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Original Research

Dynamic liver function is an independent predictor of recurrence-free survival after curative liver resection for HCC - A retrospective cohort study

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ABSTRACT

Background: Hepatocellular carcinoma is the fifth most prevalent cancer worldwide. High tumour recurrence is the most common cause of the impaired 5-year survival rate of 26–58% after hepatectomy. The aim of this study was to investigate the impact of preoperative dynamic liver function on long-term outcome.

Materials and methods: A total of 146 patients that underwent curative resection for HCC at our department from 2005 to 2016 were analysed. Univariate analysis was calculated using Kaplan-Meier method. Multivariable analysis was carried out with Cox regression.

Results: The cumulative 1-, 3-, 5-year survival rates were 83%, 42% and 14%, respectively. Multivariable Cox regression yielded that overall survival depends on disease recurrence, haemoglobin, number of tumours, liver cirrhosis, lymphatic vessel invasion, UICC stage and postoperative complications.

The corresponding 1-, 3-, 5-year disease-free survival rates were 73%, 32% and 10%, respectively. Multivariable analysis yielded preoperative liver function capacity (HR 2.421; $p = 0.014$), vascular invasion (HR 2.116; $p = 0.034$) and UICC stage (HR 2.200; $p = 0.037$) as risk factors associated with disease-free survival. A subanalysis with respect to the degree of functional impairment implicated that severity of liver function impairment is correlated with the disease-free survival rate.

Conclusion: This study shows that preoperative dynamic liver function assessed by LiMAx test as well as severity of underlying liver disease have a significant impact on recurrence-free survival after curative hepatectomy. Patients presenting with impaired liver function should be evaluated for other treatment e.g. liver transplantation or receive closer oncological follow-up.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer worldwide [1]. Apart from liver transplantation, liver resection remains the treatment of choice with curative intention. Although perioperative mortality and morbidity have improved due to advancements in anesthesiological management, operative techniques and sophisticated patient selection, long-term survival rates remain unsatisfactory because of extraordinary high 5-year recurrence rate of 60–80% [2–7]. Several parameters such as alkaline phosphatase (AP), gamma-glutamyltransferase (GGT), liver cirrhosis, multiple nodes and vascular invasion are widely accepted as prognostic markers for postoperative morbidity, mortality und recurrence rate [5,8,9]. However, due to heterogeneous investigation results, the prognostic value of a number of other parameters such as indocyanine green plasma disappearance rate (ICG-PDR), α-fetoprotein (AFP) and aspartate aminotransferase (AST) still remain unclear [6,10–12]. Additionally, prognostic algorithms have been introduced in order to overcome the limitations of single

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prognostic markers to represent global liver function. However, neither the albumin-bilirubin (ALBI) score nor the alkaline phosphatase-to-platelet count ratio index (APPRI) or Albumin-Indocyanine Green Evaluation (ALICE) grading system are widely used [13–15]. Overall, numerous risk factors and prognostic scores have been suggested to predict recurrence, however no single liver function parameter has yielded good prognostic value yet. Less is known about the impact of metabolic liver function capacity determined by LiMAx test (maximal enzymatic liver function capacity) on long-term survival. The LiMAx test, a^{13}C-based breath test, has already shown to provide reliable information on actual enzymatic liver function capacity in various clinical situations [16–18].

The aim of this study was to investigate the impact of preoperative liver dynamic function on long-term outcome after curative liver resection, as well as to define risk factors for impaired disease-free and overall survival rate.

2. Material and methods

2.1. Study concept

This is a retrospective cohort analysis of 319 patients from an institutional database including all patients who underwent liver resection for HCC with at least one dynamic liver function test during the perioperative course within the years from 2005 to 2016. Of these, 293 patients met the following inclusion criteria: first diagnosis of HCC, hepatectomy with curative intention and no extrahepatic metastases. Exclusion criteria were unavailable preoperative liver function assessment by LiMAx (n = 83), R1 resection (n = 48), fibrolamellar carcinoma (n = 3), and intraoperative additional therapy except liver resection (n = 1). Follow-up data was missing in 12 patients. Eventually 146 patients were included in this retrospective study.

The study was approved by the local ethics committee and is performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its last revision of 2013. This study is also compliant with the TRIPOD and STROCSS statement [19,20].

2.2. Diagnostic workup

HCC was diagnosed with the use of imaging studies (ultrasonography, computed tomography [CT] scans, magnetic resonance imaging [MRI]); increased α-fetoprotein levels (AFP) were used as a supporting factor. Tumour biopsy for diagnostic purposes was rarely performed and only in the case of inconclusive preoperative imaging. Hepatic resection was performed as the treatment of choice based on tumour stage, function of the future liver remnant and general patients' health state. Liver function assessment and resection planning was performed according to LiMAx algorithm [21]. Cases in which a major resection was planned, additional volume/function analysis was preferred to access future liver remnant function. Eventually, portal vein embolization was conducted to increase resectability and reduce the risk of posthepatectomy liver failure.

2.3. Dynamic liver function – LiMAx test

Dynamic liver function tests are established as standard of care in our department before liver resections. They are suggested to provide additional information on liver function by determining the livers ability to metabolize or eliminate specific substances in time [22].

