Differential significance of early surgical complications for acute and long-term recurrence-free survival following surgical resection of hepatocellular carcinoma: do comorbidities play a role?

Andrej Khandoga[a], Moritz Drefs[a], Markus Schoenberg[a], Tobias Schiergens[a], Katharina Frenes[a], Mark op den Winkel[b], Christoph Trumm[c], Martin K. Angele[a], Markus Guba[a], Jens Werner[a] and Markus Rentsch[a]

Background Postoperative complications of Clavien–Dindo grade 3 or more are of prognostic significance in patients who undergo liver resection for hepatocellular carcinoma (HCC). However, perioperative mortality and patient comorbidities represent relevant factors that interfere with postoperative long-term survival. To clarify this, a retrospective single-center study was carried out.

Patients and methods Patient data were prospectively collected in a continuously updated liver resection database. Overall, 184 consecutive patients who underwent liver resection for HCC with a curative intent between March 2003 and December 2013 were selected for the study. The patients were assigned to two groups according to the presence or absence of postoperative complications. Pre-existing comorbidities, perioperative mortality, surgical outcome, and long-term survival data were analyzed.

Results Postoperative complications requiring revision surgery were identified in 17.4% of the patients. The in-house mortality rate was 4.8%. Compared with patients without complications, patients with complications were older and had significantly more pre-existing comorbidities, more advanced tumors, more intrahepatic metastasis, longer operation times, greater blood loss, and more extensive resections. The overall 5-year survival rates were 40.1 and 52.5% in patients with or without postoperative complications, respectively. The corresponding 5-year recurrence-free survival rates were 46.3 and 46.7% (perioperative mortality excluded). Multivariate analysis showed that elevation of the Charlson Comorbidity Index was associated independently with decreased overall and recurrence-free survival.

Conclusion In patients with HCC, posthepatectomy complications are confirmed to have predictive value. However, closer analysis and exclusion of perioperative mortality effects show an independent impact of pre-existing comorbidities on long-term overall und recurrence-free survival. Eur J Gastroenterol Hepatol 29:1045–1053

Introduction

Surgical resection represents one of the curative treatment options for hepatocellular carcinoma (HCC) [1,2]. Multidisciplinary treatment of HCC, frequently in association with hepatic surgery, has significantly improved the survival rate of HCC patients [3,4]. However, a cure is still difficult to achieve because recurrence rates of HCC remain high [5,6]. Nevertheless, despite improved surgical techniques and perioperative management, mortality and morbidity rates following hepatectomy for HCC remain the highest among abdominal surgical procedures [7–10]. Recently, the adverse effects of postoperative complications on long-term survival after resection were determined in HCC patients in studies from Japan and Hong Kong [11–14]. In these studies, the overall perioperative complications impacted survival. However, perioperative complications were inconsistently defined and the significant effects on recurrence-free survival were repealed when different grades of the Clavien–Dindo classification were analyzed separately [13,14]. Furthermore, perioperative complications may have a strong correlation with pre-existing comorbidities [15,16]. Other studies identified age and perioperative blood loss as independent risk factors [17,18], which have been indirectly linked to recurrence of malignancy in various cancers [19]. Beyond this, the pathogenesis of HCC in the Asian population might not reflect the common HCC disease triggers in Europe [20,21]. Whereas in Asia, infection ratios with hepatitis B or C in patients with HCC uniformly exceed 50%, nutritive risk factors, including alcohol intake, may represent the main triggers for cirrhosis and HCC

European Journal of Gastroenterology & Hepatology 2017, 29:1045–1053

Keywords: comorbidity, liver oncology, liver resection, postoperative complications, recurrence

Departments of [a]General, Visceral, Transplant and Vascular Surgery, [b]Internal Medicine II and [c]Institute of Radiology, University of Munich, Munich, Germany

Correspondence to Markus Rentsch, MD, Department of General, Visceral, Transplant, and Vascular Surgery, University of Munich, Marchioninistrasse 15, 81377 Munich, Germany

Tel: +49 894 4000; fax: +49 8944 007 8894; e-mail: markus.rentsch@med.uni-muenchen.de

Received 31 January 2017 **Accepted** 2 May 2017

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website (*www.eurojgh.com*).

particularly in Europe. Nutritional adverse effects may not only exclusively affect the liver but also other organ systems, thus increasing the general perioperative risk [22,23]. This may have long-term implications as these differences in pathogenesis may result in regional disparities in terms of comorbidity in patients requiring surgery for HCC.

We therefore evaluated the risk of perioperative complications in relation to hepatic surgery for HCC with a special focus on preoperative comorbidities and the impact of both factors on long-term general and cancer-free survival. Different from previous studies, the effects of complications in general, complication grades 3 and 4, and only grade 4 were analyzed separately. This study provides insights into particular differences in survival and recurrence-free survival in relation to the severity of the complications in a representative Central European surgical center patient population.

Patients and methods

Patient characteristics and preoperative assessment

From January 2003 to December 2012 (10 years), a total of 1396 liver resections were performed at the Department of Surgery, Munich University Hospital, Campus Grosshadern (Munich, Germany). Among these, 184 patients (56 women and 128 men) underwent hepatic resection for HCC, who were all included in this study. The mean age was 63.7 ± 0.9 years (median: 66, range: 16–84 years). Follow-up was continued until June 2016, resulting in a mean follow-up duration of 3.5 years (median: 2.7 years). Curative resection (R0) was defined as complete removal of tumor as defined by pathologic examination. The following clinical variables were assessed: age; sex; BMI; obesity; comorbidity scores (see below); pre-existing cardiac or pulmonary diseases; laboratory parameters: serum α-fetoprotein, creatinine, bilirubin, international normalized ratio, alkaline phosphatase, γ-glutamyl transferase, alanine aminotransferase, aspartate aminotransferase; liver-specific risk factors: hepatitis B and hepatitis C seropositivity, alcohol abuse, steatosis, hepatic steatosis (including nonalcoholic fatty liver disease), liver fibrosis, liver cirrhosis; oncologic prognostic variables: number of lesions, less than one lesion, pTNM stage; perioperative data: type of surgery, duration of surgery, blood loss, liver specimen volume; postoperative complications: complications not related to surgery, hepatic dysfunction, biliary leak, bilioma (without persistent leak), abscess, hemorrhage, bowel obstruction, and septic and infectious complications; and outcome measures: surgical revision, HCC recurrence, overall survival, and recurrence-free survival.

The Charlson Comorbidity Index (CCI, Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A196*; [24]) predicts the 1-year mortality for a patient who may have a range of comorbid conditions, and may represent a more precise estimate of the general health status than the American Society of Anesthesiologists (ASA) classification [25]. The liver-specific risk was quantified by calculation of the Model for End-Stage Liver Disease (MELD) score [26]. As the vast majority of patients had Child Pugh stage A liver cirrhosis (see below), the Child score was not included in any analysis.

