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THE ALPPS PROCEDURE: IMPACT OF KINETIC GROWTH RATE AND RENAL FUNCTION

PhD thesis

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Abbreviations

AKI ..... Acute Kidney Injury
ALPPS .... *Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy*
ASA ..... *American Society of Anesthesiologists*
BMI..... *Body Mass Index*
CCC ..... *Cholangiocellular Carcinoma*
CCI ..... *Comprehensive Complications Index*
CKD..... *Chronic Kidney Disease*
CRLM..... *Colorectal Liver Metastasis*
FFP ..... *Fresh Frozen Plasma*
FLR..... *Future Liver Remnant*
GFR ..... *Glomerular Filtration Rate*
HCC..... *Hepatocellular Carcinoma*
HIDA ..... *Hepatobiliary Iminodiacetic Acid*
ICG ..... *Indocyanine Green*
INR ..... *International Normalized Ratio*
IQR ..... *Interquartile* Range
ISGLS ..... *International Study Group of Liver Surgery*
KDIGO ..... *Kidney Disease: Improving Global Outcome*
KGR..... *Kinetic Growth Rate*
LiMAx ..... *Liver Maximum Function Capacity*
MELD..... *Model for End Stage Liver Disease*
PHLF ..... *Posthepatectomy Liver Failure*
POD ..... *Postoperative Day*
PRBC..... *Packed Red Blood Cells*
PVE..... *Portal Vein Embolization*
RI ..... *Renal Impairment*
sCr..... *Serum-Creatinine Levels*
sFLR ..... *Standardized Future Liver Remnant*
SMI ..... *Sarcopenia Muscle Index*
TELV..... *Total Estimated Liver Volume*

1 Introduction

For various benign liver lesions and primary and secondary liver malignancies, the resection of the tumour is an essential component in a multidisciplinary setting for curative treatment [1–4]. In the treatment of hepatocellular carcinoma (HCC), liver resection is a treatment option and results in a 5-year survival of 50-70% at early stage [4] and 30-60% at advanced or multinodular stage [5], compared to an overall survival rate of 10-15% [4]. The same beneficial effect of liver resection can be seen for colorectal liver metastasis (CRLM) and intrahepatic cholangiocellular carcinoma (CCC). Overall 5-year survival is described between 40-70% [6–8] for patients undergoing liver resection for CRLM in contrast to 9% for unresectable patients [8]. For CCC the survival for resected patients is described at 20-40% [9, 10] and decreases to almost 0% for patients that do not receive a resection [11].

However, liver resection is associated with postoperative morbidity and mortality, which has significantly decreased over the last decades [12]. Improvements in anaesthesia, surgical technique, and intensive research in the field of outcome, complications and its risk factors made liver surgery a safe operation in experienced centres [13, 14]. In current literature morbidity after liver resection remains around 20-45% and 2-4% for mortality [15]. Risk factors for morbidity and mortality after liver resection can be classified into preoperative, intraoperative, and postoperative parameters.

1.1 Preoperative Risk Factors for Morbidity after Liver Resection

The main preoperative risk factors are comorbidities (e.g., age, ASA-Score, high body mass index (BMI), hypertension, pulmonary disease or cardiovascular disease) and liver related factors (e. g. cirrhosis, jaundice, cholangitis, bleeding disorders, or preoperative chemotherapy because of liver malignancies) [15]. In addition, several preoperative laboratory values were identified (e. g. high bilirubin, low platelet count, high transaminase levels or high creatinine levels) for a high risk of a complicated postoperative course [15].

1.1.1 Sarcopenia

Sarcopenia is a skeletal muscle disorder that involves the loss of muscle mass and function, which is related to age [16, 17]. Multiple factors causing sarcopenia have been identified, [18] occurring in 6-22% of older people [19]: The main cause for sarcopenia

is the process of aging, which involves changes in hormones, neuro-degenerative diseases, malabsorption, inflammatory factors, intermuscular fat infiltration and a transition of muscle fibres from the fast and higher glycolytic active type II to the slower type I [16, 20]. These factors can lead to an imbalanced homoeostasis, which results in a loss of hypertrophy and regeneration of muscles [16].