LiMAx (maximum liver function capacity) test was performed as previously described by Stockmann and colleagues [21]. The test procedure is based on the kinetic analysis of CYP1A2 activity by a continuous real-time breath analysis. George et al. had previously shown a strong correlation of hepatic P450 expression and actual liver function capacity [23]. Bodyweight-adjusted intravenous applied ^{13}C-labeled methacetin is exclusively metabolized by CYP1A2 in the liver into paracetamol and $^{13}CO_2$. Changes of the $^{13}CO_2/^{12}CO_2$ concentrations ratio before and after methacetin administration were recorded using a proprietary device (FLIP, Humedics GmbH, Berlin, Germany). LiMAx values > 315 μg/kg/h are considered normal [24].

2.4. Operation and postoperative management

Intraoperative ultrasonography and systemic examination of the abdomen was routinely performed. Hepatectomy was considered as major resection if three or more segments according to Couinaud's liver segmentation were removed [25]. Pringle maneuver was used on demand to reduce intraoperative blood loss [26]. An anatomical resection was defined as a HCC resection together with the tumour-containing portal vein and corresponding hepatic parenchyma as describe by Makuuchi and colleagues [27]. Laparoscopic resection was carried out as the treatment of choice in small achievable tumours. Curative hepatectomy was defined as microscopically margin-negative resection. After pathological examination all patients were staged according to the TNM staging system (TNM-7 American Joint Committee on Cancer/UICC 2002) [28]. Dindo classification were used to grade postoperative complications [29].

2.5. Follow-up

Each patient was regularly assessed every three months after hepatectomy at our outpatient department or by the referring oncologist. The follow-up consisted of clinical examination, standard blood test with tumour markers, and cross sectional imagining and/or ultrasonography. If the patient was suspected to have tumour recurrence, additional imaging and/or biopsy was performed to confirm the diagnosis.

Patients were followed up to March 2017. The mean follow-up period for the patients after liver resection was 59 ± 28 months.

2.6. Statistical analysis

Statistical analysis was performed using SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). The mean follow-up time was calculated according to the reverse Kaplan-Meier method.

All parameters were dichotomized based on the institutional laboratory cut-off values.

Univariate associations of tumour recurrence and patients' survival were calculated by Kaplan-Meier-Analysis, differences were compared by the log-rank-test. Variables that were statistically significant in the univariate analysis (p-value < 0.05) were included in a multivariable model. Multivariate analysis of factors with disease-free and overall survival were assessed using Cox proportional hazards models. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 146 patients with primary HCC who underwent curative hepatic resection with a mean age of 68.4 years were assessed. The male gender predominated with 100 patients (68.5%). Preoperative liver function assessment was performed 7.7 ± 10.6 days prior to liver resection. Demographics, clinical and perioperative data is summarized in Table 1.

3.2. Recurrence and mortality

Tumour recurrence was observed in 58 patients (39.7%) by the end of follow-up in March 2017. Local recurrence was clinically confirmed in 42 patients (72.4%) while extrahepatic recurrence was identified in only five patients (8.3%). Both local- and extrahepatic recurrence

Table 1
Main demographic, clinical and perioperative data.

Demographics	
Sex, m/f (%)[a]	100/46 (68.5/31.5)
Age (years)[a]	68.4 ± 10.3
BMI (kg/m^2)[a]	27.6 ± 12.3
HCC etiology, n (%)	
viral	31 (40.2)
NASH	10 (13.0)
alcohol	26 (33.8)
haemochromatosis	4 (5.2)
other	6 (7.8)
HCVAb positive, n (%)	19 (16.0)
HbsAg positive, n (%)	9 (7.8)
Pretreatment present, n (%)	6 (4.1)
Kind of pretreatment, n (%)	
Sorafenib	1 (16.7)
TACE	3 (50.0)
multiple	2 (33.3)
Portal vein embolization, n (%)	8 (5.5)
Medical imaging preoperative, n (%)	
No medical image	5 (3.4)
1 medical image	75 (51.3)
2 medical images	59 (40.4)
3 medical images	7 (4.8)
Recurrence, n (%)	
Local recurrence	42 (72.4)
Extrahepatic recurrence	5 (8.6)
Local and extrahepatic recurrence	11(19.0)
Preoperative liver function	**Mean ± SD**
LiMAx (μg/h/kg)	357.8 ± 117.1
AFP (μg/l)	2445.5 ± 9201.5
CA 19-9 (kU/l)	23.3 ± 35.3
MELD Score	8.2 ± 2.6
Albumin (g/dl)	4.0 ± 0.6
AST (U/l)	63.6 ± 67.6
ALT (U/l)	47.7 ± 37.6
GGT (U/l)	119.3 ± 105.8
GLDH (U/l)	8.4 ± 7.4
Total bilirubin (mg/dl)	0.6 ± 0,4
Platelet count (/nl)	236.0 ± 114.5
Alkaline Phosphatase (U/l)	112.4 ± 99.6
Prothrombin time (%)	91.7 ± 14.1
INR	1.1 ± 0.1
CRP (g/dl)	1.6 ± 3.6
Leucocytes (/nl)	7.0 ± 2.4
Creatinine (mg/dl)	1.0 ± 0,8
Haemoglobin (g/dl)	13.2 ± 1.6
Operative Data	
Laparoscopic resection, n (%)	23 (15.8)
Operative time (minutes)[a]	226.7 ± 88.1
Extent of resection, n (%)	
Right Hemihepatectomy	31 (21.2)
Extended right Hemihepatectomy	8 (5.5)
Right Trisectorectomy	7 (4.8)
Left Hemihepatectomy	15 (10.3)
Extended left Hemihepatectomy	10 (6.8)
Left lateral	10 (6.8)
Right lateral	4 (2.7)
Segmentectomy	28 (19.2)
Bisegmentectomy	7 (4.8)
Mesohepatectomy	3 (2.1)
Enucleation	23 (15.8)
Surgery, n (%)	
anatomical	96 (65.8)
atypical	23 (15.8)
anatomical and limited	27 (18.5)
Pringle's maneuver, n (%)	79 (59.4)
Pringle's maneuver time (minutes)[a]	22.0 ± 13.4

