Effect of Age on Liver Function in Patients Undergoing Partial Hepatectomy

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Keywords

Elderly · Age · LiMAx · Postresectional liver failure · Liver function

Abstract

Background: Postresectional liver failure is the most frequent cause of fatal outcome following liver surgery. Diminished preoperative liver function in the elderly might contribute to this. Therefore, the aim of the present study was to evaluate preoperative liver function in patients <60 or >70 years of age scheduled for liver resection. **Methods:** All consecutive patients aged <60 or >70 years who are about to undergo elective liver surgery between 2011 and 2013 and underwent the methacetin breath liver function test (LiMAx) preoperatively were included. Histologic assessment of the resected liver gave insight into background liver disease. Correlation between age and liver function was calculated with Pearson's test. **Results:** Fifty-nine patients were included, 31 were aged <60 and 28 were aged >70 years. General patient characteristics and liver function LiMAx values (340

(137–594) vs. 349 (191–530) µg/kg/h, $p = 0.699$) were not significantly different between patients aged <60 and >70 years. Moreover, no correlation between age and preoperative liver function LiMAx values was found ($R = 0.04$, $p = 0.810$). **Conclusion:** Liver function did not seem to differ between younger and older patients.

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Introduction

Liver resection is associated with considerable morbidity rates. The perioperative mortality rate is usually below 5% [1–4] and about 10% in patients undergoing complex major liver resections [5–8]. One of the main reasons for adverse postoperative outcome after hepatectomy is postresectional liver failure (PLF). A remnant liver that either is too small or has inadequate function is prone to this severe and often lethal complication. At least 25–30% of the total liver volume needs to be preserved to prevent PLF [9, 10] in otherwise healthy livers. For a safe liver resection

in patients with liver steatosis or fibrosis, it is already known that a larger remnant liver needs to be preserved.

The LiMAx methacetin liver function breath test is currently considered one of the most accurate liver function tests [11]. A remnant LiMAx value of over 100 µg/kg/h is considered sufficient to prevent PLF [11]. Despite improvements in preoperative assessment of patients undergoing major liver resections, PLF still occurs in up to 5% of all patients and remains difficult to predict [12].

In many centers, old age is a relative contraindication for resection of malignancies located in the liver because several multicenter nationwide studies have indicated that major morbidity and mortality rates have increased in the elderly [13, 14]. Hypothetically, elderly patients might have diminished liver function already preoperatively and this might explain or contribute to the higher mortality in this patient group. Preservation of a larger remnant might therefore be necessary for the elderly.

The aim of the present study was to evaluate preoperative liver function in patients undergoing partial hepatectomy <60 or >70 years of age.

Material and Methods

Patients

This study was conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul). In this retrospective study, all consecutive patients <60 or >70 years of age, undergoing elective liver surgery between January 2011 and September 2013, and who underwent a LiMAx [15, 11] methacetin liver function breath test prior to surgery at the RWTH University Hospital Aachen, were included. The decision for LiMAx evaluation was based on clinical indications (such as resection of 4 or more liver segments and known or suspected fibrosis or cirrhosis) and was made by the responsible surgeons. Patients who underwent portal vein embolization (PVE) prior to resection were only included when a pre-PVE LiMAx-test was performed. This pre-PVE test was then used as initial preoperative value.

Methods

Liver Function Test

The LiMAx test was used to assess hepatocyte specific metabolic function. This test is based on the metabolization of ¹³C-labelled methacetin (Euriso-top, Saint-Aubin Cedex, France) by the cytochrome P450 1A2 enzyme in the liver [15, 11]. After intravenous injection, ¹³C-labelled methacetin is instantly metabolized and the ratio between exhaled ¹³CO₂ and normal non-enriched background ¹²CO₂ is registered over a period of 60 min [11]. In patients undergoing resection of large volumes of the liver with limited LiMAx values, liver volumetry was performed to predict the future remnant LiMAx liver function value. A future remnant LiMAx liver function of 100 µg/kg/h was considered sufficient to prevent PLF [15]. If the surgical strategy would indicate leaving behind an insufficient liver remnant, a PVE or an ALPPS [16, 17]

(associating liver partition and portal vein ligation for staged hepatectomy) procedure was performed to enlarge the volume and function of the future liver remnant.

