplementary Information. The same holds true for

doi: 10.4172/2325-9612.1000136

non-specific complications that were seen in 36 patients (26.7%) receiving a major hepatectomy and 20 patients (10.4%) after minor hepatectomy (*p*<0.001) (Table 2) (Supplementary Information). Liver failure was documented in 11 of the patients (3.4%). Most of the cases occurred after major hepatectomy (n=8; 5.9%), only three patients (1.6%) with minor hepatectomy had liver failure. However, this result was not significant. Mortality was also not significantly different. There was a tendency for higher mortality in the group of patients receiving major hepatectomy (7.4% vs. 4.2%). The mean length of stay was 17.7 days in patients receiving major hepatectomy, and 14 days in patients after minor hepatectomy, and this was statistically significant (*p*=0.002) (Table 2).

Multivariate analysis of risk factors for surgical complications

Mean LOS (length of stay) for patients without surgical complications was 13.95 days (SD 9.6) and the mean LOS for patients with surgical complications was 21.46 days (SD 12.8) and this difference was statistically significant (*p*<0.001). Univariate analysis showed that patients with surgical complications had a higher mortality (n=9, 13.2%) than patients without surgical complications (n=9, 3.5%) (*p*=0.004). To identify risk factors for the incidence of surgical complications we performed univariate and multivariate analysis. Univariate analysis showed that ASA classification, INR, amount of blood loss and performed procedures were significant risk factors. However, multivariate analysis only retained blood loss during operation (OR 1.72; *p*<0.044) and ASA classification (OR 1.95; *p*=0.023) as independent risk factors (Table 3).

Multivariate analysis of risk factors for incidence of liver failure

Mean LOS of patients with (23.1 days, SD 19.0) and without (14.2 days, SD 7.2) liver failure was significantly different (*p*<0.001). Patients with liver failure had a high mortality (n=10, 90.9%). Patients without liver failure only had a mortality of 2.5% (n=8) (*p*<0.001). Univariate analysis showed that the ASA classification, presence of cardiac diseases or diabetes mellitus, the Child-Pugh score, an elevated preoperative ASAT value, a low preoperative albumin serum value, and performed procedure were significant risk factors for liver failure. Multivariate analysis showed only significance for ASAT (OR 19.7, *p*=0.03) and Albumin (OR 7.55, *p*=0.039) (Table 4).

Multivariate analysis of risk factors for non-specific complications

Mean LOS for patients without non-specific complications was 13.9 days (SD 7.2), mean LOS for patients with non-specific complications was 23.1 days (SD 18.9) and this difference was statistically significant (*p*<0.001). Patients with non-specific complications had a higher mortality (n=17, 30.4%) than patients without these complications (n=1, 0.4%) (*p*<0.001). Univariate analysis showed that ASA classification, a low preoperative haemoglobin value, an elevated preoperative ASAT value, a low preoperative Albumin value, the performed procedure and amount of blood loss during operation were significantly correlated with incidence of non-specific complications. Multivariate analysis retained the performed procedure (OR 3.6; *p*=0.001), ASAT value (OR 6.7; *p*=0.019), and a low Albumin value prior to operation (OR 3.4; *p*=0.007) as independent risk factors (Table 5).

Multivariate analysis of risk factors for incidence of mortality

Although there was a tendency to a higher mortality in major hepatectomies this was not significant (Table 2). We aimed to analyse predictors for mortality and significant factors in univariate analysis comprised patients` age, ASA classification, diabetes mellitus, Child-Pugh classification, a low preoperative hemoglobin value, a high preoperative ASAT value, a low preoperative Albumin value, and a low preoperative cholinesterase value. The performed procedure was not significantly associated with mortality. Multivariate analysis proofed patients` age (OR 4.57; *p*=0.042), preoperative haemoglobin value (OR 8.7; *p*=0.001), and preoperative ASAT value (OR 18.35; *p*=0.03) as independent risk factors (Table 6).

Discussion

It is known that minor and major hepatectomies show a difference in quantity and quality of complications during the postoperative course [3,4]. In our department two different clinical pathways for both major and minor hepatectomies were implemented. The aim of the present study was to analyse the differences in the postoperative course of the two groups and to possibly identify risk factors associated with morbidity. By analysing such risk factors we hoped to improve perioperative management in the sense of evidence based medicine.