The latest studies on sarcopenia in hepatobiliary surgery show evidence of increased morbidity and mortality after major liver surgery in patients with CRLM and hepatocellular carcinoma [21–23]. Furthermore, a smaller total estimated liver volume [24], as well as negative effects in combination with other severe diseases have been connected to the skeletal muscle disorder [25–29]. Recent work showed that sarcopenia reduces the hypertrophy after portal vein embolization (PVE) and therefore seems to be a negative cofactor for hypertrophy [21, 30].

1.2 Intraoperative Risk Factors for Morbidity after Liver Resection

The most common intraoperative parameters for an impaired postoperative outcome are prolonged operative time, open surgery, major hepatectomies, pedicular clamping time and blood loss including transfusions [15].

1.2.1 Extended Liver Resections

The extend of liver resections is dictated by tumour size, location, and aetiology. It is known, that a minor liver resection comes along with a lower morbidity compared to a major liver resection (>3 segments) [31]. In a large retrospective study, a trisectionectomy had a 2,54-fold increase in complications and 5,07-fold increase in posthepatectomy liver failure compared to partial hepatectomies. This increase is also seen in laparoscopic liver resections [32]. The loss of liver tissue (up to 70% of the total parenchyma) because of the resection correlates with the morbidity and mortality after resection [33].

1.2.2 Associating liver partition and portal vein ligation for staged hepatectomy

When the future liver remnant (FLR), the remaining liver tissue after resection, is too low and the risk for a posthepatectomy liver failure (PHLF) is too high, there are several hypertrophy-procedures available. A surgical solution to a larger FLR is the Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure. This is a surgical two-step procedure for the treatment of malignancies in the liver, which was first described in 2012 [34, 35]. During the first step the right portal vein is ligated, and

the parenchyma is dissected in the future resection line. Is there is tumour in the FLR, local resections are performed. In the interstage-phase the FLR increases in size and studies show that the regenerative response is much higher compared to PVE [36]. The second step – the major hepatectomy – can only be performed with a sufficient FLR, otherwise the risk of PHLF and postoperative mortality increases [9, 34, 35, 37]. First studies about ALPPS showed a very high morbidity and mortality and therefore this technique was highly discussed and criticised [38–40]. It became evident, that a strict patient selection is necessary to avoid a high risk of postoperative complications and mortality [41, 42] and several modifications were introduced to lower the surgical trauma [34, 39]. Despite the critique of ALPPS, most comparative studies showed similar results regarding complications, completion rate or long term outcome [36, 43–46].

1.3 Hypertrophy of the Future Liver Remnant

Regarding the FLR, a minimum future FLR volume of 25-30% seems necessary in a healthy liver to reduce the risk of a PHLF. However, in a pre-exposed liver (e.g., due to liver cirrhosis, chronic hepatitis) the required FLR varies between 30-50% [47, 48].

The hypertrophy rate can vary among individual patients [49, 50]. Many studies have been analysing different influences on the FLR[21, 51]. Factors such as hepatic steatosis, a high BMI, previous infections, high plasma total protein, and neoadjuvant chemotherapy have been associated with a decreased liver hypertrophy following PVE [49, 51, 52]. PVE can be used as an alternative to ALPPS, if the FLR has no tumour, and it can be assumed that the same factors influencing the hypertrophy also apply to ALPPS. The kinetic growth rate (KGR) is established as an independent and important parameter for monitoring the hypertrophy after PVE or ALPPS [53, 54]. The KGR declares how much percentage per week the FLR has increased. For PVE a study showed that a KGR of <2%/week is associated with a high PHLF-rate [55]. A KGR of >2%/week had no PHLF. There is, however, limited information available on how the KGR is being influenced during ALPPS.

1.4 Postoperative Risk Factors for Morbidity after Liver Resection

After liver resection, the use of blood transfusions and a decrease of albumin levels are associated with an impaired outcome and increase in complications [15]. Also high

bilirubin and lactate levels after surgery are described as predictive factors for complicated postoperative course [15].

