

# Low Surgical Morbidity and Mortality After Fast-Track Liver Surgery for Colorectal Liver Metastases: A Study of Complications in a High-Volume Centre

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## Research article

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# Abstract

## Background

For colorectal liver metastases, surgery is a high-risk procedure due to perioperative morbidity. The objective was to assess complications after fast-track liver surgery for colorectal liver metastases.

## Methods

All patients were treated according to the same fast-track programme. Complications were graded according to the Clavien-Dindo classification for patients undergoing surgery from 2013 to 2015. Correlation between complications and length of stay was analysed by multivariate linear regression.

## Results

564 patient cases were included of which three patients died within 3 months (0.53%, 95% CI: 0.17-1.64%). Complications were common with Grade 2 in 167 patients (30%) and  $\geq$ Grade 3a in 93 (16%). Patients without complications had a mean length of stay of 4.1 days, which increased with complications: 1.4 days (95% CI: 1.3 – 1.5) for Grade 2, 1.7 days (1.5 – 2.0) for Grade 3a, 2.3 days (1.7 – 3.0) for Grade 3b, 2.6 days (1.6 – 4.2) for Grade 4a, and 2.9 days (2.8 – 3.1) for Grade 4b. Following were associated with increased length of stay: complication severity grade, liver insufficiency, ascites, and biliary, cardiopulmonary, and infectious complications.

## Conclusions

Complications after liver surgery for colorectal liver metastases, in a high-volume centre, were associated with low mortality, few severe complications, and short but increased length of stay.

## Introduction

The surgical approach to colorectal liver metastases (CRLM) has become increasingly aggressive, resulting in more patients as candidates for resection, without hampering the survival rate<sup>1-4</sup>. For patients with resectable disease, five-year survival has improved significantly during the last few decades, and is currently reported as high as 50%<sup>5-10</sup>. Due to improved surgical techniques and downstaging neoadjuvant oncological therapies, extensive surgery for advanced metastatic disease is now an option<sup>10-12</sup>.

Complications after liver resection are common, occurring in 4 to 48% of cases, depending on tumour type, extent of resection, and how complications are assessed<sup>13-23</sup>. Furthermore, complications are associated with impaired long-term outcomes<sup>5,24,25</sup>.

The Clavien-Dindo classification of post-surgery complications is widely accepted and validated<sup>26,27</sup>. However, complications in patients undergoing resection for CRLM have yet to be described sufficiently,

according to type, incidence, severity, risk factors, impact on survival, and length of hospital stay. In addition, patients resected for CRLM may differ from patients undergoing liver resection, with respect to type of resection, chemotherapy, and comorbidity.

We hypothesised that patients undergoing fast-track liver resection for CRLM had few severe complications and low mortality, and that complications after liver resection led to increased length of stay. This would be assessed in a large homogenous cohort treated in a validated, standardised fast-track surgery setting<sup>28</sup>.

The aim of this study was to assess incidence, type, and severity of postoperative complications, as well as impact on length of stay, with short-term being 6 months mortality after liver resection for CRLM in a fast-track setting. Furthermore, risk factors of severe complications were similarly investigated.

## Methods

### Study design and patient selection

This retrospective single-centre cohort study included patients who underwent liver resection for CRLM with the Department of Surgery and Transplantation, Rigshospitalet, Copenhagen University Hospital, Denmark (between 1 January 2013 and 31 December 2015). All patients were evaluated for resectability by a multidisciplinary team to determine the best possible treatment option.

For patients entered as cases, some patients then underwent multiple liver resections.

The inclusion criteria were: CRLM treated with liver resection or open/laparoscopic radiofrequency ablation (RFA), and age  $\geq 18$  years. Exclusion criteria were: combined primary colorectal resection and liver resection, other procedures in addition to liver resection (except ventral hernia repair), unresectable disease, and percutaneous RFA.

Patients were identified in the hospital surgery management system (Orbit, EVRY Healthcare Systems AB, Malmö, Sweden) with a search on all liver resection procedure codes, according to the ICD-10 codes. After the initial search, all cases were reviewed for inclusion.

This study was reported according to the “STrengthening the Reporting of OBservational studies in Epidemiology” (STROBE) statement<sup>29</sup>.