Surgical technique and procedures

None of the patients required intraoperative ablation therapy such as ethanol injection or radiofrequency ablation. In general, at our center, local ablation therapy in connection with hepatic resection (therapeutic splitting) is performed using interventional radiology, which was not required among the analyzed cohort.

Assessment of perioperative morbidity and mortality

Postoperative complications within 1 month of hepatectomy included liver-specific complications. The types of complications and frequency are listed in Table 1. Grade 3 hyperbilirubinemia and prolonged prothrombin time/international normalized ratio on postoperative day 5 were defined as liver dysfunction according to the criteria of the International Study Group of Liver Surgery [27].

As the accuracy of the definition of complications has been inconsistent in previous studies and conclusions are not easy to draw in terms of all complications, we grouped postoperative complications into three separate categories corresponding to a stepwise narrowing of the Clavien–Dindo grades of complication.

Besides the general occurrence of complications (corresponding to grades 2–5), those fulfilling the criteria of Clavien grades 3 and 4 complications and the subgroup of patients who needed surgical revision were separately registered and statistically evaluated (Fig. 1). All in-house fatal postoperative clinical courses were classified as grade 5 complications.

Surgical procedures and patient selection

Surgical resection for HCC was considered according to our center's algorithm adopted from the Barcelona Clinic Liver Cancer algorithm for the treatment of HCC [2,28].

Table 1. Overview of postoperative complications

Type of complication	*n*
Liver specific	
Hepatic dysfunction	16
Biliary leak or bilioma	11
Biliary tract stenosis	1
Portal vein thrombosis (partial)	2
Ascites	21
Surgery related/abdominal	
Postoperative hemorrhage	8
Bowel obstruction	12
Bowel perforation	2
Appendicitis	1
Chylus fistula	1
Septic complications	
Abscess	7
Wound infection	10
Unspecific infection/cholangitis/urinary tract infection	12
Pulmonary	
Pneumonia	8
Respiratory insufficiency	7
Pulmonary embolism (hemodynamically irrelevant)	5
Pleural effusion/seropneumothorax	9
Renal dysfunction	7
Cardiac arrhythmia/ myocardial infarction	8/1
Neurological dysfunction	4
Others (nausea, vomiting, diarrhea)	7
Total	173

Note: more than one complication could be registered in each patient; the list does not show the severity of the complications.

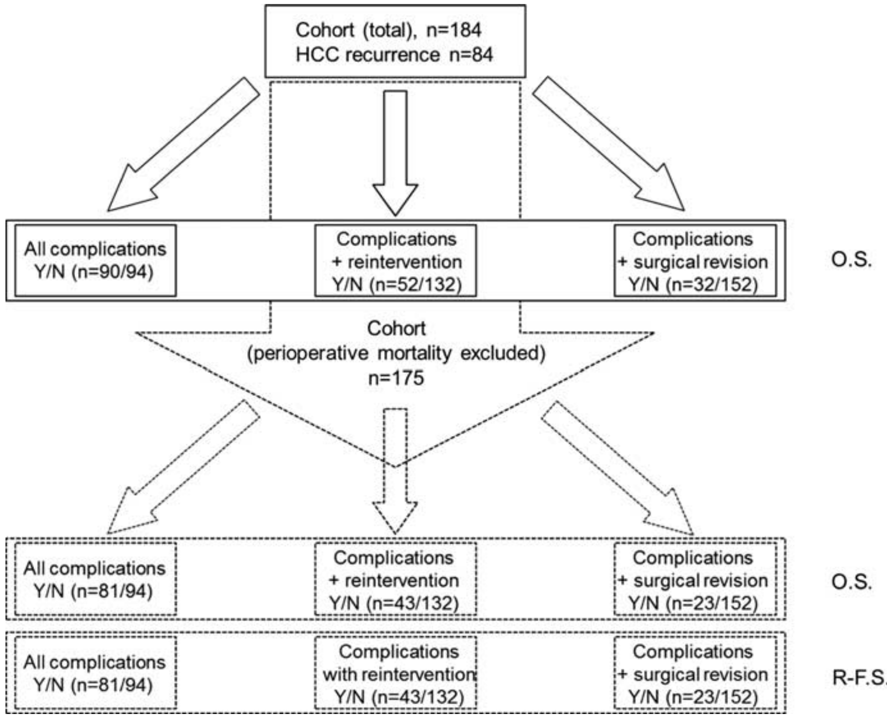

Fig. 1. Study design algorithm. Patients' data were analyzed in two steps after stratification of the different grades of complications: (i) all complications, (ii) complications requiring any reintervention, and (iii) complications requiring revision surgery. First, the overall survival of the complete cohort was analyzed ($n = 184$). Second, overall and recurrence-free survivals were evaluated after elimination of the perioperatively deceased patients ($n = 175$). HCC, hepatocellular carcinoma; N, no; OS, overall survival; R-FC, recurrence-free survival; Y, yes.

In simple terms, technically resectable single tumors (≤ 5 cm) in patients with Child A liver cirrhosis were considered to be surgically removed. Special attention was paid to rule out uncontrollable ascites or bilirubin serum levels above 2 mg/dl before surgery. This rule was slightly modified in the case of individual therapeutic approaches. No special functional tests were performed before surgery. Surgical access was achieved by a right-sided J-shaped incision, followed by slow and gentle hepatic dissection using an ultrasonic dissector with a coagulator (Integra, Plainsboro, New Jersey, USA or Söring, Quickborn, Germany) and systematic ligation of all sizable vessels under close ultrasonographic guidance along the transection line. Intraoperative vascular control was achieved using the Pringle maneuver.

Follow-up and assessment of tumor progression

Every patient undergoing liver surgery at our center is registered in a specially designed database (Filemaker, Santa Clara, California, USA). From this database, all patients with a diagnosis of HCC undergoing surgical therapy were extracted. From the original 195 patients, 11 were excluded from further analysis as the surgical maneuver was interrupted with or without probe excision for various reasons. Patient data are maintained continuously by the documentation department of our clinic. In the years 2013 and 2016, all patients alive received a questionnaire or were interviewed by telephone about their current health status, evidence of tumor recurrence and subsequent diagnostic procedures, and eventually follow-up therapy in the case of recurrence. All data registration was approved by the local ethics committee of the Munich University Hospital.

Statistical analysis

Comparisons between groups were performed using standard univariate tests: Student's *t*-test for analysis of parametric data (after regular rank transformation when indicated by Shapiro–Wilk statistics) and χ^2-test for nonparametric data.