Table 2: Short term results after different minor and major resectional procedures. *P*-values for categorical variables were tested with chi-square test apart from * that were tested with Fisher´s Exact Test. Samples with a continuous measurement were tested with the Mann-Whitney Test.

	n (%)	Surgical complications n (%)	Non-specific complications n (%)	Overall morbidity n (%)	Liver failure n (%)	Mortality n (%)	LOS days (mean ±SD)
Minor hepatectomies	192 (58.7)	31 (16.1)	20 (10.4)	56 (29.2)	3 (1.6)	8 (4.2)	14.0 (8.5)
Major hepatectomies	135 (41.3)	37 (27.4)	36 (26.7)	63 (46.7)	8 (5.9)	10 (7.4)	17.7 (13.0)
p- value		0.019	<0.001	0.001	0.056*	n.s.	0.002
All	327 (100)	68 (20.8)	56 (17.1)	119 (36.4)	11 (3.4)	18 (5.5)	15.5 (10.8)

Table 3: Multivariate analysis of risk factors for the incidence of specific complications (ASA: American Society of Anesthesiologists).

	Patients (n=327)	Complications n (%)	OR	95% CI	
				Lower	Upper
Blood loss					
<1500ml	293	55 (18.8)	1.72	1.01	2.93
>1500ml	34	13 (38.2)			
ASA classification					
1 - 2	214	36 (16.8)	1.95	1.1	3.46
3 - 4	113	32 (28.3)			

doi: 10.4172/2325-9612.1000136

Table 4: Multivariate analysis of risk factors for the incidence of liver failure.

	Patients (n=327)	Complications n (%)	OR	95% CI	
				Lower	Upper
ASAT value					
Normal	278	7 (2.5)	19.7	2.75	141.37
>150 U/l	9	3 (33.3)			
Albumin value					
Normal	232	2 (0.9)	7.55	1.1	51.5
<32 g/dl	39	5 (12.8)			

Table 5: Multivariate analysis of risk factors for the incidence of non-specific complications.

	Patients (n=327)	Complications n (%)	OR	95% CI	
				Lower	Upper
Performed procedure					
Minor	192	20 (10.4)	3.6	1.74	7.46
Major	135	36 (26.7)			
Albumin value					
Normal	232	30 (12.9)	3.39	1.40	8.19
<32 g/dl	39	15 (38.5)			
ASAT value					
Normal	278	46 (16.5)	6.78	1.38	33.45
>150 U/l	9	6 (66.7)			

Table 6: Multivariate analysis of risk factors for the incidence of mortality (ASA: American Society of Anesthesiologists).

	Patients (n=327)	Complications n (%)	OR	95% CI	
				Lower	Upper
Age					
<75	284	12 (4.2)	4.57	1.05	19.78
>75	43	6 (14.0)			
Haemoglobin value					
Normal	234	8 (3.4)	8.72	2.31	32.87
<12 g/dl	72	10 (13.9)			
ASAT value					
Normal	278	14 (5.0)	18.35	2.67	126.1
>150 U/l	9	3 (33.3)			

Between 1998 and 2010 we performed 327 minor or major liver resections in our centre. Overall morbidity in our center was 36.4% and this is in accordance to previous publications [4-7,12,13]. To evaluate the significance of the extent of the operation on the postoperative course we grouped the complications in those that are immanent to hepatic resections and such complications that are not specific for hepatic surgery. We observed and analysed liver failure in isolation. As an objective parameter we also determined the impact of the performed procedure on the length of the hospital stay and mortality.

The present study showed that the performed procedure has indeed a relevant impact on the postoperative course. Major Hepatectomies showed a significantly higher rate of surgical complications, non-specific complications and a significantly longer hospital stay. The complications in major hepatectomies occurred twice as often as in minor hepatectomies and are therefore clinically relevant. Interestingly, mortality and the rate of liver failures were not significantly elevated in major hepatectomies. However, the data support our decision to implement clinical pathways for major and minor hepatectomies.

To find possible additional predictors for each kind of complication we performed a multivariate analysis. We tested different parameters that were shown to be important in previous studies. The dignity of the tumour, however, was not tested as the function of the liver parenchyma seems to be more important. In a first step we tried to identify predictors for the incidence of surgical complications. Univariate and multivariate analysis revealed that the performed procedure was no independent risk factor. However, the ASA classification and the amount of blood loss were significantly correlated with the incidence of surgical complications. These risk factors were already described in previous studies on liver surgery [3,4]. Total blood loss is generally an important parameter for postoperative complications. Because of its predictive value it is included in different risk scores like the POSSUM score [14]. The amount of blood loss might indicate difficult and tasking operations. ASA classification, too, is a known risk factor for complications in general surgery but also in hepatic surgery [3,12,13]. The ASA classification reflects the status of the patient's co-morbidities. Although it is a rather vague and somewhat subjective classification, it seems to be a good and consistent predictive value.