### Fast-track programme

All patients were treated according to a previously described fast-track program, with a consistent surgical approach<sup>28</sup>. The standard perioperative care principles in the fast-track programme is multimodal and includes: standardized analgesic regime with epidural, removal of nasogastric tube after surgery, removing abdominal drain and urine catheter, laxatives and early mobilization. The programme is modified marginally according to laparoscopic, minor and major resection.

## **Surgical procedure**

All resections were done according to international standards favouring oncological results, with a parenchymal-sparing liver surgery philosophy. RFA were only done when resection was not feasible either due to comorbidity or technical difficulties. Every operation report was manually evaluated to ensure correct coding. We registered the number of segments resected, the number of local resections, and the number of RFAs. Furthermore, extrahepatic resections, two-stage procedures, and open or laparoscopic approaches were registered. All questionable cases were reviewed by two researchers to ensure consistency.

## **Complications**

Complications were graded according to the Clavien-Dindo classification<sup>26</sup>. Only complications Grade 2 or higher, occurring within 30 days of surgery, were registered. Grade 1 complications were not recorded, as the normal postoperative course definition is highly variable between centres. Each complication was described and categorised post hoc. Two-stage procedures were treated as distinct cases with separate complications.

## **Data collection**

All data were collected retrospectively in 2017, using Research Electronic Data Capture (REDCap), in which all data were stored on a case level<sup>30</sup>.

Basic data were extracted from the surgical management system and imported into REDCap. These included age, gender, and surgery time. Preoperative data collected from patient records included: the American Society of Anaesthesiologists (ASA) score, tumour type and previous liver resection. Two reviewers collected postoperative data from patient records, which involved grading of complications and length of hospital stay (from day of surgery to discharge). The method for grading complications was validated in the first 100 cases to achieve consensus. Mortality was assessed using the National Patient Register, thereby ensuring complete follow-up.

## **Statistical analysis**

The study size was determined by the number of eligible procedures in the period; pre hoc power calculation was not done. Cases with missing data were excluded from analysis. General characteristics were described as mean with standard deviation (SD) for continuous variables and number with percentage for categorical variables. Complications were reported as the most severe complication grade, as well as the number of complications per case. The complication categories and severity grades were described. The statistical analysis was not independent and was therefore corrected using a clustered effect.

To describe the survival rate, Kaplan Meier survival estimates were performed. The impact of complications on mortality was analysed by Cox regression, with cases entered at the time of liver

resection and clustered by ID.

To assess risk factors for Grade 3a or more severe complication, a univariate logistic regression was done. Significant variables, with a P-value < 0.1 in the univariate analysis, were assessed in a stepwise multivariate model. Complication impact on the length of stay (natural logarithm transformed) was analysed with linear regressions and a multivariate backwards stepwise model. Logistic regression with a stepwise model was done to describe differences in type of complication between major and minor hepatectomy. A P-value of 0.05 or less was considered significant. Statistical analysis was done in Stata (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX, USA: StataCorp LP).

## Ethics

The study was approved by the Danish Patient Safety Authority (Case Number: 3-3013-1881/1/, Reference: BELK) and by the Danish Data Protection Agency. All data in REDCap were anonymised and only the investigators had access to the patient identification key.

## Results

### Patient characteristics

In total, 957 cases were initially extracted based on procedure codes from the hospital's surgery database. This study included 564 procedures for 462 patients, of which 373 had one, 77 had two, 11 had three, and one had four resections in the study period. No patients were lost to follow-up at six months, with the mean follow-up at 182 days. The total follow-up was 102.492 days.

General characteristics are described in **Table 1**. Male gender was prominent (63%), and mean age at surgery was 67 years (SD 10). Local resection alone or combined with RFA was done in 274 (48%) cases. RFA was the only treatment in 34 (6%) of cases.

### Complications

Overall morbidity ( $\geq$  Grade 2) within 30 days of surgery occurred in 260 cases (46%). **Figure 1** describes complication grades further, most notably 93 cases (16%) had a complication of Grade 3 or higher. More than half, 304 (54%) cases, had no complications, 157 (28%) had one, 58 (10%) had two, 28 (5%) had three, and 17 (3%) had four or more. All complications were categorised in **Table 2**. Wound dehiscence occurred in 18 (3%) cases. A complete list of complications, and their categorisation, is shown in **Supplemental Table 1**.