Outcome Parameters

Standard demographics, therapeutic, operative and outcome data were collected and subsequently analysed. Postoperative morbidity was graded according to the Dindo–Clavien classification [18]. Complications with a grade ≥3a were considered major complications. As the incidence of many liver surgery specific complications is low, differences between groups are difficult to analyse. Therefore, postoperative morbidity was also scored according to a liver-specific composite end point (LSCEP) consisting of ascites, PRLF, bile leakage, intra-abdominal hemorrhage, intra-abdominal abscess and operative mortality [19]. Morbidity and mortality rates are provided as 90-day morbidity and 90-day mortality rates, including all complications that were not present at discharge, but which led to readmissions or death within 90 days.

Liver Resection

Liver resection was performed as described previously [20]. After mobilization of the liver, intraoperative ultrasound provided insight into the feasibility of the preoperatively planned surgical procedure. To prevent excessive blood loss, central venous pressure was maintained below 5 cm H₂O during transection. Hilar inflow occlusion (Pringle maneuver) was performed for a maximum of 30 min in case of increased bleeding. If tumors invaded main bile structures and were still considered resectable, then a biliary tract resection and Roux-en-Y hepaticojejunostomy was performed. Need for vascular and portal vein resections and potential reconstruction were not considered to be the criteria for irresectability but were performed when needed. All liver resections were classified in accordance with the IHPBA Brisbane nomenclature [21].

Histopathology

One pathologist (N.G.) performed all pathologic examinations. Fibrosis of background liver tissue was classified using the Metavir score which among others consists of a 5-point fibrosis scale [22]. The degree of non-alcoholic steatohepatitis (NASH) was analyzed using the NASH Scoring system (NAS score) [23]. Finally, sinusoidal dilatation was scored on a 4-point scale as a measure of sinusoidal obstruction syndrome [24].

Statistical Analysis

Data were analyzed with SPSS version 20.0 (SPSS Inc., Chicago, Ill., USA) and Prism 5.0 for Macintosh (GraphPad software, Inc., San Diego, Calif., USA). Data were expressed as median (range). Chi-square tests were used to analyze categorical data while continuous data were analyzed with Mann–Whitney U tests. A level of *p* < 0.05 was considered statistically significant. Correlation between age and liver function was performed in patients with relatively healthy livers, that is, livers without cirrhosis (Metavir fibrosis scale stage 4 [22]), NASH (NAS score ≥ 5 [23]) or severe sinusoidal dilatation (sinusoidal dilatation score = 3 [24]). Patients without pathologic examination of liver tissue were excluded for correlation analysis. Correlation between age and liver function was calculated with Pearson's test. The resulting regression line was described as a linear equation and the correlation coefficient (*r*) was calculated.