Table 1 (*continued*)

Demographics	
Biliodigestive anastomosis, n (%)	7 (5.0)
Intraoperative blood transfusions[a]	0.6 ± 1.6
Intraoperative fresh frozen plasma[a]	2.4 ± 3.3
Pathological examination	
Liver cirrhosis, n (%)	61 (41.8)
Steatosis (%)[a]	12 (58.2)
Tumour size (mm)[a]	72.6 ± 46.4
Tumour grading, n (%)	
G1	21 (14.5)
G2	95 (65.5)
G3	28 (19.3)
G4	1 (0.7)
Number of tumours, n (%)	
Solitary	107 (73.3)
Multiple	39 (26.7)
Vascular invasion, n (%)	28 (19.2)
Lymphatic vessel invasion, n (%)	12 (8.2)
Tumour stage UICC, n (%)	
I	93 (63.7)
II	24 (16.4)
IIIA	18 (12.3)
IIIB	4 (2.7)
IIIC	3 (2.1)
IVA	4 (2.7)
Postoperative Data	
Intensive care, days[a]	3.8 ± 7.8
Hospitalization, days[a]	17.0 ± 13.4
Duration mechanical ventilation, h[a]	8.8 ± 15.1
Postoperative complications, n (%)	
No complications	46 (31.5)
Dindo I	26 (17.8)
Dindo II	26 (17.8)
Dindo IIIa	21 (14.4)
Dindo IIIb	12 (8.2)
Dindo IVa	5 (3.4)
Dindo IVb	2 (1.4)
Dindo V	8 (5.5)

BMI, body mass index; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis; HCVAb, hepatitis C antibody; HbsAg, hepatitis B surface antigen; TACE, transarterial chemoembolization; LiMAx, maximum liver function capacity; AFP, α-fetoprotein; CA 19-9, carbohydrate antigen 19-9; MELD, model of end-stage liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; GLDH, glutamate dehydrogenase; INR, international normalized ratio; CRP, C-reactive protein.

[a] Mean ± SD.

occurred in 11 patients (19.0%). Tumour recurrence was treated with Sorafenib (n = 12), second resection (n = 11), transarterial chemoembolization (n = 4), selective internal radiation therapy (n = 4), chemotherapy (n = 2), brachytherapy (n = 4), multiple treatment (n = 9) and other therapeutic options (n = 2). Nine patients (15.5%) were treated by best-supportive care (data not shown). At the end of follow-up 75 patients (51.4%) were still alive (60 without recurrence and 15 with recurrence).

3.3. Univariate and multivariable analysis – disease-free survival

The mean disease-free survival (DFS) was 28 ± 22 months. The 1-, 3-, 5-year disease-free survival rate (DSR) rates were 72.6%, 31.5% and 9.6%, respectively. Univariate analysis showed that the DSR was significantly and negatively correlated with decreased LiMAx (p = 0.028), prothrombin time (p = 0.014) and elevated AST (p = 0.017) as well as

Table 2
Univariate analysis data of disease-free and overall survival. HbsAg, hepatitis B surface antigen; HCVAb, hepatitis C antibody; LiMAx, maximum liver function capacity; AFP, α-fetoprotein; MELD, model of end-stage liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl-transferase.

Main Data	Disease-free survival		overall survival	
	Mean survival (95% CI)	p-value	Mean survival (95% CI)	p-value
Sex				
female (n = 46)	48.85 (35.30; 62.40)		53.12 (40.43; 65.82)	
male (n = 100)	63.24 (53.53; 72.96)	0.075	52.66 (44.48; 60.85)	0.883
Age (years)				
≤70 (n = 68)	65.13 (53.96; 76.31)		59.52 (49.50; 70.36)	
> 70 (n = 78)	49.38 (40.59; 58.18)	0.252	44.18 (36.72; 51.64)	0.059
HbsAg				
positive (n = 9)	65.56 (35.36; 95.77)		67.11 (37.64; 96.58)	
negative (n = 107)	53.86 (46.67; 61.06)	0.948	50.87 (43.73; 58.01)	0.280
HCVAb				
positive (n = 19)	34.81 (21.27; 48.34)		41.08 (26.92; 55.23)	
negative (n = 100)	63.40 (53.96; 72.87)	0.087	53.94 (46.09; 61.79)	0.354
Pretreatment				
present (n = 6)	31.17 (6.13; 56.20)		54.00 (30.17; 77.84)	
absent (n = 140)	60.08 (51.64; 68.52)	0.175	52.09 (45.20; 58.99)	0.472
Medical imaging preoperative				
No medical image (n = 4)	29.00 (0.00; 60.11)		60.00 (31.12; 88.88)	
1 medical image (n = 75)	51.36 (42.44; 60.28)		50.35 (41.24; 59.46)	
2 medical images (n = 59)	66.24 (53.83; 78.65)		55.88 (44.70; 67.06)	
3 medical images (n = 7)	43.14 (51.11; 67.42)	0.157	47.71 (31.42; 64.01)	0.883
Recurrence				
present (n = 58)	–	–	38.90 (30.93; 46.87)	
absent (n = 88)	–	–	67.04 (57.54; 76.55)	< 0.001