1.4.1 Acute Kidney Injury

Acute kidney injury (AKI) after liver resection occurs approximately in 8-15% of the cases [56–58]. The incidence of AKI increases after major hepatectomy compared to a minor hepatectomy [56, 59]. Liver resection is associated with an increased morbidity and mortality when AKI occurs [56–58, 60].

There are two main mechanisms to develop an AKI after liver resection. Large amounts of blood loss during resection and intraoperative hemodynamic instability can lead to a renal hypoperfusion and therefore an impaired renal function [59–61]. On the other hand, a postoperative liver dysfunction or even liver failure leads to disarranged circulatory changes and hepatorenal syndrome [60].

Risk factors for AKI after liver resection can be divided into pre-, intra- and postoperative parameters. The most common preoperative risk factors are age, comorbidities (kidney disease, heart failure, diabetes) and an elevated alanine transaminase [58] or increased Model for End-Stage Liver Disease (MELD)-Score [57]. During the operation, the use of hepaticojejunostomies, prolonged operative time [57, 62] and the number of blood transfusions [56–58, 62, 63] are described to lead to an AKI. Therefore, the primary risk factor for AKI remains the complexity of liver resection. This is because certain parameters, such as blood loss or operation duration, are often a surrogate marker for the extent and complexity of liver surgery. Several studies investigating risk factors for AKI included minor and major hepatectomy, and therefore risk factors are often related to the extent of resection. Furthermore, no study included ALPPS. With a long operative time, high blood loss and high morbidity [38] an increased incidence of AKI can be presumed. In addition, a study identified elevated serum creatinine level before stage-2 as a risk factor for mortality [42].

2 Objectives

Study #1 – The aim of this study was to investigate the impact of the kinetic growth rate within the ALPPS procedure. An investigation will be conducted to determine whether there is a cut off value of KGR to develop PHLF and a correlation of sarcopenia with renal complications subsequent to the second stage.

Study #2 – The aim of this study was to perform a detailed investigation of renal function during ALPPS, particularly in the interstage interval. It is unknow, if an interstage renal failure leads to severe outcome and if a recovery of the renal function lowers the risk of postoperative outcome.

Study #3 – The aim of this study was to analyse the effect of AKI on the perioperative outcome after ALPPS. Furthermore, the study investigates whether ALPPS is a risk factor for AKI in a cohort of high- risk patients (extended liver resections including ALPPS).

3 Methods

3.1 Patient selection and databases

During the study period from January 2010 until December 2020, 1910 patients underwent liver resection at the Division of Hepatobiliary and Pancreatic Surgery in the Asklepios Hospital Barmbek, Hamburg, Germany and those were screened for retrospective analysis.

For study #1 [64], all patients undergoing ALPPS were included for KGR-evaluation. Patients that did not proceed with the second step of ALPPS were not excluded. For study #3 [65], the study period was from January 2010 until May 2018 and patients were excluded if they did not undergo the second step of ALPPS, because this study focuses on the renal function after major resections. In this study patients receiving an extended left hepatectomy, extended right hepatectomy or ALPPS were included to investigate differences in AKI incidences.

For the assessment of renal function during ALPPS-procedure (study #2 [66]), data was obtained from the International ALPPS Registry (www.alpps.net) from 2010 until 2018, which uses the data capture system SecuTrial (Interactive System, Berlin, Germany). The ALPPS-Registry is registered at ClinicalTrials.gov (NCT01924741). Data export took place on August 21th, 2018. The database was screened for preoperative serum-creatinine levels (sCr). When preoperative sCr levels were not available, the patient was excluded. In the database, sCr level were entered before stage-1, on postoperative day (POD) 5 after stage-1, before stage-2 and on POD 5 after stage-2.

3.2 Ethical approval

Approval of the local ethical committee was obtained (WF-009/21 and WF-007/19). For the ALPPS-Registry, an approval of the Scientific Committee of the Registry was obtained.