Table 1. Clinical characteristics

Variables	All patients (n = 59)	Age <60 years (n = 31)	Age >70 years (n = 28)	p value
<i>Patient characteristics</i>				
Age, years, median (range)	58 (28–85)	54 (28–58)	74 (70–85)	<0.001
Gender, female	21 (35.6)	10 (32)	11 (39)	0.573
Height, m, median (range)	1.72 (1.55–1.93)	1.76 (1.60–1.93)	1.69 (1.55–1.89)	0.003
Weight, kg, median (range)	79 (47–109)	80 (50–109)	77 (47–104)	0.627
Body mass index, kg/m ² , median (range)	25.0 (18.7–37.7)	24.5 (18.7–37.7)	25.8 (19.2–36.0)	0.324
<i>ASA classification</i>				
ASA 1	5 (8.5)	4 (13)	1 (4)	0.199
ASA 2	26 (44.1)	13 (42)	13 (46)	0.728
ASA 3 or 4	28 (47.5)	14 (45)	14 (50)	0.710
Portal vein embolisation	21 (35.6)	11 (35)	10 (36)	0.985
<i>Preoperative liver function</i>				
LiMAx liver function, µ/kg/h, median (range)	340 (137–594)	340 (137–594)	349 (191–530)	0.699
<i>Preoperative laboratory details, median (range)</i>				
INR, ratio	1.03 (0.87–1.32)	1.01 (0.88–1.30)	1.05 (0.87–1.32)	0.485
Bilirubin, mg/dl	0.6 (0.2–3.7)	0.7 (0.2–2.5)	0.6 (0.2–3.7)	0.427
<i>Background liver</i>				
Metavir score, median (range)	1 (0–6)	2 (0–6)	1 (0–6)	0.192
NAS score, median (range)	1 (0–5)	1 (0–4)	1 (0–5)	0.236
Sinusoidal dilatation score, median (range)	0 (0–3)	0 (0–3)	0 (0–2)	0.228
Percentage with severe back-ground liver disease (cirrhosis, NASH or sinusoidal dilatation grade 3)	10.0	12	8	0.637
<i>Indication</i>				
Colorectal liver metastases	17 (28.8)	8 (26)	9 (32)	0.592
Other metastases	5 (8.5)	4 (13)	1 (4)	0.199
Hepatocellular carcinoma	7 (11.9)	3 (10)	4 (14)	0.585
Cholangiocarcinoma	25 (42.4)	13 (42)	12 (43)	0.943
Benign lesions	3 (5.1)	2 (6)	1 (4)	0.615
Other	2 (3.4)	1 (3)	1 (4)	–
<i>Laesion, median (range)</i>				
Size largest lesion, cm	5 (0–16)	5 (0–16)	6 (1–12)	0.215
Number of lesions	1 (0–6)	1 (0–5)	1 (1–6)	0.801
<i>Chemotherapy</i>				
Preoperative chemotherapy	12 (20.3)	7 (23)	5 (18)	0.653

Results

Patients

A total of 59 patients were included in the present study. Thirty-one patients were <60 and 28 were >70 years of age. General patient characteristics were comparable (table 1). PVE, to enlarge the future remnant liver volume before resection, was performed in 21 patients (35.6%). Most patients who were included underwent resection for cholangiocarcinoma (n = 25, 42.4%), colorectal liver metastases (n = 17, 28.8%) or hepatocel-

lular carcinoma (n = 7, 11.9%). No difference in indication between the 2 age groups was observed (table 1).

Liver Function

Liver function LiMAx values were 340 (137–594) µg/kg/h in patients <60 years and 349 (191–530) µg/kg/h in patients >70 years (p = 0.699). No correlation between age and preoperative liver function LiMAx values was found (R = 0.04, p = 0.810; fig. 1). Preoperative INR and bilirubin levels were comparable between the groups (table 1).

Fig. 1. Correlation graph between LiMax liver function value and age.

Fig. 2. LiMax liver function values according to complication grade. In the grey boxplot, all patients included in the present study are depicted. In the white boxplots, patients without complications, with Dindo–Clavien grade 1 or 2, 3 or 4 and 5 are shown, respectively.

Also, LiMax values were comparable between patients without complications and patients with Dindo–Clavien grade 1 or 2 ($p = 0.967$), grade 3 or 4 ($p = 0.856$) and grade 5 ($p = 0.889$; fig. 2).

Background Liver

Histologic evaluation was performed in 84.7% ($n = 50$) of all patients. The pathologist was unable to retrospectively analyze the background liver tissue in the remain-

ing 9 patients due to insufficient amount of background liver tissue. Three (6.0%) patients had liver cirrhosis. All cirrhotic patients were men and 2 were under the age of 60 years. There were 2 (4.0%) patients with severe sinusoidal dilatation and 1 (2.0%) patient had NASH (NAS score ≥ 5). However, there were no differences in Metavir, NAS and sinusoidal dilatation scores between patients <60 and >70 years. Moreover, presence of severe background disease was comparable in the 2 groups ($p = 0.637$; table 1).

Liver Resection

Operative details are depicted in table 2. Twenty-seven (45.8%) patients underwent an extended left or right hemihepatectomy, 19 (32.2%) patients underwent a left or right hemihepatectomy and 13 (22.0%) underwent smaller resections in livers with altered parenchyma due to fibrosis or cirrhosis. Surgical strategies were comparable between the 2 groups. However, patients <60 years more often underwent additional procedures, that is, ALPPS [17, 16], pylorus-preserving pancreaticoduodenectomy (PPPD) and vascular or biliary resections and/or reconstructions (22 (37.3%) vs. 7 (11.9%), $p = 0.002$). Consequently, the duration of surgery was significantly longer in patients <60 years than in the elderly (315 (120–510) vs. 253 (113–444) min, $p = 0.012$). An oncological complete resection without microscopic residual tumor was reached in 89.3% of patients <60 and 88.5% of patients >70 years ($p = 0.923$).