Laboratory Chemistry	Mean survival (95% CI)	p-value	Mean survival (95% CI)	p-value
LiMAx (µg/h/kg)				
≤315 (n = 49)	42.83 (31.80; 53.75)		45.30 (35.36; 55.24)	
> 315 (n = 97)	66.33 (56.85; 75.81)	0.028	56.49 (48.02; 64.97)	0.151
AFP (µg/l)				
≤11 (n = 53)	62.96 (50.32; 75.60)		56.31 (45.24; 67.38)	
> 11 (n = 65)	49.93 (39.45; 60.41)	0.079	43.28 (34.44; 52.12)	0.098
MELD Score				
≤8 (n = 99)	56.43 (47.43; 65.26)		55.56 (47.35; 63.76)	
> 8 (n = 42)	59.58 (43.87; 75.28)	0.908	41.77 (29.87; 53.66)	0.056
Albumin (g/dl)				
≤4.0 (n = 40)	48.13 (36.67; 59.59)		34.38 (24.87; 43.90)	
> 4.0 (n = 47)	52.03 (40.33; 63.73)	0.932	59.63 (48.63; 70.62)	0.005
AST (U/l)				
≤50 (n = 88)	64.56 (54.29; 74.83)		58.14 (49.58; 66.71)	
> 50 (n = 55)	45.84 (34.45; 57.23)	0.017	40.62 (31.19; 50.05)	0.014
ALT (U/l)				
≤45 (n = 70)	53.75 (43.27; 64.24)		55.46 (45.70; 65.22)	
> 45 (n = 47)	54.08 (42.06; 66.11)	0.913	48.05 (37.95; 58.15)	0.378
Alkaline Phosphatase (U/l)				
≤90 (n = 63)	56.19 (45.99; 66.38)		60.32 (50.46; 70.18)	
> 91 (n = 52)	52.87 (40.63; 65.11)	0.327	43.05 (32.83; 53.27)	0.016
Total bilirubin (mg/dl)				
≤1.2 (n = 126)	59.31 (50.55; 68.07)		53.12 (45.75; 60.49)	
> 1.2 (n = 12)	52.87 (22.50; 51.39)	0.464	32.11 (16.46; 47.75)	0.180
Prothrombin time (%)				
≤80 (n = 27)	26.81 (18.77; 34.85)		35.58 (24.39; 46.77)	
> 80 (n = 116)	63.06 (54.12; 72.00)	0.014	54.67 (47.13; 62.13)	0.061

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Table 2 (*continued*)

Main Data	Disease-free survival		overall survival	
	Mean survival (95% CI)	p-value	Mean survival (95% CI)	p-value
Platelet count (/nl)				
≤150 (n = 97)	61.00 (52.09; 69.91)		55.33 (47.51; 63.15)	
> 150 (n = 47)	45.93 (23.39; 68.46)	0.057	34.12 (15.30; 52.94)	0.012
Haemoglobin (g/dl)				
≤12 (n = 33)	47.70 (37.64; 57.76)		38.51 (24.40; 52.63)	
> 12 (n = 112)	45.93 (49.15; 66.90)	0.836	56.24 (48.44; 64.04)	0.012
Pathological Examination	**Mean survival (95% CI)**	**p-value**	**Mean survival (95% CI)**	**p-value**
Liver cirrhosis				
present (n = 61)	38.29 (24.33; 52.25)		44.42 (33.09; 55.74)	
absent (n = 88)	63.61 (55.01; 72.21)	0.005	50.50 (50.67; 66.37)	0.014
Steatosis				
present (n = 12)	36.31 (23.97; 48.65)		38.43 (26.55; 50.32)	
absent (n = 69)	64.80 (53.05; 76.55)	0.565	55.71 (45.33; 66.09)	0.975
Tumour size (mm)				
≤5 (n = 60)	55.18 (42.18; 68.18)		52.93 (41.86; 64.01)	
5–10 (n = 52)	53.63 (44.78; 62.47)		47.19 (38.34; 56.03)	
> 10 (n = 33)	56.73 (41.88; 71.58)	0.823	54.66 (40.43; 68.89)	0.961
Tumour grading				
G1 (n = 21)	45.13 (29.32; 60.94)		45.96 (32.30; 59.62)	
G2 (n = 95)	57.11 (47.77; 66.45)		53.05 (44.83; 61.28)	
G3 (n = 28)	63.11 (45.85; 80.36)	0.672	51.33 (35.92; 66.74)	0.919
Number of tumours				
solitary (n = 107)	63.81 (54.69; 72.94)		57.02 (49.22; 64.82)	
multiple (n = 39)	40.02 (23.59; 56.44)	0.022	39.25 (27.23; 51.28)	0.015
Vascular invasion				
present (n = 28)	35.80 (20.77; 50.84)		43.77 (28.71; 58.83)	
absent (n = 118)	63.23 (54.02; 72.43)	0.001	54.78 (46.99; 62.57)	0.157
Lymphatic vessel invasion				
present (n = 12)	25.21 (8.77; 41.65)		22.01 (8.75; 35.30)	
absent (n = 134)	61.53 (53.14; 69.91)	0.004	54.94 (47.92; 61.97)	0.001
Tumour stage UICC				
I (n = 93)	64.14 (54.06; 74.22)		57.45 (48.90; 65.99)	
II (n = 24)	52.85 (35.98; 69.71)		55.79 (38.63; 72.94)	
IIIA (n = 18)	46.37 (24.60; 68.13)		40.21 (23.97; 56.45)	
IIIB (n = 4)	30.67 (9.33; 52.00)		14.75 (0.00; 31.43)	
IIIC (n = 3)	4.33 (4.90; 13.60)		6.33 (11.25; 19.25)	
IVA (n = 4)	9.25 (51.40; 67.67)	< 0.001	15.25 (11.25; 19.25)	< 0.001
Intraoperative Data	**Mean survival (95% CI)**	**p-value**	**Mean survival (95% CI)**	**p-value**
Laparoscopic resection				
yes (n = 23)	57.47 (40.34; 74.61)		60.39 (43.36; 77.43)	
no (n = 123)	58.45 (49.72; 67.18)	0.408	50.60 (43.47; 57.73)	0.099
Operative time (minutes)				
≤200 (n = 65)	59.30 (47.02; 71.58)		50.33 (39.99; 60.66)	
> 200 (n = 79)	55.34 (46.24; 64.44)	0.962	53.51 (44.42; 62.60)	0.593
Extent of resection				
minor hepatectomy (n = 72)	43.63 (35.14; 52.12)		50.10 (41.84; 58.36)	
major hepatectomy (n = 74)	65.63 (55.04; 76.23)	0.248	52.58 (43.13; 62.03)	0.888
Surgery				
anatomical (n = 96)	64.93 (55.41; 74.44)		52.71 (44.48; 60.94)	
atypical (n = 23)	29.58 (20.45; 38.70)		53.51 (38.77; 68.24)	
anatomical and limited (n = 27)	56.59 (41.83; 71.36)	0.028	53.30 (39.33; 67.27)	0.941
Pringle's maneuver				