3.3 Data and definitions

The International Study Group of Liver Surgery (ISGLS) definition was used to characterise posthepatectomy liver failure. PHLF was defined as postoperative deterioration in the ability of the liver to synthesise, excrete, and detoxify substances, manifested by hyperbilirubinemia (Bilirubin $\geq$ 1,2 mg/dl) and increased International

Normalized Ratio (INR) (INR > 2) on or after POD 5. Corresponding to the severity of PHLF, it is partitioned to three grades. Grade A has abnormal laboratory values, but no change in clinical management. For grade B, the clinical management deviate from the standard management, but does not require invasive interventions. Grade C, requires invasive treatment [67]. In the ALPPS-Registry, the PHLF is defined according to the according to the 50-50 criteria [68], defined as hyperbilirubinemia with >50 μmol/L and a prothrombin time of <50% on the 5th postoperative day. For summarisation of the comorbidities, the Charlson-Comorbidity Index was calculated based on the published formula [69]. All complications occurred after liver resection were graded with the Clavien Classification [70]. Grade 0 is classified as no complication, and grade I as a deviation from normal postoperative course without the need for pharmacological treatment (this does not include the use of electrolytes, antipyretics, diuretics, analgesics, and antiemetics). For grade II, a pharmacological treatment, other than medication allowed for grade I, is needed, which includes parenteral nutrition and blood transfusions. Grade IIIa complications require interventions without general anaesthesia (e.g. endoscopy) and grade IIIb require interventions under general anaesthesia (e.g. re-operation). A single organ failure is defined as grade IVa and multiorgan dysfunction as grade IVb. The death of a patient is graded as grade V. Those complications were cumulated with the Comprehensive Complications Index (CCI) [71].

According to Kidney Disease: Improving Global Outcome (KDIGO) [72], an AKI was defined as an increase of sCr by ≥ 0.3 mg/dL within the first postoperative 48 hours or an increase of sCr to ≥ 1.5 times of the preoperative baseline. According to the definition, stage 1 is defined as an increase of sCr 1.5-1.9 times the baseline or ≥0.3 mg/dL, stage 2 as an increase of sCr 2-2.9 times the baseline, and stage 3 as an increase of sCr 3 times baseline or ≥4 mg/dL. To calculate the Glomerular filtration rate (GFR), the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation [73] was used. In the ALPPS-Registry study, sCr values were entered on the 5th postoperative day, therefore interstage renal impairment (RI) (based on the AKI-KDIGO-criteria) was defined as an increase of sCr on the 5th postoperative day of ≥0.3mg/dl or ≥1.5x compared to the preoperative value.

3.4 Volumetric measurements

For all included patients a volumetric evaluation of the FLR was performed. For the AKI and sarcopenia studies, preoperative computed tomography scans with 5mm reconstructions the FLR was manually outlined on axial planes. On an Advantage Workstation 4.1.2 (GE Healthcare) the volumetric calculation was performed. If necessary, masses such as tumour, cysts and portal branches and bile ducts were excluded. The total estimated liver volume (TELV) was calculated using the body surface area [74, 75]. The TELV was then used to calculate the standardized future liver remnant (sFLR) for each patient. For staged procedures, a volumetric analysis was performed before each step or intervention. Absolute growth (ml), KGR, relative growth (%) and degree of hypertrophy were calculated [55, 74, 75].

For the ALPPS-Registry study, the analysis was performed within the hospital with the available software.

3.5 Sarcopenia muscle index

The axial planes of the preoperative computer tomography were used to assess the sarcopenia muscle index. On the 3rd lumbar vertebra, the area of both psoas major muscles was measured using the Picture Archiving Communication System (PACS: IDS 7 Sectra, Linköping, Sweden). The sarcopenia muscle index (SMI) was calculated: left and right psoas major muscle [cm^2] divided by the squared height of the patient [m^2].