The Kaplan–Meier method and log-rank testing were used to determine differences in survival between the groups (univariate testing). Independent factors increasing the likelihood of revision surgery were estimated using a logistic regression model, including the variables age, sex, liver parenchyma injury (including cirrhosis, fibrosis and steatosis) (yes/no), 'Charlson Comorbidity Index', 'MELD score', 'ASA score', 'BMI', resection volume (>/<500 ml), 'operation time', and 'intraoperative blood loss'.

For the identification of specific risk factors of survival and recurrence-free survival, a Cox proportional hazards model was used, including the variables 'postoperative complication', 'complication Clavien grades 3 and 4', 'surgical revision', 'septic complications', 'Charlson Comorbidity Index', 'MELD score', 'ASA score', 'BMI', and 'intraoperative blood loss', which were entered into the mathematic model using the backward stepwise Wald method. All calculations were carried out using IMB SPSS, version 23.0 (IBM SPSS Inc., Armonk, New York, USA).

Results

Patient characteristics and general data

In our patients, a total of 173 complications of different grades of severity (Clavien–Dindo grades 1–4b) were registered. Postoperative mortality was 4.8% (grade 5 complication). In all, 51 patients had grades 3 and 4 complications. Of these, 20 patients were managed by an endoscopic and/or a radiologic intervention, and 31 (17.4%) required surgical revision (subgroup of grades 3 and 4). The mean time in intensive care was 2.79 ± 0.55 days (median: 1, range: 0–62 days). An overview of the complications is presented in Table 1. Most frequently, postoperative ascites, bowel obstruction, and minor infectious complications were registered; however, these were managed conservatively. From clinical experience, factors specific to hepatic surgery were considered most relevant to the clinical course and the potential need for revision surgery; these include hepatic dysfunction (8.7% of all patients), biliary leak (3.3%), bilioma without leak (2.7%), perihepatic abscess (3.8%), postoperative hemorrhage (3.8%), sepsis and unspecific infections (14.6% each), and small bowel obstruction (6.5%).

In all, 45% of our patients experienced tumor recurrence during the observation period. Time to recurrence was 16.2 ± 1.9 months (range: 1–58.5 months). Of these, 15.2% underwent a second surgery at our center for recurrent HCC. Malignancy-associated death in the observation period occurred in 28.8%.

Besides the risk of surgery and associated factors underlying a complicated course after hepatic surgery, a relevant spectrum of patient-associated comorbidities was noted in our patient cohort. These were indicated by an average ASA score of 2.72 ± 0.04 (median: 3, range: 2–4) and a CCI of 7.2 ± 0.14 (median: 7, range: 3–12). Furthermore, impaired liver function was indicated by a score of 7.72 ± 0.18. The average BMI was 26.5 (mean: 26.3, range: 18–38.6), indicating overweight in a relevant subgroup of our patients. Obesity was registered as a diagnosis in the medical history of 61% of the patients. Liver-specific diagnoses in the patients' medical history with potential alteration of the hepatic tissue and thus increased risk of surgery were alcohol abuse (24%), hepatic steatosis (60.7%), fibrosis or cirrhosis (60.7%), hepatitis B (13%), and hepatitis C (15.8%).

Histopathologic results and perioperative data

A total of 117 HCC were stage I according to the TNM classification, and 28, 33, and six tumors were stage 2, 3, and 4, respectively. A reliable lymph node count was achieved in 104 patients. Of the total, 34 (32.7%) patients were lymph node positive and 31 patients had positive resection margins [21 (11.9%) R1, 10 (5.6%) R2]. R2 situations included macroscopic tumor as nonresectable remnant in vascular proximity or as nonresectable satellite to be treated by a radiologic intervention or radiotherapy. An overview of the types of hepatic resections in the two subgroups of patients with and without complications is shown in Table 2. The mean duration of the surgical procedures was 170.4 ± 5.1 min (range: 25–347 min), with a mean blood loss of 984.2 ± 102.4 ml (0–7500 ml).

Differences in patient characteristics according to grades of complication

An analysis of the perioperative patient characteristics after stratification into the three different comparison models [(i) overall complications (yes/no), (ii) Clavien–Dindo grades 3 and 4 complications (yes/no), and (iii) surgical revision (yes/no)] yielded similar results. However, neither preoperative medical history parameters (i.e. liver parenchyma alteration, obesity) nor clinical chemistry parameters were correlated with the risk of complication as shown in Table 3. The sole exception were serum levels of bilirubin and aspartate aminotransferase, which were uniformly significantly elevated in all subgroups with complications ($P < 0.05$). However, the comparisons (Table 3) clearly showed that patients with complications were older and had higher comorbidities as assessed by the ASA score, the CCI, and the MELD score. It is noteworthy that this difference was equal when the following subgroups were analyzed: all complications, all complications treated with intervention or repeat surgery, and complications requiring surgical revision.

Predictors of postoperative complications

By means of a logistic regression model, predictors of postoperative complications were determined. Significant factors associated with adverse surgical outcome were age at the time of surgery and intraoperative blood loss, which were uniformly associated with an increased probability of overall as well as Clavien–Dindo grades 3 and 4 complications, as well as requirement of surgical revision (Table 4).

Survival following resection

Overall survival following surgical resection of HCC was 68.6% after 1 year, 52.4% after 3 years, and 40.1% after 5 years when patients developed complications. This was a significantly lower survival rate than in those without complications (1 year: 89.7%, 3 years: 69.6%, 5 years: 52.5%) (Fig. 2a). Restriction of the analysis to Clavien–Dindo grades 3 and 4 complications and to complications requiring surgical revision reconfirmed this difference. Corresponding survival rates were 57.2 versus 88.8% (1 year), 45.6 versus 67.8% (3 years), and 42.1 versus 48.7% (5 years) comparing Clavien–Dindo 3 and 4 versus lower grade (0–2) complications (Fig. 2b). When complications requiring surgical revision were compared with all other patients, this difference was even more pronounced [50.0 vs. 85.6% (1 year), 32.7 vs. 66.9% (3 years), and 16.4 vs. 50.0% (5 years); $P < 0.0001$] (Fig. 2c). However, these data showed one important aspect of the survival analysis. Most of the deceased patients in this analysis died in the very early days after surgery or onset of the complication. This led us to analyze the above subgroups after exclusion of perioperatively deceased patients ($n = 9$), which abolished the significant difference in survival between the complication groups and those with no complications in all comparisons; however, a difference by trend remained. The 1-year, 3-year, and 5-year survival was then 77.7, 59.4, and 45.4%, respectively for all complications (Fig. 3a), 70.8, 56.4, and 52.1%, respectively for Clavien–Dindo grades 3 and 4 (Fig. 3b), and 73.7, 48.2, and 24.1%, respectively for surgical revision only (Fig. 3c).