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Table 2 (*continued*)

Main Data	Disease-free survival		overall survival	
	Mean survival (95% CI)	p-value	Mean survival (95% CI)	p-value
present (n = 79)	59.65 (48.88; 70.42)		58.47 (48.46; 68.47)	
absent (n = 54)	50.66 (41.49; 59.83)	0.920	48.64 (38.56; 58.73)	0.293
Intraoperative blood transfusion				
present (n = 26)	44.25 (31.59; 56.91)		30.05 (19.33; 40.78)	
absent (n = 116)	60.26 (51.35; 69.16)	0.424	55.41 (47.98; 62.85)	0.004
Postoperative Data	**Mean survival (95% CI)**	**p-value**	**Mean survival (95% CI)**	**p-value**
Intensive care (days)				
≤1 (n = 82)	58.58 (47.23; 67.50)		59.69 (51.17; 68.22)	
> 1 (n = 64)	59.23 (47.44; 71.01)	0.941	42.10 (32.26; 51.94)	0.010
Hospitalization (days)				
≤12 (n = 67)	57.37 (47.23; 67.50)		58.74 (50.09; 67.40)	
> 12 (n = 79)	60.28 (48.68; 71.88)	0.707	46.66 (37.22; 56.10)	0.015
Postoperative complications				
no complications (n = 47)	53.33 (42.79; 63.88)		59.28 (50.00; 68.55)	
DINDO I (n = 26)	61.11 (44.55; 77.67)		67.25 (51.59; 82.90)	
DINDO II (n = 27)	46.83 (33.09; 60.57)		51.51 (38.98; 64.05)	
DINDO IIIa (n = 21)	57.75 (44.56; 70.94)		40.08 (25.79; 54.37)	
DINDO IIIb (n = 13)	59.36 (42.26; 76.47)		34.65 (19.58; 49.73)	
DINDO IVa (n = 5)	30.40 (7.40; 53.40)		29.20 (11.33; 47.07)	
DINDO IVb (n = 2)	59.00 (3.56; 114.44)	0.763	69.00 (27.42; 110.59)	0.032

the presence of vascular (p = 0.001) and lymphatic invasion (p = 0.004), liver cirrhosis (p = 0.005), multiple tumour nodules (p = 0.022), atypical resection (p = 0.028) and high UICC stage ($p < 0.001$).

Multivariable analysis identified decreased LiMAx test (p = 0.015), vascular invasion (p = 0.035) and high UICC stage (p = 0.038) as independent risk factors affecting the disease-free survival.

A detailed synopsis of univariate and multivariable analysis of risk factors is presented in Tables 2 and 3 and Fig. 1A.

We conducted a subanalysis in order to stratify the patient's liver function capacity into three levels of impairment. The subanalysis with respect to the degree of functional impairment provide the following mean survival: LiMAx < 240 μg/h/kg with mean survival of 30.82 (95% CI 20.18; 41.45) months; LiMAx 240–315 μg/h/kg with mean survival of 50.34 (95% CI 35.64; 65.05) months and LiMAx > 315 μg/h/kg with mean survival of 66.33 [95% CI 56.85; 75.81) months (data not shown). The three levels of impairment were negatively correlated with the DSR as depictured in Fig. 1B.

3.4. Univariate and multivariable analysis – overall survival

The mean overall survival was 34 ± 23 months. The 1-, 3-, and 5-year overall survival rates (OSR) were 82.9%, 41.8% and 13.7%, respectively. Univariate analysis regarding overall survival showed that increased AST (p = 0.001), AP (p = 0.014), leucocyte count (p = 0.012), as well as multiple tumour nodules (p = 0.015), liver cirrhosis (p = 0.014), high UICC stage ($p < 0.001$), intraoperative blood transfusions (p = 0.004), postoperative complications (p = 0.032), prolonged intensive care unit (ICU) stay (p = 0.010) and prolonged hospitalization (p = 0.015) were significantly associated with shorter OSR. Univariate prognostic factors are depictured in Fig. 2.