### Risk factors for severe complications

Complications of  $\geq$  Grade 3a were considered severe, and risk factors associated with these are listed in **Table 3**. Cases were stratified by major resection with  $\geq$  3 segments, 134 (24%) cases; resection of three or more segments was associated with severe complications.

Severe complication risk factors in the multivariate model were male gender (OR 2.35, 95% CI: 1.37 - 4.04, P = 0.002), surgery duration (OR 1.12 per 30 minutes, 95% CI: 1.01 - 1.24, P = 0.04), and major resection (OR 2.37, 95% CI: 1.41 - 3.98, P = 0.001). Three or more liver resections was nonsignificant (OR 1.83, 95% CI: 0.83 - 4.02, P = 0.1).

### **Impact on length of hospital stay**

Patients without any complications had a mean length of stay of 4.1 days, which increased with complications: 1.4 days (95% CI: 1.3 – 1.5) for Grade 2, 1.7 days (1.5 – 2.0) for Grade 3a, 2.3 days (95% CI: 1.7 – 3.0) for Grade 3b, 2.6 days (95% CI: 1.6 – 4.2) for Grade 4a, and 2.9 days (95% CI: 2.8 – 3.1) for Grade 4b. Only 20% of patients had a length of  $\geq 6$  days. Complications were associated with increased length of stay (**Table 4**). Following were associated with increased length of stay in the multivariate model: highest complication grade, infections, biliary and cardiopulmonary complications, liver insufficiency, and ascites. Notably, postoperative bleeding was not significantly associated with length of stay, and occurred in 7 cases (1.6%), of which one was Grade 3b.

### **Predictor of short-term survival**

The study includes a total of 564 cases. Three patients died within three months (mortality rate 0.5%, 95% CI: 0.2-1.6%) and ten patients died within six months (mortality rate 1.6%, 95% CI: 0.8-3.0%). Two deaths may be attributed to surgery: one was caused by thrombosis of the superior mesenteric artery (two days after surgery) and one by biliary leak (120 days after surgery). One died from cardiac decompensation (day 26). Three patients died from chemotherapy infections and multi-organ failure (days 53, 114, and 177). One patient died of sudden cardiac arrest at home (day 115). Cause of death was unknown in the last three cases (days 155, 165, and 183).

Complication Grade 3a or higher were not significantly associated with mortality (Hazard Ratio (HR) 3.46, 95% CI: 0.90 - 13.32, P = 0.07), while neither involved a number of complications (HR 1.33, 95% CI: 0.95 - 1.86, P = 0.1).

### **Difference in complications between major and minor liver surgery**

Comparison of complications between cases requiring major hepatectomy or not were analysed (**Supplemental Table 2**). In a multivariate model, cases who required major surgery had significantly more and severe complications, and the incidence of liver insufficiency, ascites, wound complications, and other surgical complications were higher.

## **Discussion**

In this study of fast-track colorectal liver metastasis surgery in a high-volume centre, the three months mortality rate was only 0.53%, and  $\geq$  Grade 3a complications occurred after 16% of the procedures. Overall complications occurred after 46% of procedures. Infections followed by liver insufficiency and wound complications were the most common. Biliary and bleeding complications were rare, but occurred

in 4 and 1% of cases. Complications led to increased length of stay, including severity grade, infections, biliary and cardiopulmonary complications, and liver insufficiency. Complications did not increase the risk of dying in this study, however only three patients died within three months. We found that male gender, duration of surgery, and major hepatectomy were independently associated with increased risk of severe complications.

The Clavien-Dindo classification is a concise and validated method, which makes it an excellent registry tool, as lack of quality may be difficult to assess if not collected in a standardised manner, based on the intervention. However, focus on intervention, rather than type of complication may limit the clinical impact. To improve treatment, quality of care and decreased length of stay are important for detailed knowledge of each complication, preferably to be prospectively and continuously evaluated. Fast-track liver resection is a successful strategy to lower length of stay<sup>31</sup>. We established the precise type of complications after liver resection for CRLM, which will be used to improve the fast-track strategy.