Recurrence-free survival was likewise analyzed without the perioperatively deceased patients (Fig. 4). It was worse in all comparisons; however, no significant differences were noted when analyzing patients with or without postoperative complications by the log-rank test (1 year: 75.6 vs. 79.3%; 3 years: 48.9 vs. 63.2%; 5 years: 46.3 vs. 47.4%).

Table 2. Comparisons of complication according to different grades of severity (and corresponding Clavien –Dindo grading)

	Comparisons of complication according to different grades of severity (and corresponding Clavien–Dindo grading)								
	All complications (corresponding to grades 1–5)			Complications with reintervention (corresponding to grades 3 and 4)			Complications with surgical revision (subgroup of grades 3 and 4)		
Variables	Yes (*n*=90)	No (*n*=94)	*P* value	Yes (*n*=52)	No (*n*=132)	*P* value	Yes (*n*=32)	No (*n*=152)	*P* value
Sex (women/men)	63/27	65/29	1.0	16/36	40/92	1.0	7/25	49/103	0.29
Age (years)	65.6	61.9	0.02	68.3±1.4	63.2±1.3	0.006	69.5±1.3	62.5±1.0	0.01
ASA	2.82±0.04	2.61±0.05	0.003	2.90	2.65	0.003	2.91±0.07	2.68±0.04	0.01
Charlson Index	7.5±0.2	6.8±0.2	0.019	7.7±0.2	7.0±0.17	0.01	7.9±0.28	7.0±0.15	0.02
BMI	26.8±0.4	26.1±0.4	0.25	27.1±0.5	26.1±0.34	0.10	27.1±0.7	26.3±0.3	0.29
MELD	8.2±0.3	7.2±0.2	0.001	8.31±0.42	7.49±0.2	0.02	8.34±0.51	7.6±0.2	0.04
Alcohol consumption	16	8	0.1	7	17	0.55	5	19	1.0
Steatosis	56	55	1.0	35	76	0.11	23	88	0.1
Fibrosis	35	37	1.0	19	53	0.73	12	60	1.0
Cirrhosis	41	39	0.76	25	55	0.51	14	66	1.0
Hepatitis B	12	12	1.0	8	16	0.63	6	18	0.38
Hepatitis C	17	12	0.31	8	21	1	5	24	1.0
Obesity	56	52	0.76	37	71	0.13	23	85	0.23
Creatinine (mg/dl)	1.07±0.03	1.03±0.04	0.068	1.04±0.03	1.06±0.04	0.36	1.07±0.03	1.05 ±0.03	0.13
Bilirubin (mg/dl)	1.13±0.11	0.84±0.07	0.014	1.26±0.2	0.88±0.06	0.002	1.17±0.16	0.95±0.73	0.02
INR	1.09±0.01	1.06±0.01	0.049	1.09±0.01	1.07±0.01	0.11	1.09±0.16	1.07±0.01	0.2
ALAT (mg/dl)	76.8±10.7	56.5±7.5	0.15	76.2±18	62.5±5.4	0.86	94.5±25.4	60.5±4.7	0.88
ASAT (mg/dl)	94.6±14.2	67.1±9.7	0.021	103.2±19.9	73.1±9.1	0.02	117.3±27.5	72.7±8.4	0.04
γ-GT (mg/dl)	167.8±18.7	132.3±13.6	0.15	166.9±24.9	143.5±12.9	0.43	137.5±20.7	152.8±13.5	0.97
AP (mg/dl)	131.0±12.5	112.9±7.4	0.14	126.7±9.2	120.6±9.5	0.17	127.2±12.0	121.3±8.4	0.17
>1 Tumor location	24	19	0.38	14	29	0.56	9	34	0.50
Stage T3/4	21	18	0.71	14	25	0.2	8	31	0.45
N+	17	17	1.0	9	25	0.8	4	30	0.76
R+	18	13	0.32	11	20	0.4	4	27	0.61
AFP elevation (above normal)	33	42	0.62	17	52	1.0	10	59	1.0
Blood loss (ml)	1293±175	681±99	0.02	1401±235.8	814.5±104.5	0.02	1381±285.9	898.3±107.3	0.04
Operation time (min)	182.5±7.7	158.7±6.5	0.02	182±10.3	165.5±5.9	0.08	178.2±13.9	168.7±5.5	0.45
Volume liver specimen (ml)	439.6±50.1	355.9±44.9	0.27	487.8	360.7	0.06	512.4±86.5	372.7±36.3	0.1
HCC recurrence	44	40	0.74	22	62	0.29	10	79	0.04

Note: numbers indicate either the total number of patients or the mean±SEM.
AFP, α-fetoprotein; ALAT, alanine aminotransferase; ALST, aspartate aminotransferase; AP, alkaline phosphatase; ASA, American Society of Anesthesiologists; HCC, hepatocellular carcinoma; INR, international normalized ratio; γ-GT, γ-glutamyl transferase; MELD, Model for End-Stage Liver Disease.
N+, node-positive tumor; R+, tumor-positive resection margin.

Table 3. Overview types of hepatic resection

	n	
Types of resection	With complication	Without complication
Nonanatomic resection (including subsegmentectomies)	34 (1)	32 (8)
Segmentectomy	16	21
Central resection (segments 4/5/8)	5	2
Left lobectomy (segments 2/3)	5	11
Left hemihepatectomy	3	10
Right hemihepatectomy	22	6
Extended right hemihepatectomy	4	4

Table 4. Logistic regression model of predictive factors for postoperative complications

			95% Confidence interval	
Variables	*P*	Exp (*β*)	Lower limit	Upper limit
Liver parenchyma injury	702	0.850	702	1.960
sex	0.583	1.280	0.531	3.087
BMI	0.473	1.036	0.941	1.140
Resection volume <500 ml	0.463	0.714	0.291	1.755
MELD	0.330	1.072	0.932	1.234
Operation time	0.269	1.003	0.998	1.009
Charlson Comorbidity Index	0.225	1.153	0.916	1.450
Age	0.007	1.051	1.013	1.090
Intraoperative blood loss (ml)	0.008	1.000	1.000	1.001

MELD, Model for End-Stage Liver Disease.

Equally, on comparing the cohorts with and without Clavien–Dindo grades 3 and 4 complications, the difference was not significant (64.1 vs. 81.2%; 50.8 vs. 61.6%; and 36. vs. 42.9), which was confirmed by analyzing the groups with or without surgical revision (67.7 vs. 78.2%; 54.1 vs. 59.5%; and 27.1 vs. 42%).

Factors affecting long-term recurrence-free survival

For estimation of independent determinants of long-term survival, a Cox proportional hazards model including the most relevant variables identified in univariate statistics was used. Table 5 shows the results of the analysis carried out after exclusion of perioperatively deceased patients. This model showed the CCI to be a significant factor affecting overall and recurrence-free survival.