The multivariable analysis showed that the OSR were significantly and negatively correlated with disease recurrence ($p < 0.001$), haemoglobin (p = 0.005), number of tumours (p = 0.016), liver cirrhosis (p = 0.002), lymphatic vessel invasion (0.017), UICC stage (p = 0.004) and postoperative complications (p = 0.006).

More detailed data regarding the multivariable analysis of overall survival are shown in Table 4.

Table 3
Multivariate analysis data of disease-free survival.

Factors	Relative Risk	(95% CI)	p-value
LiMAx ≤ 315 μg/h/kg	2.395	(1.184–4.843)	0.015
Vascular invasion	0.474	(0.237–0.948)	0.035
UICC ≥ IIIA	2.191	(1.044–4.599)	0.038

LiMAx, maximum liver function capacity.

4. Discussion

In this paper, we demonstrated that disease-free survival is significantly affected by preserved liver function. Moreover, severity of liver function impairment determined by LiMAx test showed a significant correlation with the disease-free survival in our study population.

In Europe 80–90% of HCCs are caused by an underlying chronic liver cirrhosis, complicating diagnosis and therapy [30,31]. While advancements have been made with respect to surgical technique and perioperative management, long-term outcome remains impaired by high tumour recurrence rates [2–7]. Thus, the identification of prognostic factors for tumour recurrence after liver resection is crucial to improve long-term outcome.

Many author emphasised the superior value of liver function parameter to tumour related factors [11,32]. Although several investigators have suggested that preoperative liver enzymes e.g. AP, AST or GGT are potentially valuable predictors for disease-free and overall survival, the results remain controversial [3,5,11].

To overcome the limitations of standard liver function tests representing global liver function, Fukuda et al. carried out a survival analysis with the dynamic liver function test ICG. This study identified for the first time that decreased ICG test adversely influences long-term survival [10]. Further investigations lead to controversial study results, but in synopsis, the results of standard liver function tests and dynamic

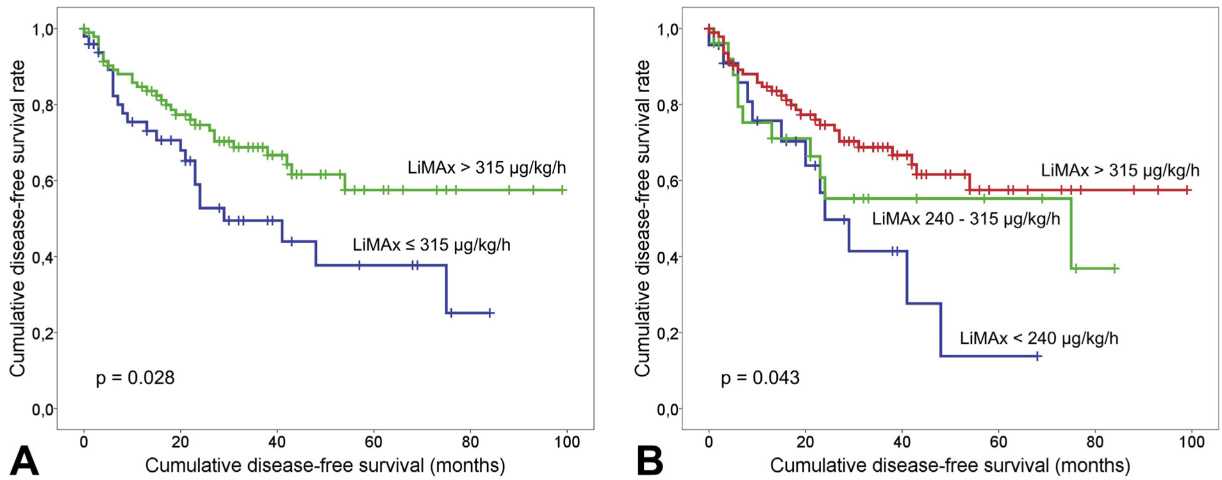

Fig. 1. Disease-free survival depending on dynamic liver function (LiMAx). Impaired liver function capacity assessed by the LiMAx test correlates significantly with the disease-free survival rate (A) Severity of functional impairment correlates significantly with the disease-free survival rate (B)
LiMAx, maximum liver function capacity.

ICG measurements suggest that there might be a correlation between liver function and disease-free survival [4,9]. Of note, the ICG elimination test is not liver-specific and is strongly influenced by hepatic blood flow, hyperbilirubinemia and cholestasis [33,34]. Hence the results of our patient cohort do not show an association between ICG test and oncologic outcome in multivariable analysis. These limitations might also explain why the ICG test failed in several previous studies. In contrast, in this study we found that liver function determined by LiMAx test was strongly associated with disease-free survival in both uni- and multivariable analysis. Additionally, LiMAx was also the single preoperative parameter significantly decreasing DFS in multivariable analysis.

Novel metabolic tests such as the LiMAx test provide reliable information on liver function in comparison to standard liver function assessment within different clinical situations e.g. LiMAx test has been shown to carry substantial diagnostic as well as prognostic value with respect to postoperative outcome following liver surgery [17]. Jara et al. found that the LiMAx test predicted short-term outcome in cirrhotic patients with a prognostic accuracy comparable to the well-known MELD score and ICG test [35]. Furthermore, volume-function analysis by LiMAx test has recently shown the prognostic value to predict postoperative morbidity as well as postoperative liver failure in noncirrhotic and cirrhotic patients [36]. Dynamic liver function tests assess liver function more comprehensively and enable a detailed grading of liver function [37]. This might explain why the LiMAx test was superior in terms of its prognostic value compared to standard liver function enzymes in multivariable analysis (Table 3). These findings emphasize the importance of impaired liver function in the context of recurrence.