3.6 Statistical analysis

Continuous variables are reported as median (interquartile range, IQR), as mean (standard deviation) and as numbers with proportions (%), where appropriate. The differences of proportions from categorical data were compared using the Pearson $\chi 2$ tests and continuous variables were compared using the Mann–Whitney U or Students-t-Test, where appropriate. To calculate a cut-off value for KGR for PHLF, an area under the curve measurement was performed. For multivariate analysis, a backward stepwise logistic regression analysis was performed to calculate independent risk factors. Kaplan-Meier curves were used to perform survival analysis, and the log-rank test was used for analysis. Patients who were lost to follow-up or whose follow-up time ended were censored. For all tests, a p-value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS statistical software v23© or v25© for Mac.

4 Results

4.1 Kinetic Growth Rate during Associating liver partition and portal vein ligation for staged hepatectomy

During the study period from January 2010 to December 2020, 90 patients underwent ALPPS. This cohort contained 62 patients with CRLM (69%), 10 with non-colorectal-non-neuroendocrine liver metastasis (11%), eight with HCC (9%), seven with intrahepatic CCC (8%), two with perihilar CCC (2%), and one with gallbladder cancer (1%). Only 12 patients (13%) did not undergo the second step of the ALPPS-Procedure. Lack of hypertrophy (six patients), tumour progression (five patients) and death due to complications (one patient) were the reasons for not proceeding to the second step. Of the five patients who failed the second step due to tumour progression, three had CRLM, one hepatocellular carcinoma and one intrahepatic cholangiocellular carcinoma.

4.1.1 Cut-off value calculation of Kinetic Growth Rate for Posthepatectomy Liver Failure

Calculations of the area under the curve showed that a KGR of 7%/week or more is required to achieve a significant reduction in the incidence of PHLF. Figure *1* shows the probability of PHLF regarding the KGR. In the group with a KGR below 7%, 16 patients (31%) experienced PHLF. Only two patients (7%) with a higher KGR experienced PHLF

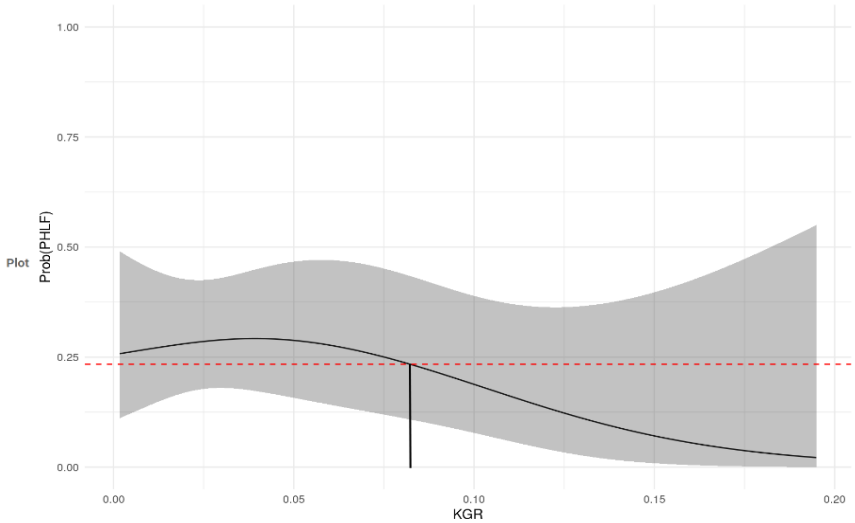

Figure 1 – Kinetic Growth Rate of >7%/week reduces the incidence of PHLF [55]. AUROC analisis revealed a cutoff value for KGR at >7%/week. Patients with a KGR <7%/week had a high rate of PHLF (31%)

(p=0.02). The sensitivity was 88% and the specificity 43%. 61 patients (67%) had a KGR <7%/week and 29 (33%) a KGR >7%/week.

4.1.2 Preoperative Characteristics regarding Kinetic Growth Rate

Preoperative characteristics showed no differences between patients with a low KGR (<7%/week) and a high KGR (>7%/week) regarding sex, age, comorbidities, and neoadjuvant chemotherapy (**Table 1**). The kidney function was also comparable between both groups.