It is noteworthy that if the factor age was included as a continuous variable in the statistical model, as opposed to a categorized variable as part of the CCI, it significantly affected long-term overall and recurrence-free survival ($P<0.05$) (Rentsch M, unpublished data).

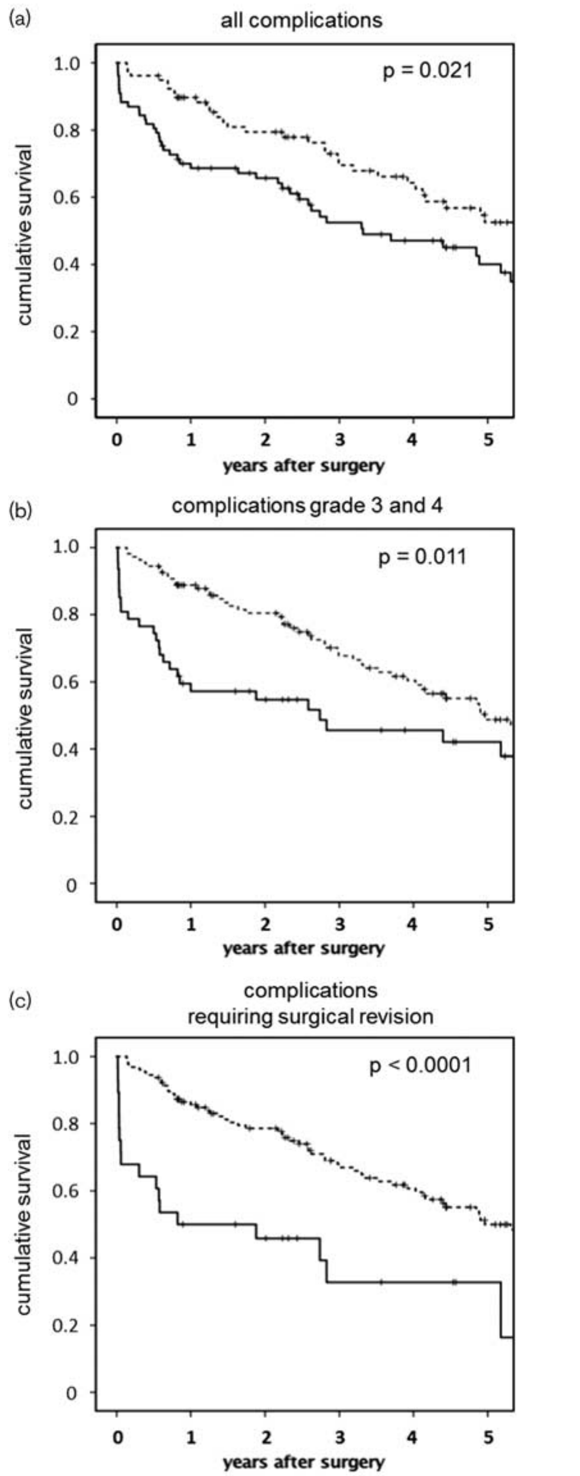

Fig. 2. General survival of the complete cohort: perioperative mortality included. Kaplan–Meier plots of overall survival comparing the groups with or without complications at all (a), with our without complication grades 3 and 4 according to the Clavien–Dindo classification (b), and comparing those requiring revision surgery or not (c). Dashed curve: patients without complications; solid curve: patients with complications.

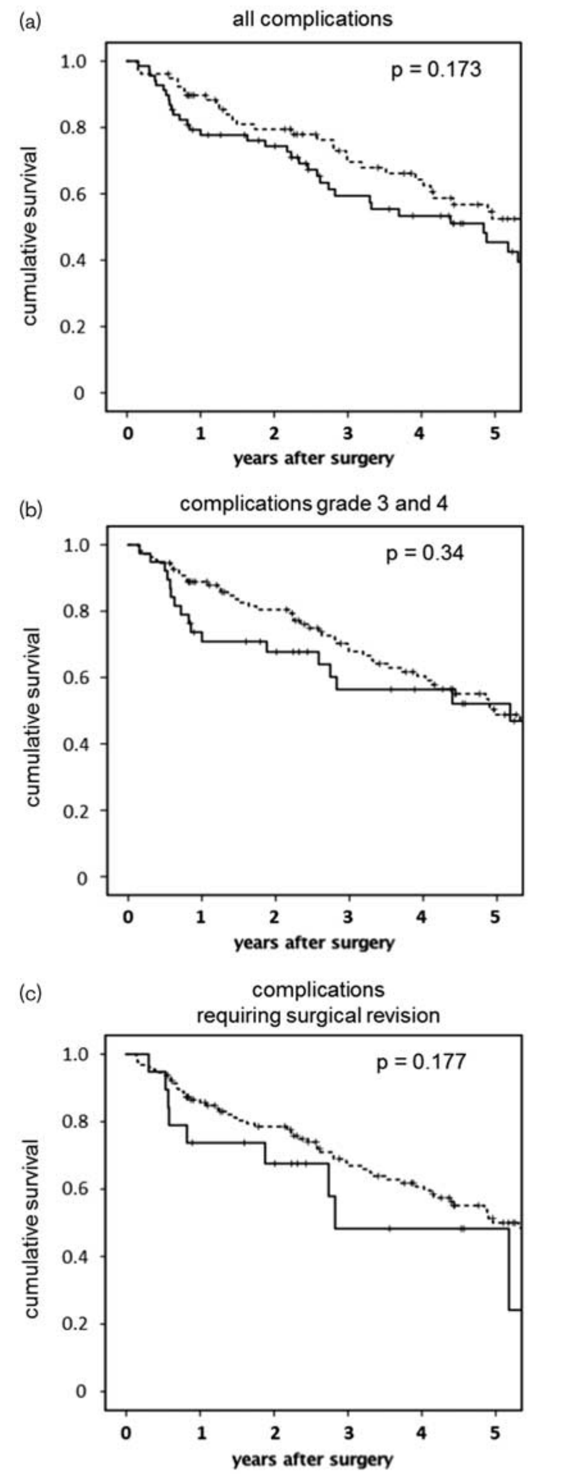

Fig. 3. General survival of the complete cohort: perioperative mortality excluded. Kaplan–Meier plots of overall survival comparing the groups with or without complications at all (a), with our without complication grades 3 and 4 according to the Clavien–Dindo classification (b), and comparing those requiring revision surgery or not (c). Dashed curve: patients without complications; solid curve: patients with complications.