Underlying liver cirrhosis is a well-known precancerous state leading to a 6–15% higher risk of recurrence in comparison to noncirrhotic liver [38]. Nevertheless, pathophysiologic mechanisms of recurrence in compromised liver have not been fully clarified. Recent research suggested that this may be a direct result of higher hepatocarcinogenic potential due to increased rate of random mutations and promotion [39,40]. In line with this hypothesis, Sakai et al. showed that recurrence in liver cirrhosis patients derived from micrometastases and de novo recurrence, whereas recurrence in patients with noncirrhotic liver was a result of recurrence from residual cancer [38]. In our study, liver cirrhosis was associated with LiMAx values in univariate analysis, however this effect was no longer detectable in multivariable regression analysis (Tables 2 and 3). We attribute this finding to the superior predictive value of LiMAx test compared to the histological differentiation between cirrhotic and non-cirrhotic liver parenchyma. Malinowski et al. has already shown that the LiMAx test allows the grading of disease severity of patients with liver cirrhosis [41]. Our subanalysis with respect to severity of liver function impairment yielded that the degree of functional impairment determines the disease-free survival rate (Fig. 1B). In view of the above considerations, the continuous functional graduation by LiMAx may represent both impact of severity of underlying liver disease as well as carcinogenic potential in the underlying liver. This also suggests that routinely applied preoperative liver function test by LiMAx may be a useful tool for optimal treatment selection and identification of high-risk patients to reduce recurrence rate.

Numerous previous studies have focused on tumour characteristics affecting overall survival [5,6]. Some authors pointed out that non-tumour related factors such as postoperative complications, patients' age or preoperative liver function may be more relevant for long-term outcome than tumour characteristics [8,42,43]. In line with this hypothesis, we identified preoperative markers (haemoglobin), liver function (liver cirrhosis), and postoperative markers (complications) as risk factors affecting overall survival in the multivariable analysis (Table 4). These results suggest that careful patient selection and perioperative management in term of improving long-term outcome. However, we did not find dynamic liver function determined by LiMAx test to be an independent predictor of survival in multivariable analysis. Although patients with impaired liver function had a poorer prognosis, the results were not statistically significant. However, it is noteworthy that especially local disease recurrence is an important influencing factor in terms of overall survival and is mainly determined by preoperative liver function. Further larger independent cohort analyses are warranted in order to validate these findings.

This study has several limitations need to be mentioned, including its retrospective character. Hence, some data is missing as is often the case in retrospective analyses such as encephalopathy and ascites for Child-Pugh score calculation. However, we do not regard this as a weakness of our study since the Child-Pugh score has often been criticised for its wide variation of liver function in each group and the aforementioned two relatively subjective included parameters, which may lead to an underestimation or overestimation of liver function [44]. Therefore, we tried to focus on a more objective liver function test. Furthermore, for some patients followed-up examination was performed irregularly which may result in late detection of recurrence. Unfortunately, an analysis of the influence of treatment after recurrence on survival was not feasible with our data. Finally, the histological examination was performed by different pathologist which may result variable histological exam results.