Liver failure is one of the most severe complications after hepatic resection. Its incidence is dependent on the volume of resected liver parenchyma and the functional capacity of the remaining parenchyma. The incidence of liver failure in our patient cohort was 3.1% and this is within the range of previous studies using the new ISGLS definition [15]. Although the incidence of liver failure was low in the present study, this complication had a very high mortality of 90.9%. Of the 22 deaths in our patient cohort, ten were due to liver failure. We could identify a low preoperative albumin value and an elevated ASAT value as independent risk factors for liver failure. We could not find significance for the performed procedure or ASA classification on the incidence of liver failure. However there might be bias, because patients that undergo major hepatectomy are highly selected. Patients with a limited liver function or with co-morbidity will not be elected for major hepatectomy. In this regards, ASAT and albumin might be interesting indicators for a limited liver function in patients that do not have evident liver cirrhosis [5,16]. Advanced cirrhosis was not associated with liver failure in our study and this again indicates a high patient selection. In addition of being a surrogate marker for impaired liver synthesis, a low albumin level might also reflect a poor nutritional status. From other surgical disciplines and especially colorectal surgery, it is known that low albumin levels are associated with a range of postoperative complications [17,18]. It is now consensus that efforts should be made to improve patients' preoperative nutritional status with enteral or, in selected cases, parenteral supplemental nutrition. In colorectal surgery, a conveniently accepted boundary for preoperative albumin levels below which nutritional therapy is recommended is 30 g/dl. This corresponds to our results, which also show an elevated risk of postoperative complications for patients with preoperative albumin levels below this threshold. As a direct consequence of these findings, we have adapted our clinical pathways so that all patients undergo timely preoperative serum albumin ascertainment and, if below 30 g/dl, receive short-term nutritional therapy prior to surgery. This seems particularly relevant for patients with hepatic metastases of upper or lowers gastrointestinal cancers, which have a history undergone major gastrointestinal resections predisposing to malabsorption.

Non-specific complications according to our definition are not directly associated to liver surgery, but can also develop in other surgical procedures. These complications develop during the postoperative course and can prolong the hospital stay significantly. Regarding non-specific complications, we could validate the performed procedure as well as ASAT value and a low albumin value prior to operation as independent risk factors. Patients with major hepatectomies had a significant longer hospital stay and this long stay might be due to these non-specific complications.

It is not clear how ASAT and albumin value influence the incidence of non-specific complications. As already mentioned both parameters correlate with postoperative liver failure. Such an impaired postoperative liver function could prolong the hospital stay and therefore raise the risk of developing complications.

Mortality in the observed group of patients was 5.5% and this seems to be higher than some previous studies reported [3-5,19]. We already mentioned that the performed procedure was not significantly correlated with mortality and this was validated by multivariate analysis. We found that patients\` age, an elevated pre-operative ASAT value and a preoperative haemoglobin value below 12 g/dl to be independent risk factors for mortality. Especially the latter is an interesting finding, as a low preoperative haemoglobin value can be controlled in the perioperative management. The role of patients' age is not clear. Previous studies showed heterogeneous results concerning the influence on age on the incidence of complications [3-5,19]. However, the studies that could not show an influence of patients´ age had a relatively low mean age between 52 and 55 years [3,4]. The study that could proof an influence of age had a relatively higher mean age of 59 years and this is also true for our patient cohort that had a mean age of 62 years [5].

In conclusion, major hepatectomies have a higher surgical and non-surgical morbidity compared to minor hepatectomies. This is mirrored in a prolonged hospital stay. We found additional predictors for morbidity. Surgical complications were influenced by intra-operative blood loss and ASA classification. Both factors seem not amenable to interventions. The preoperative laboratory values ASAT and albumin had a significant correlation to liver failure and non-specific complications. While the albumin value could be improved by enteral or parenteral nutrition ASAT can hardly be improved. However, the latter should be considered in the perioperative management especially in patient that show other risk factors because patients with elevated ASAT prior to operation also have a higher mortality.

Mortality is also elevated in aged patients and patients with low preoperative haemoglobin levels. The haemoglobin value is potentially amenable to preoperative intervention.

Surgeons should be aware of the impact of the identified risk factors, which could influence the postoperative course. Our data suggests that patients undergoing liver resections are already highly selected, and the identified factors should only be used on an individual level.

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