Length of Hospitalization

Postoperative nights spent in hospital were 17 (2–86) vs. 12 (5–81) nights in patients <60 and >70 years, respectively ($p = 0.171$).

Mortality

One (3.2%) patient <60 years of age suddenly died from cardiopulmonary failure due to a coronary stenosis after he had recovered completely from surgery. In the group of patients >70 years, 3 (10.7%) patients died, 2 of septic complications and 1 of PLF and bowel ischemia. The difference in mortality did not reach statistical significance ($p = 0.253$; table 3).

Morbidity

Twenty-six (83.9%) patients aged <60 years and 18 (64.3%) patients aged >70 years developed complications ($p = 0.084$). Major complication rates did not differ statistically between the groups, 58.1 vs. 39.3% in patients <60 and >70 years, respectively ($p = 0.150$). Thirty-two

Table 2. Comparison of surgical strategies, pathological details and length of hospital stay

Variables	All patients (n = 59)	Age <60 years (n = 31)	Age >70 years (n = 28)	p value
<i>Resection</i>				
Right hemihepatectomy	17 (28.8)	9 (29.0)	8 (28.6)	0.969
Left hemihepatectomy	2 (3.4)	0 (0.0)	2 (7.1)	0.130
Right extended hemihepatectomy	25 (42.4)	15 (48.4)	10 (35.7)	0.325
Left extended hemihepatectomy	2 (3.4)	1 (3.2)	1 (3.6)	–
Uni-segmentectomy or multi-metastasectomy	6 (10.2)	4 (12.9)	2 (7.1)	0.465
Multi-segmentectomy	7 (11.9)	2 (6.5)	5 (17.9)	0.176
<i>Operative details</i>				
Estimated blood loss, ml, median (range)	1,000 (100–5,500)	600 (100–5,500)	1,350 (300–2,500)	0.480
Duration of operation, min, median (range)	284 (113–510)	315 (120–510)	253 (113–444)	0.012
Percentage with Pringle manoeuvre	10.5	6.5	15.4	0.274
ALPPS procedure	6 (10.2)	4 (12.9)	2 (7.1)	0.465
Combined with PPPD	2 (3.4)	2 (6.5)	0 (0.0)	–
Additional vascular or biliary procedure	21 (35.6)	16 (51.6)	5 (17.9)	0.007
<i>Postoperative laboratory details, median (range)</i>				
INR on POD 5, ratio	1.11 (0.94–1.45)	1.13 (0.94–1.45)	1.09 (1.00–1.38)	0.599
Bilirubin POD 5, mg/dl	0.8 (0.4–5.1)	0.8 (0.5–5.1)	0.7 (0.4–3.7)	0.134
Peak bilirubin, mg/dl	1.7 (0.5–23.1)	1.8 (0.9–23.1)	1.5 (0.5–10.2)	0.060
<i>Pathology</i>				
Percentage with R0 resections	88.9	89.3	88.5	0.923
Percentage with R1 resections	11.1	10.7	11.5	0.923
<i>Length of hospital stay, days, median (range)</i>				
Intensive care unit	1 (0–38)	1 (1–31)	1 (0–38)	0.585
Postoperative nights	15 (2–86)	17 (2–86)	12 (5–81)	0.171
LOS	17 (6–112)	18 (7–87)	15 (6–112)	0.174
<i>Readmissions</i>				
Number of patients readmitted	15 (25.4)	11 (35.5)	4 (14.3)	0.062
Postoperative nights including readmission, days, median (range)	15 (5–90)	19 (5–90)	13 (5–81)	0.106

(54.2%) patients developed one or more items of the LSCEP. Thus, 19 (61.3%) patients <60 years and 13 (46.4%) patients >70 years met at least one of the criteria for the LSCEP ($p = 0.253$). Detailed comparison of all complications is depicted in table 3.