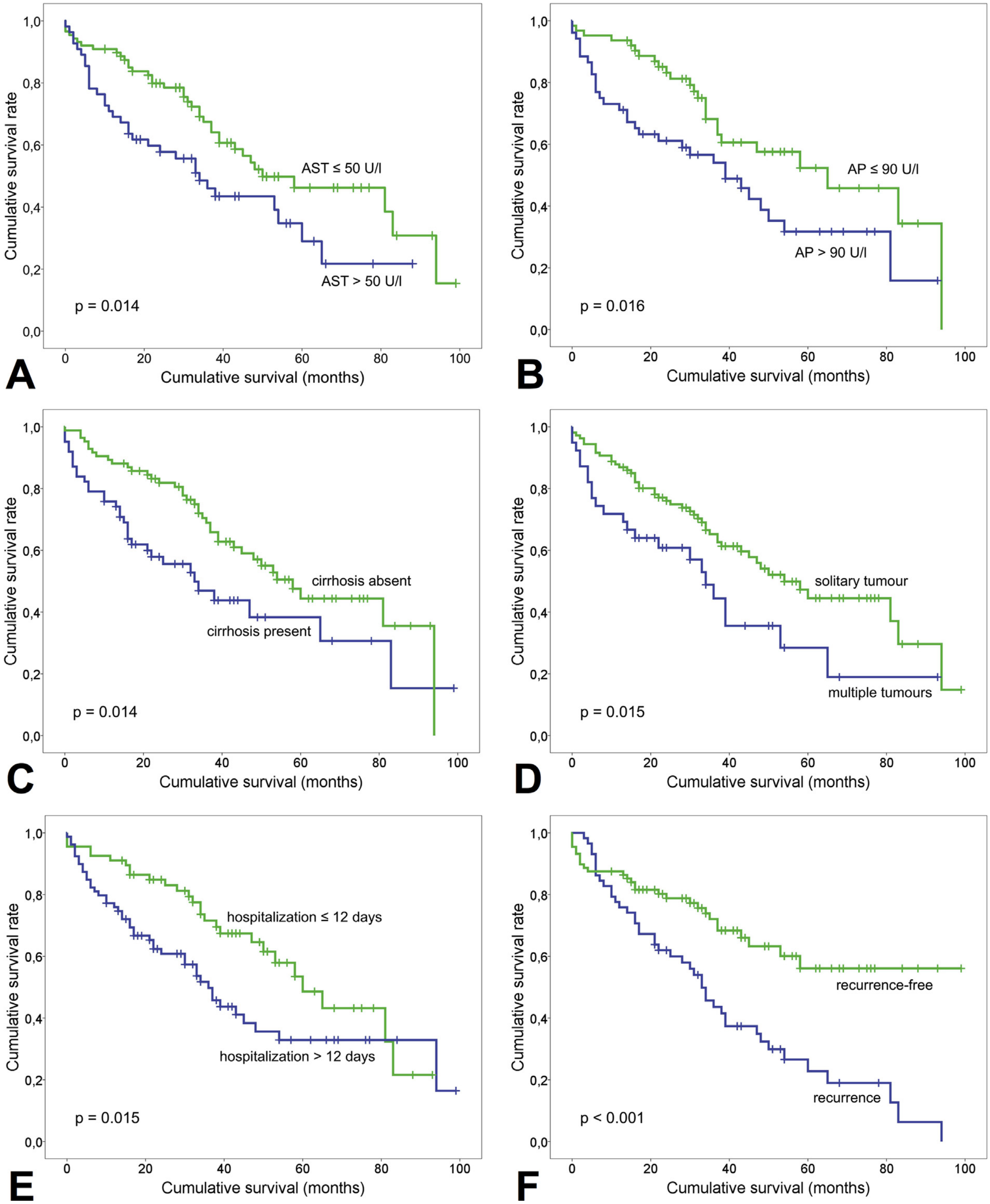

Fig. 2. Kaplan–Meier curves of the clinicopathological factors affecting the overall survival in the univariate analysis: A: Aspartate transaminase; B: Alkaline phosphatase; C: Liver cirrhosis; D: Tumour nodes; E: Hospitalization; F: Recurrence.

5. Conclusion

In conclusion, we have shown that disease-free survival is significantly affected by lymphatic invasion, UICC staging and impaired liver function by LiMAx test. Liver function capacity assessed by LiMAx test was the single parameter preoperatively available for clinical decision-making. Furthermore, this study identified that the severity of underlying liver disease has a significant impact on disease-free survival. Patients with impaired liver function determined by LiMAx test may be more likely to benefit from alternative treatment options such as liver transplantation or receive closer oncological follow-up.

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Table 4
Multivariate analysis data of overall survival.

Factors	Relative Risk	(95% CI)	p-value
Recurrence	4.885	(2.269–10.515)	< 0.001
Haemoglobin ≤12 g/dl	2.669	(1.349–5.281)	0.005
Multiple tumours	4.133	(1.299–13.148)	0.016
Liver cirrhosis	3.308	(1.550–7.060)	0.002
Lymphatic vessel invasion	3.534	(1.248–10.006)	0.017
UICC ≥ IIIA	5.993	(1.743–20.600)	0.004
Dindo ≥ IIIa	2.892	(1.357–6.163)	0.006

Declaration of interest

Martin Stockmann is the inventor of the LiMAx test and has capital interest in Humedics, the company marketing the LiMAx test. Jan Bednarsch received travel reimbursement from Humedics. Remaining authors have no conflicts of interest to declare. All authors acknowledge that the conflict of interest disclosure is complete for both themselves and their co-authors.

CRediT authorship contribution statement

Elisabeth Blüthner: Conceptualization, Methodology, Validation, Formal analysis, Data curation. **Jan Bednarsch:** Conceptualization, Methodology, Validation, Formal analysis, Writing - review & editing. **Maciej Malinowski:** Conceptualization, Validation, Writing - review & editing. **Phung Binder:** Formal analysis, Writing - review & editing. **Johann Pratschke:** Validation, Resources, Writing - review & editing. **Martin Stockmann:** Conceptualization, Validation, Resources, Data curation. **Magnus Kaffarnik:** Conceptualization, Methodology, Validation, Resources, Data curation.

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Abbreviations

HCC	hepatocellular carcinoma
AP	alkaline phosphatase
GGT	gamma-glutamyltransferase
ICG-PDR	indocyanine green plasma disappearance rate
AFP	α-fetoprotein
AST	aspartate aminotransferase
LiMAx	maximum liver function capacity
DFS	disease-free survival
DSR	disease-free survival rate
OSR	overall survival rate
ICU	intensive care unit
MELD	model of end-stage liver disease

Ethical approval

The study concept was approved by the Charité institutional ethics committee (EA2/032/14).

Source of funding

None.

Author contribution

Study concepts: EB, JB, MM, MS, MK.
Study design: EB, JB, MK.
Data acquisition: EB, PB.
Quality control of data and algorithms: EB, JB, MM, JP, MS, MK.
Data analysis and interpretation: EB, JB, PB.
Statistical analysis: EB, PB.
Manuscript preparation: EB, MS, MK.
Manuscript editing: EB, JB, MM, PB, JP, MS, MK.
Manuscript review: EB, JB, MM, PB, JP, MS, MK.

Conflicts of interest

Martin Stockmann is the inventor of the LiMAx test and has capital interest in Humedics, the company marketing the LiMAx test. Jan Bednarsch received travel reimbursement from Humedics. Remaining authors have no conflicts of interest to declare. All authors acknowledge that the conflict of interest disclosure is complete for both themselves and their co-authors.

Trial registry number

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Guarantor

Elisabeth Blüthner and Magnus Kaffarnik are fully responsible for this work.

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