Improving treatment outcomes after liver resection for CRLM require benchmarking between centres, despite different thresholds for interventions when complications occur. In other studies, the overall complication rate was 20 to 42% and severe complications was found in approximately 10 to 20% of cases, but not all cases were CRLM<sup>5,32-34</sup>. Mortality after liver resection for CRLM was rare, but the rate varied considerably between centres from 1.6 to 7%<sup>5,33,35,36</sup>. The results presented in this study were comparable to other large centres. Previous publications on fast-track liver resection from our institution showed similar complication and mortality, as reported in this study<sup>28,31</sup>. This study highlights the safety of fast-track liver surgery.

The results presented illustrate that complications that can be considered medical and surgical increase the length of stay, such as pneumonia and biliary leak. This emphasises that surgeons must improve the care of patients both prior to and after surgery. A focus on decreasing general infections as well as cardiopulmonary infections, and preventing liver insufficiency will increase quality of care and could further decrease length of stay. These complications may suggest nonadherence to standard of care, which in this case was a fast-track program. Novel methods to predict the postoperative remnant liver function using hepatobiliary scintigraphy or other techniques for patients undergoing major liver resection can identify those at an increased risk of liver insufficiency. Surgical complications occurred as wound complications in 58 cases (10%), biliary complications in 25 (4%), other surgical issues in 8 (1%), and bleeding in 7 (1%), with a total of 88 (16%) cases. It is equally important to understand and improve these complications.

Risk factors for complications identified in our study were not surprisingly male gender, surgery duration, and major hepatectomy<sup>13,34</sup>. However, these risk factors were difficult to modify, without potentially compromising the optimal oncological resection. Other studies suggested that elevated postoperative bilirubin, aspartate aminotransferase, resection beyond the liver, ASA score and indication are associated with complications<sup>13,34,37</sup>. However, risk factors may reflect liver-related comorbidity or the extensiveness

of surgery. ASA score was not associated with complications in our study. Other risk factors may contribute to increased risk of complications, such as parenchymal status of the liver<sup>38</sup>.

The study was limited by its retrospective nature. The correlation between complications and mortality could not be evaluated sufficiently, as very few cases died. Readmission rates were not available, as patients may have been hospitalized outside our hospital, but our overall readmission rate was between 15 and 19% during this period. Compared to other large studies, this study has a lower rate of major hepatectomies, but was also more recent with a parenchymal sparing strategy. Grade 1 complications were not included, as the normal postoperative course is wide-term and the definition may vary between centres due to the variation in standard of care. Many potential risk factors for complications could not be investigated in our study setting, such as comorbidity, neoadjuvant chemotherapy, and functional liver capacity, etc.

Studies conducted after this study period have shown that laparoscopic liver surgery may have advantages compared to open surgery by lowering complication rates and length of stay<sup>39</sup>. However, in our study the length of stay was 4 days with the majority of patients undergoing open surgery similar to large cohorts undergoing laparoscopic surgery<sup>40</sup>. The results found in this study of patients undergoing fast-track liver surgery is applicable in the laparoscopic field as well.

This material includes one of the largest on resection of colorectal liver metastases, from a modern high-volume centre for three years, using standardised surgical techniques and a fast-track approach in all patients as the standard of care. Other large studies on liver resection for CRLM were conducted for longer periods, increasing the risk of bias. We had no missing data on surgery or complications due to electronic medical records.

## **Conclusion**

In conclusion, fast-track liver surgery with the majority done as open cases, carries a low mortality and severe morbidity rate, also the length of stay is short. However, complications increase the length of stay and in this study, we have identified the specific complications which warrants a focus to improve outcome after liver surgery.

## **Declarations**

### **Ethics approval**

The study was approved by the Danish Patient Safety Authority (Case Number: 3-3013-1881/1/, Reference: BELK) and by the Danish Data Protection Agency.

### **Consent for publication**

Not applicable.

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request according to the Danish law on Data Protection of healthcare data.

## Competing interests

The authors have no competing interests.

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## Authors' contributions

Charlotte Egeland contributed to project design, data collection, analysis and manuscript writing.

Andreas Arendtsen Rostved contributed to project design, data collection, analysis and manuscript writing.

Nicolai Aagaard Schultz contributed to project design and manuscript reviewing.

Hans-Christian Pommergaard contributed to analysis and manuscript reviewing.

Thomas Røjkjær Daugaard contributed to data collection and manuscript reviewing.

Line Buch Thøfner contributed to data collection and manuscript reviewing.

Jens G. Hillingsø contributed to project design and manuscript reviewing.