Discussion

Large nationwide studies have indicated that morbidity and mortality rates have increased in elderly patients undergoing liver resection [13, 14]. As this might be because of preoperatively diminished liver function, the present study aimed at evaluating the effect of age on preoperative liver function in patients scheduled for partial hepatectomy. Preoperative liver function as-

sessed with the LiMAx test was not significantly different between patients <60 and >70 years of age. Moreover, no correlation between age and liver function was found.

As the present study has shown that the preoperative LiMAx liver function values were not significantly different between patients <60 and >70 years of age, the hypothesis that elderly patients show higher mortality rates due to diminished preoperative liver function and predisposition for PLF seems difficult to sustain. However, it could still be that the liver's ability to regenerate after partial resection is diminished causing increased risk of PLF and increased mortality after hepatectomy [13, 14]. The latter is also supported by a recent study of Shirabe et al. [25] showing that age was inversely correlated with liver regeneration in the first week after hepatectomy.

Table 3. Complications

Variables	All patients (n = 59)	Age <60 years (n = 31)	Age >70 years (n = 28)	p value
<i>Grading of complications</i>				
Number of patients with complications	44 (74.6)	26 (83.9)	18 (64.3)	0.084
Minor complications present	15 (25.4)	8 (25.8)	7 (25.0)	0.943
Clavien–Dindo grade 1	1 (1.7)	1 (3.2)	0 (0.0)	–
Clavien–Dindo grade 2	14 (23.7)	7 (22.6)	7 (25.0)	0.827
Major complications present	29 (49.2)	18 (58.1)	11 (39.3)	0.150
Clavien–Dindo grade 3a	17 (28.8)	12 (38.7)	5 (17.9)	0.077
Clavien–Dindo grade 3b	5 (8.5)	3 (9.7)	2 (7.1)	0.727
Clavien–Dindo grade 4a	2 (3.4)	1 (3.2)	1 (3.6)	–
Clavien–Dindo grade 4b	1 (1.7)	1 (3.2)	0 (0.0)	–
Clavien–Dindo grade 5	4 (6.8)	1 (3.2)	3 (10.7)	0.253
<i>LSCEP</i>				
Number of patients with 1 or more items of LSCEP	32 (54.2)	19 (61.3)	13 (46.4)	0.253
Ascites	8 (13.6)	5 (16.1)	3 (10.7)	0.544
Postresectional liver failure	1 (1.7)	0 (0.0)	1 (3.6)	–
Bile leak	11 (18.6)	7 (22.6)	4 (14.3)	0.414
Intra-abdominal hemorrhage	7 (11.9)	4 (12.9)	3 (10.7)	0.795
Intra-abdominal abscess	16 (27.1)	9 (29.0)	7 (25.0)	0.728
Mortality	4 (6.8)	1 (3.2)	3 (10.7)	0.253
<i>Other liver-related complications</i>				
Hepatic encephalopathy	1 (1.7)	1 (3.2)	0 (0.0)	–
Cholangitis	3 (5.1)	3 (9.7)	0 (0.0)	0.091
Portal vein thrombosis	1 (1.7)	1 (3.2)	0 (0.0)	–
<i>Other complications</i>				
Sepsis	4 (6.8)	2 (6.5)	2 (7.1)	0.916
Cardiovascular	6 (10.2)	2 (6.5)	4 (14.3)	0.320
Pulmonary	13 (22.0)	7 (22.6)	6 (21.4)	0.915
Renal	3 (5.1)	1 (3.2)	2 (7.1)	0.494
Gastrointestinal	15 (25.4)	9 (29.0)	6 (21.4)	0.503
Dermatologic	2 (3.4)	0 (0.0)	2 (7.1)	–
Wound infection	4 (6.8)	1 (3.2)	3 (10.7)	0.253
Fascial dehiscence	2 (3.4)	1 (3.2)	1 (3.6)	–

Comparing morbidity between patients <60 and >70 years of age in the present study was not really appropriate as the extent of surgery (i.e., ALPPS strategy, additional PPPD, additional vascular or biliary procedures) differed between the groups. Although this resulted in fewer complications in the elderly, the mortality rate, though not significantly, still tended to be increased in this group. Tzeng et al. [13] already concluded in a large multicenter study on predictors for morbidity and mortality in elderly that if elderly patients develop severe complications, the chance of fatal outcome is increased due to diminished physiologic reserve. The data in the present study seem in line with that conclusion.