Discussion

The present study investigated the impact of surgical complications on long-term overall as well as recurrence-free survival in a patient cohort with HCC over a 10-year period at a single center. Our study in part confirms previous observations from Japan, which showed a clear correlation between early postoperative complications following hepatectomy and recurrence-free survival for HCC [12–14] in single-center and multicenter analyses. The present study, however, is the first to address the long-term effects of postoperative complications on overall and recurrence-free survival in a Central European cohort.

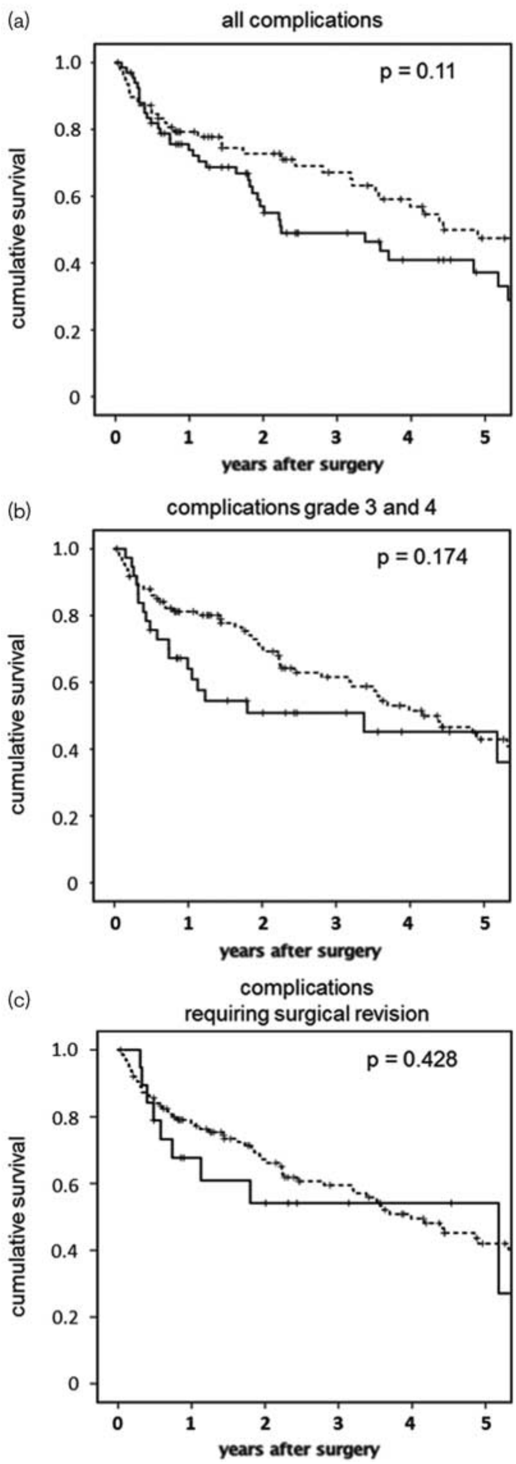

Fig. 4. Recurrence-free survival. Kaplan–Meier plots of recurrence-free survival comparing the groups with or without complications at all (a), with our without complication grades 3 and 4 according to the Clavien–Dindo classification (b), and comparing those requiring revision surgery or not (c). Dashed curve: patients without complications; solid curve: patients with complications.

Besides liver transplantation as the superior form of treatment, surgical therapy represents an accepted curative therapeutic approach to HCC treatment [2,3]. Nevertheless, a substantial ratio of patients in Europe have to be considered for resection instead of transplantation because of the well-known donor organ shortage and patient-sided contraindications for transplantation [1,2]. Despite substantial improvements in liver surgery, patient selection, and preoperative conditioning, and the development of new surgical strategies and techniques [7–10,29], morbidity and mortality remain high. In the present study, a meticulous search for complications was performed on the basis of patients' files, which resulted in an overall complication rate of 48%, similar to other single-center studies [12,13]. At first glance, this rate seems high; however, not all complications may have an impact on survival. Complications Clavien–Dindo grades 3 and 4 occurred in 28%; however, one-third of these complications were managed by a radiologic/endoscopic intervention, whereas 17% required revision surgery. The number of complications Clavien–Dindo grades 3 and 4 in the Japanese multicenter study was 17.1% whereas the two other studies reported a perioperative mortality of 4.5 and 7%, respectively [12–14].

Thus, we analyzed the effects of complications in our cohort using the three different comparison models mentioned above. In doing so, we searched for different effects of the severity of complications on long-term survival. This was motivated by the assumption that complications managed conservatively may be less harmful than those treated by reintervention and/or revision surgery. This idea has been described in the second-hit concept of revision surgery [30,31].

For perioperative data, no considerable difference from previous reports was detected in terms of type of resection, intraoperative blood loss, surgery time, and pathologic criteria [11–14], indicating the reliability of our results.

According to the results of this study, not only postoperative complications are significantly correlated with long-term outcome. Univariate testing also showed significant differences in preoperative risk factors for patient subgroups with and without complications, indicating some impact. Irrespective of the degree of complication (by analyzing all complications, complication grades 3 and 4 according to the Clavien–Dindo classification, and complications requiring repeat surgery), a significant impact of comorbidities and age was notable. This was evident in univariate analyses in all three comparisons, but also using a Cox proportional hazards model, as long as the complete study population was analyzed. To this point, our results are absolutely in line with the studies from Japan. However, a long-term observation seems to make more sense if the effect of early, perioperative mortality is eliminated as these patients have no influence on long-term survival or disease recurrence. However, the mentioned studies included this subgroup of patients (Clavien–Dindo grade 5), which is shown either by separating the patient subgroup in a Kaplan–Meier subanalysis [14] or by the drop of the survival curves within month 0 and the missing significance when grade 5 complications are eliminated [13].

By elimination of the perioperative mortality from the analysis in our study for all calculations, the significant effect of 'postoperative complications' on long-term overall and recurrence-free survival existed as a visible trend in Kaplan–Meier plots; however, it failed to qualify as an independent predictor of survival.