Allan Rasmussen contributed to project design and manuscript reviewing.

## Acknowledgement

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## Tables

### Table 1: General characteristics

	Number of cases	
Age at surgery, mean (SD)	564	67 (10)
Male, n (%)	564	353 (63 %)
ASA score	548	
1		49 (9 %)
2		358 (65 %)
3		140 (26 %)
4		1 (0 %)
Liver resection number	564	
1	-	406 (72 %)
2	-	121 (21 %)
3	-	26 (5 %)
4	-	7 (1 %)
5	-	4 (1 %)
Surgery duration minutes, mean (SD)	564	158 (66)
Two-stage, n (%)	564	50 (9 %)
Laparoscopic, n (%)	564	35 (6 %)
Right hepatectomy, n (%)	564	81 (14 %)
Left hepatectomy, n (%)	564	27 (5 %)
S5 and S8 hepatectomy, n (%)	564	5 (1 %)
S6 and S7 hepatectomy, n (%)	564	18 (3 %)
S2 and S3 hepatectomy, n (%)	564	25 (4 %)
One segment, n (%)	564	61 (11 %)
Other two segments, n (%)	564	12 (2 %)
Other three segments or more, n (%)	564	26 (5 %)
Local resection only, n (%)	564	274 (48 %)
One local resection, n (%)	564	142 (52 %)
Two local resections, n (%)	564	70 (26 %)
Three local resections, n (%)	564	31 (11 %)

Four or more local resection, n (%)	564	31 (11 %)
Only RFA, n (%)	564	34 (6 %)
Extrahepatic resection, n (%)	564	39 (7 %)
Length of stay, median (IQR)	539	4 (3-6)

General characteristics of the population. Length of stay is defined as day of surgery to discharge. N, number. RFA, radio-frequency ablation. ASA, American Society of Anaesthesiologists score. IQR, interquartile range. S, segment.

## Table 2: Description of complications

	Total	Grade 2	Grade 3a	Grade 3b	Grade 4a	Grade 4b	Grade 5
Infection, n (%)	95 (17%)	92 (97%)	-	1 (1%)	2 (2%)	-	-
Biliary, n (%)	25 (4%)	2 (8%)	19 (76%)	4 (16%)	-	-	-
Post-operative bleeding, n (%)	7 (1%)	4 (57%)	2 (29%)	1 (14%)	-	-	-
Cardio-pulmonary, n (%)	29 (5%)	14 (48%)	11 (38%)	-	4 (14%)	-	-
Liver insufficiency, n (%)	59 (10%)	57 (97%)	1 (2%)	-	-	1 (2%)	-
Anemia, n (%)	44 (8%)	44 (100%)	-	-	-	-	-
Gastrointestinal, n (%)	48 (9%)	48 (100%)	-	-	-	-	-
Wound, n (%)	58 (10%)	6 (10%)	16 (28%)	36 (62%)	-	-	-
Ascites, n (%)	11 (2%)	8 (73%)	2 (18%)	1 (9%)	-	-	-
Other surgical, n (%)	8 (1%)	-	1 (13%)	6 (75%)	-	-	1 (13%)
Other medical, n (%)	34 (6%)	30 (88%)	4 (12%)	-	-	-	-

Description of complications by total and each grade in numbers and percent. N, number.

## **Table 3: Risk factors for severe complications**

	Univariate		Multivariate	
	OR for ≥Grade 3a (95 % CI)	P-value	OR for ≥Grade 3a (95 % CI)	P-value
Age at surgery per 10 year	1.1 (0.9 - 1.4)	0.161		
Male	2.5 (1.5 - 4.2)	<b>0.001</b>	2.3 (1.4 - 4.0)	<b>0.002</b>
ASA				
1	Ref	Ref		
2	1.1 (0.5 - 2.6)	0.808		
3 or more	1.5 (0.6 - 3.7)	0.394		
Liver surgery number			1.8 (0.8 - 4.0)	0.135
One, n (%)	Ref	Ref		
Two, n (%)	1.1 (0.6 - 1.9)	0.790		
Three or more, n (%)	2.0 (0.9 - 4.3)	0.066		
Surgery duration per 30 minutes			1.1 (1.0 - 1.2)	<b>0.038</b>
Laparoscopic	NA	NA		
Number of local resection				
One	Ref			
Two	0.4 (0.1 - 1.1)	0.079		
Three	0.4 (0.1 - 1.9)	0.260		
Four or more	1.3 (0.5 - 3.4)	0.541		
Type of surgery				
Local resection only			Ref	Ref
4 or more segments	3.4 (1.9 - 6.0)	<b>&lt;0.001</b>		
3 segments	3.8 (1.7 - 8.7)	<b>0.001</b>		
2 segments	1.1 (0.5 - 2.7)	0.800		
1 segment	1.3 (0.6 - 3.1)	0.540		
RFA only	2.2 (0.9 - 5.1)	0.080		
Local resection 4 or more	1.8 (0.7 - 4.5)	0.190		
Extrahepatic resection	0.6 (0.2 - 1.6)	0.286		