The whole cohort mortality rate in the present study (6.8%) is fairly high when compared with other studies looking at the overall population with predominantly plain resections [1–4]. All patients included in the present study however were operated in a tertiary referral center and underwent preoperative LiMAx testing, which is done mainly in case of large resections; therefore, a selection bias was present. Almost 80% of all patients underwent major hepatectomy (resection of 3 or more segments) and almost half (49.1%) of all patients underwent additional procedures. When these additional procedures are taken into account, the overall mortality rate of 6.8% and mortality rate in elderly of 10.7% seem reasonable and are comparable with other studies evaluating out-

come after extensive liver resection (5.4–25.0%) [5–8]. Also the high complication rate of 74.6% in the present study is in line with other studies looking into large and complex liver resection that showed morbidity rates of up to 76% [26].

Studies evaluating the safety of liver surgery do not use a standard cutoff value to define the elderly. Most studies define the ‘elderly’ as patients >70 [27, 28] or 75 [29], while others use 65 [30] or even 80 [31] years of age. When the elderly are compared with younger patients, practically all studies choose to include all patients above and under a certain age (e.g., comparing patients >75 with patients <75 years) [9, 13, 27–29, 31]. Borderline elderly in studies conducted according to such definitions might well affect the clarity of the results and messages as slight differences in age may put patients in different cohorts. The design of the present study therefore left a gap of 10 years between the elderly population and the relatively young population to avoid ‘cross contamination’ and hence enhance possible differences in preoperative liver function.

This study included patients in a small period of time in which perioperative care has not changed and this may be considered a strong point of this study. To date, there is no gold standard for evaluation of the liver function. However, the use of the LiMAx methacetin breath test seems a relative strong point of the study as conventional liver function analysis using blood parameters or scoring systems (i.e., the Model of End-Stage Liver Disease score and the Child-Pugh score) have shown to be insufficient for reliable prediction of the remnant liver function after partial hepatectomy [32–34]. Multiple dynamic tests, such as the Indocyanin Green clearance or the LiMAx methacetin breath test, have been proposed and seem to provide more information on liver function [15, 35]. Moreover, the LiMAx test is believed to be able to validly determine liver function [15]. The high complication rate underlines the adequate complication registration in RWTH University Hospital Aachen. Many studies underestimate mortality and morbidity rates as they use 30, 60 days or in hospital morbidity and mortality, which underestimate the actual numbers. Complications leading to readmissions are therefore often not reported. The present study used 90-day morbidity and mortality, and consequently also included all complications when patients were readmitted. The small sample size, however, is a downside as some parameters might have reached significance if the sample size would have been larger. Although no significant differences between the groups were found on background liver disease and in-

dication for surgery, the heterogeneity of the study population and therefore of the background liver disease is a weakening factor possibly influencing the results. This probably also explains the large differences in LiMAx values between patients (fig. 1). Larger studies evaluating preoperative liver function and postoperative functional regeneration in a homogenous population of patients <60 and >70 years of age are needed to clarify the effect of age on regeneration capacity and to investigate whether diminished regeneration capacity is the actual cause of increased morbidity and mortality in elderly patients. As in recent years the indications for resection have been broadened triggered by continuous improvements in surgical technique and perioperative care [3, 36, 37], the effect of age on morbidity and mortality might also possibly have changed. New larger studies, in modern day cohorts, are therefore needed to investigate the effect of age on complications as it might be that old age should no longer be considered a relative contraindication for resection.

In conclusion, elderly patients scheduled for liver resection do not seem to have impaired preoperative liver function. Thus, the present study could not confirm a link between age and diminished liver function that might explain any increased morbidity and mortality rates in the elderly undergoing liver resection. Mortality rates, though not significant, tended to be increased in the elderly.

Statement of Ethics

This study did not require informed consent nor review/approval by the appropriate ethics committee.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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