Instead, preoperative comorbidities showed increased capacity as potential outcome predictors. We identified the CCI as a significant factor decreasing survival following liver resection in an HCC cohort. The relevance of this index [32] as a prognostic factor for long-term survival has been shown in patients with stage 4 HCC with extrahepatic metastases as well as in patients with liver cirrhosis

Table 5. Coxproportional hazard model of clinical characteristics on recurrence-free survival

	Overall survival (without perioperatively deceased)				Recurrence-free survival (without perioperatively deceased)			
			95% Confidence interval				95% Confidence interval	
Variables	*P*	Exp (β)	Lower limit	Upper limit	*P*	Exp (β)	Lower limit	Upper limit
ASA	0.619	1.148	0.665	1.982	0.603	1.153	0.675	1.970
MELD	0.979	1.001	0.905	1.108	0.720	1.018	0.923	1.123
Charlson Comorbidity Index	0.019	1.175	1.027	1.344	0.042	1.149	1.005	1.313
BMI	0.544	0.981	0.922	1.044	0.337	0.969	0.909	1.033
Intraoperative blood loss (ml)	0.847	1.000	1.000	1.000	0.796	1.000	1.000	1.000
Complications (yes/no)	0.248	1.336	0.817	2.184	0.159	1.428	0.870	2.343
Complication grades 3 and 4	0.919	0.964	0.472	1.969	0.630	0.816	0.356	1.868
Septic complications	0.159	0.605	0.301	1.217	0.538	0.802	0.397	1.621
Surgical revision	0.995	1.003	0.375	2.685	0.621	1.214	0.562	2.624

ASA, American Society of Anesthesiologists; MELD, Model for End-Stage Liver Disease.

following surgical procedures [16,33]. However, studies analyzing long-term recurrence-free survival in relation to earlier complications did not focus on the assessment of pre-existing comorbidities. Furthermore, following liver resection for various indications, our group was previously able to prove the significance of comorbidities for long-term overall survival [34,35]. Recent studies from Taiwan and Nanjing also discussed the use of the CCI in the context of liver resection for HCC. A particular advantage is proposed for the preoperative evaluation of elderly patients as, besides other comorbidities, age constitutes one of the variables included in the index [8,9].

Nevertheless, despite an equal study focus, the mentioned studies on long-term (recurrence-free) survival in relation to early complications are not completely comparable with each other. Furthermore, they may not be comparable to a study from Europe as high disparities in the epidemiology and incidence of liver cirrhosis and HCC exist [20,36]. In addition, comorbidities, such as risk factors associated with an elevated BMI and the incidence of NAFLD, may be more frequent in Europe, triggered by regional nutritional habits [37,38]. The underlying reasons are difficult to analyze, but may be found in the different racial susceptibility to diseases defining comorbidity [39,40]. Furthermore, the genesis of HCC in the Asian population may not be comparable to that in Europe. Whereas nutritive toxic factors may play a key role in Western countries [37], Asian studies attribute HCC to hepatitis B and C infection in up to 50% of patients in surgically treated cohorts [14,36]. In other words, a fictitious patient with HCC of the same size, differentiation, and intrahepatic location may not experience the same risk of complications and recurrence in Asia compared with Europe. Therefore, it seemed of particular value to carry out a study on the impact of postoperative complications on recurrence-free survival outside of Asia. In our cohort, obesity was present in more than 60%, the median BMI was 26, 24% had a history of cardiac disease, and diabetes was present in one-third of our patients (Rentsch M, unpublished data). The cumulation of comorbidities resulted in a median ASA score of 3 (indicating severe systemic disturbance from any cause or causes) and a median CCI of 7 (indicating a severe risk of mortality). An elevated BMI of greater than 25 has been reported to improve the prognosis in HCC patients [41]; however, it may increase the surgical risk [22,23]. Cardiopulmonary complications, which are not related to technical problems, accounted for one-fifth of the complete spectrum in our cohort; moreover, more than half of the complications were comorbidity associated. These numbers reconfirm observations of a study by Schroeder *et al.* [15], who tested several scores in terms of their predictive value for posthepatectomy morbidity and mortality.

Different from other variables of comorbidity, the preoperative MELD score was close to normal in our cohort. This is in line with the center's policy that liver function impairment does not have to exceed the Child A stage before resection. This composition of risk factors, which was significantly different in patients with versus without complications, may explain why comorbidities had a higher impact in multivariate analysis in our cohort compared with previous reports [14].

Perioperative complications and comorbidities might potentially influence the choice of treatment strategy for recurrent HCC and in this way affect overall and recurrence-free survival. To assess this issue, we examined all recurrence cases [84 (45%) patients] in our patient cohort. In terms of perioperative complications, we found that these had no impact on the treatment choice for HCC recurrence. In fact, most of the patients developed tumor recurrence after 1 year and longer upon surgery (16.2 ± 1.8 months; median: 11.8 months). At this time point, they have usually completely recovered from surgery irrespective of perioperative complications. In terms of comorbidities, we observed that the CCI and the ASA score did not differ between the complete study cohort (CCI: 7.19 ± 0.1, ASA: 2.72 ± 0.3) and the patients with recurrent HCC (CCI: 7.17 ± 0.2, ASA: 2.71 ± 0.05). Thus, comorbidities did not affect the decision of the treatment strategy for the treatment of recurrent HCC in our cohort.

Conclusion

Our study confirms previous data from Asian single-center and multicenter studies investigating outcomes after liver resection for HCC. Overall and recurrence-free survival may be affected by perioperative complications also in Europe, where comorbidities may have a stronger impact on postoperative recovery in general and in patients with HCC in particular as the pathogenesis of this malignancy involves triggers that also promote comorbidity. After elimination of the effects of immediate perioperative mortality, the CCI was an independent factor associated with long-term overall and recurrence-free survival. Future studies from Europe would have to evaluate whether the preoperative determination of comorbidity indexes is useful in identifying subgroups of patients with beneficial or adverse long-term outcomes following liver resection for HCC.

Acknowledgements

The authors thank Cathleen McSharry for professional proof-reading of the manuscript.

Conflicts of interest

There are no conflicts of interest.