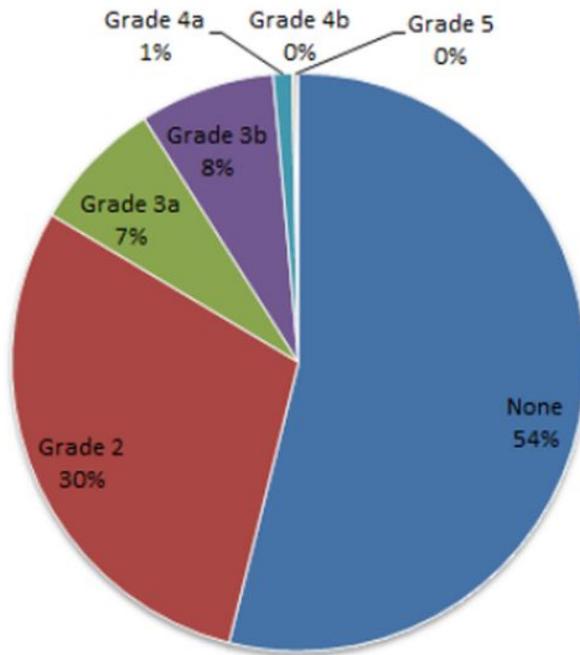
To analyse risk factors for severe complications ( $\geq$ Grade 3a) univariate and multivariate logistic regression models were done. Major resection were comprised from the results of the univariate model, thus were other types of surgery not included in the multivariate model. NA (non-applicable) is used as there were no severe complications. OR, odds ratio. N, number. RFA, radio-frequency ablation. ASA, American Society of Anaesthesiologists score.

## Table 4: Correlation between complications and length of stay

Complication	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
<b>Number of complications</b>	1.3 (1.3-1.4)	<0.001		
<b>Highest complication per increase</b>	1.2 (1.2-1.3)	<0.001	1.1 (1.1-1.1)	<0.001
<b>Type of complication</b>				
Infection	1.5 (1.3-1.8)	<0.001	1.2 (1.1-1.4)	0.005
Biliary	2.7 (1.9-3.8)	<0.001	1.9 (1.4-2.6)	<0.001
Post-operative bleeding	1.3 (0.7-2.6)	0.381		
Cardio-pulmonary	2.0 (1.5-2.6)	<0.001	1.3	0.016
Liver insufficiency	1.9 (1.6-2.3)	<0.001	1.3 (1.1-1.5)	<0.001
Anemia	1.5 (1.3-1.8)	<0.001	1.1 (1.0-1.3)	0.064
Gastrointestinal	1.4 (1.1-1.6)	0.001		
Wound	1.4 (1.1-1.7)	0.001		
Ascites	2.9 (2.2-4.0)	<0.001	1.9 (1.5-2.3)	<0.001
Other surgical	2.2 (1.1-4.3)	0.020		
Other medical	1.5 (1.2-1.8)	0.002		

To analyse the correlation between complications and length of stay uni- and multivariate linear regressions were done. Length of stay was defined as time from surgery to discharge. OR, odds ratio.

## Figures



Highest grade complication	
None	304 (54 %)
Grade 2	167 (30 %)
Grade 3a	42 (7 %)
Grade 3b	43 (8 %)
Grade 4a	6 (1 %)
Grade 4b	1 (0 %)
Grade 5	1 (0 %)

**Figure 1**

Distribution of highest grade complication Highest grade complication after liver surgery for colorectal liver metastases according to Clavien-Dindo classification.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [09.10.20SupplementalTables.docx](#)