References

1 Fong ZV, Tanabe KK. The clinical management of hepatocellular carcinoma in the United States, Europe, and Asia: A comprehensive and evidence-based comparison and review. *Cancer* 2014; 120:2824–2838.
2 Yu SJ. A concise review of updated guidelines regarding the management of hepatocellular carcinoma around the world: 2010–2016. *Clin Mol Hepatol* 2016; 22:7–17.
3 Colombo M, Sangiovanni A. Treatment of hepatocellular carcinoma: beyond international guidelines. *Liver Int* 2015; 35 (Suppl 1):129–138.
4 Rampone B, Schiavone B, Martino A, Viviano C, Confuorto G. Current management strategy of hepatocellular carcinoma. *World J Gastroenterol* 2009; 15:3210–3216.
5 Sotiropoulos GC, Drühe N, Sgourakis G, Molmenti EP, Beckebaum S, Baba HA, *et al*. Liver transplantation, liver resection, and transarterial chemoembolization for hepatocellular carcinoma in cirrhosis: which is the best oncological approach? *Dig Dis Sci* 2009; 54:2264–2273.
6 Regimbeau JM, Abdalla EK, Vauthey JN, Lauwers GY, Durand F, Nagorney DM, *et al*. Risk factors for early death due to recurrence after liver resection for hepatocellular carcinoma: results of a multicenter study. *J Surg Oncol* 2004; 85:36–41.
7 Zhong JH, Rodríguez AC, Ke Y, Wang YY, Wang L, Li LQ. Hepatic resection as a safe and effective treatment for hepatocellular carcinoma involving a single large tumor, multiple tumors, or macrovascular invasion. *Medicine (Baltimore)* 2015; 94:e396.
8 Fan HL, Hsieh CB, Chang WC, Huang SH, Chan DC, Yu JC, *et al*. Advanced age is not a contraindication for liver resection in cases of large hepatocellular carcinoma. *Eur J Surg Oncol* 2014; 40:214–219.
9 Yu DC, Chen WB, Jiang CP, Ding YT. Risk assessment in patients undergoing liver resection. *Hepatobiliary Pancreat Dis Int* 2013; 12:473–479.
10 Dokmak S, Ftériche FS, Borscheid R, Cauchy F, Farges O, Belghiti J. 2012 liver resections in the 21st century: we are far from zero mortality. *HPB (Oxford)* 2013; 15:908–915.
11 Chok KS, Ng KK, Poon RT, Lo CM, Fan ST. Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma. *Br J Surg* 2009; 96:81–87.
12 Kusano T, Sasaki A, Kai S, Endo Y, Iwaki K, Shibata K, *et al*. Predictors and prognostic significance of operative complications in patients with hepatocellular carcinoma who underwent hepatic resection. *Eur J Surg Oncol* 2009; 35:1179–1185.
13 Okamura Y, Takeda S, Fujii T, Sugimoto H, Nomoto S, Nakao A. Prognostic significance of postoperative complications after hepatectomy for hepatocellular carcinoma. *J Surg Oncol* 2011; 104:814–821.
14 Harimoto N, Shirabe K, Ikegami T, Yoshizumi T, Maeda T, Kajiyama K, *et al*. Postoperative complications are predictive of poor prognosis in hepatocellular carcinoma. *J Surg Res* 2015; 199:470–477.
15 Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006; 243:373–379.
16 Sato M, Tateishi R, Yasunaga H, Horiguchi H, Matsui H, Yoshida H, *et al*. The ADOPT-LC score: a novel predictive index of in-hospital mortality of cirrhotic patients following surgical procedures based on a national survey. *Hepatol Res* 2017; 47:E35–E43.
17 Katz SC, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR, *et al*. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg* 2009; 249:617–623.
18 Huang J, Li BK, Chen GH, Li JQ, Zhang YQ, Li GH, Yuan YF. Long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma undergoing hepatectomy. *J Gastrointest Surg* 2009; 13:1627–1635.
19 Schiergens TS, Rentsch M, Kasparek MS, Frenes K, Jauch KW, Thasler WE. Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases. *Dis Colon Rectum* 2015; 58:74–82.
20 Dhanasekaran R, Limaye A, Cabrera R. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis, and therapeutics. *Hepat Med* 2012; 4:19–37.
21 McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis* 2015; 19:223–238.
22 Mathur AK, Ghaferi AA, Osborne NH, Pawlik TM, Campbell DA, Englesbe MJ, Welling TH. Body mass index and adverse perioperative outcomes following hepatic resection. *J Gastrointest Surg* 2010; 14:1285–1291.
23 Ringbäck Weitoft G, Eliasson M, Rosén M. Underweight, overweight and obesity as risk factors for mortality and hospitalization. *Scand J Public Health* 2008; 36:169–176.
24 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40:373–383.
25 Aronson WL, McAuliffe MS, Miller K. Variability in the american society of anesthesiologists physical status classification scale. *AANA J* 2003; 71:265–274.
26 Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for end-stage liver disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. *AnnSurg* 2005; 242:244–251.
27 Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, *et al*. Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). *Surgery* 2011; 149:713–724.
28 op den Winkel M, Nagel D, Sappl J, op den Winkel P, Lamerz R, Zech CJ, *et al*. Prognosis of patients with hepatocellular carcinoma. Validation and ranking of established staging-systems in a large western hcc-cohort. *PLoS One* 2012; 7:e45066.
29 Cauchy F, Fuks D, Belghiti J. HCC: current surgical treatment concepts. *Langenbecks Arch Surg* 2012; 397:681–695.
30 Ching SS, Muralikrishnan VP, Whiteley GS. Relaparotomy: a five-year review of indications and outcome. *Int J Clin Pract* 2003; 57:333–337.
31 Martínez-Casas I, Sancho JJ, Nve E, Pons M-J, Membrilla E, Grande L. Preoperative risk factors for mortality after relaparotomy: analysis of 254 patients. *Langenbecks Arch Surg* 2009; 395:527–534.
32 Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; 47:1245–1251.
33 Chang YS, Huang JS, Yen CL, Wang CH, Lai CH, Wu TH, *et al*. The Charlson comorbidity index is an independent prognostic factor for treatment-naive hepatocellular carcinoma patients with extrahepatic metastases. *Hepatogastroenterology* 2015; 62:1011–1015.
34 Schiergens TS, Stielow C, Schreiber S, Hornuss C, Jauch KW, Rentsch M, Thasler WE. Liver resection in the elderly: significance of comorbidities and blood loss. *J Gastrointest Surg* 2014; 18:1161–1170.
35 Schiergens TS, Lindenthaler A, Thomas MN, Rentsch M, Mittermeier L, Brand K, *et al*. Time-dependent impact of age and co-morbidities on long-term overall survival after liver resection. *Liver Int* 2016; 36:1340–1350.
36 Kew MC. Hepatocellular carcinoma: epidemiology and risk factors. *J Hepatocell Carcinoma* 2014; 1:115.
37 Liangpunsakul S, Haber P, McCaughan GW. Alcoholic liver disease in Asia, Europe, and North America. *Gastroenterology* 2016; 150:1786–1797.
38 Fan JG, Peng YD. Metabolic syndrome and non-alcoholic fatty liver disease: Asian definitions and Asian studies. *Hepatobiliary Pancreat Dis Int* 2007; 6:572–578.
39 Huxley RR, Barzi F, Woo J, Giles G, Lam TH, Rahimi K, *et al*. A comparison of risk factors for mortality from heart failure in Asian and non-Asian populations: an overview of individual participant data from 32 prospective cohorts from the Asia-Pacific region. *BMC Cardiovasc Disord* 2014; 14:61.
40 Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, Forouhi NG, *et al*. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, south Asians, and African Caribbeans: SABRE (southall and brent revisited) – a prospective population-based study. *J Am Coll Cardiol* 2013; 61:1777–1786.
41 Itoh S, Ikeda Y, Kawanaka H, Okuyama T, Kawasaki K, Eguchi D, *et al*. The effect of overweight status on the short-term and 20-y outcomes after hepatic resection in patients with hepatocellular carcinoma. *J Surg Res* 2012; 178:640–645.