Table 1 - Preoperative patient characteristics stratified by kinetic growth rate

	Low KGR <7%/week		**High KGR >7%/week**		**p value**
Females, n (%)	19	(31,1)	6	(20,7)	0.301
Age (years), median (IQR)	61	(50-72)	56	(53-68)	0.185
BMI [kg/m^2], median (IQR)	25	(22-29)	24	(22-27)	0.369
Comorbidities, n (%)					
Diabetes mellitus, n (%)	8	(13)	1	(4)	0.166
Hypertension, n (%)	24	(39)	11	(38)	0.996
Kidney disease, n (%)	4	(6)	0	(0)	0.166
sCr (mg/dl), median (IQR)	0,8	(0.8-1.0)	0.9	(0.8-0.9)	0.975
GFR (ml/min), median (IQR)	89	(75-90)	88	(82-90)	0.647
Anemia, n (%)	33	(54)	11	(38)	0.152
Neoadjuvant chemotherapy, n (%)	33	(54)	18	(64)	0.367
Charlson Index, median (IQR)	7	(5-8)	7	(6-8)	0.854
Skeletal muscle index, mean (IQR)	5.7	(4.8-6.7)	6.9	(5.8-7.5)	**0.017**

4.1.3 Sarcopenia Muscle Index as a risk factor for a low KGR

Patients with low KGR (<7%/week) had an SMI of 5.7 cm^2/m^2 (4.8 - 6.7), whereas patients with high KGR (>7%/week) had an SMI of 6.9 cm^2/m^2 (5.8 - 7.5) (p=0.017, Figure *2*). SMI was the only preoperative factor showing a statistically significant difference between groups.

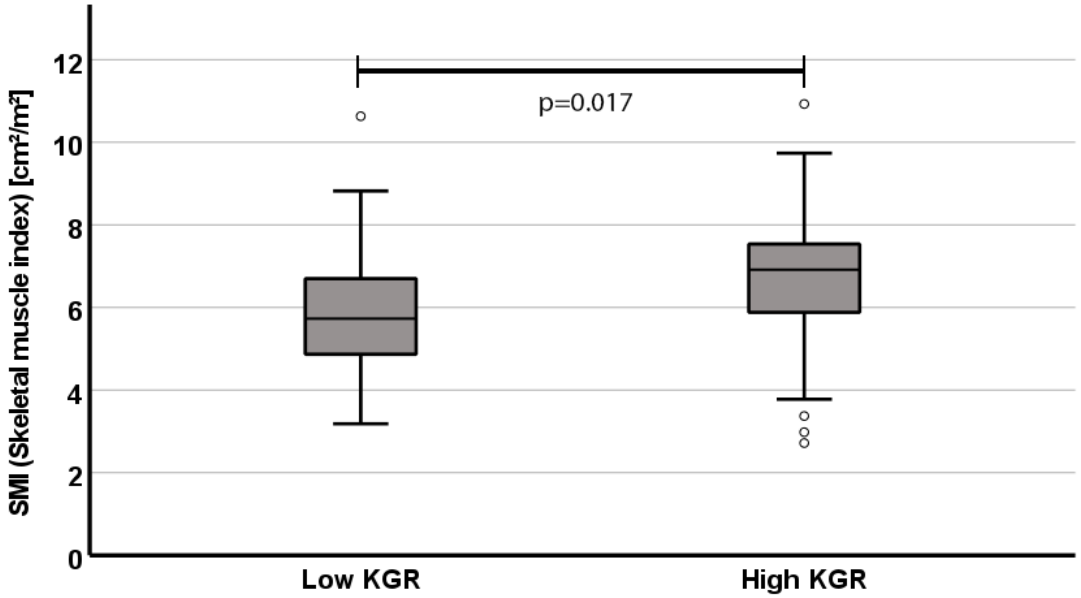

Figure 2 – SMI and KGR [55]. Patients with a low KGR (<7%/week) had a lower SMI compared to a high KGR. SMI was the only significant preoperative parameter.

An elevated BMI (p=0.021) and a decreased SMI (p=0.008) were the only independent risk factors for a low KGR (**Table 2**) in the multivariate logistic regression analysis. Parameters such as the preoperative FLR, Age, comorbidities or complications between steps were not significant.

Table 2 - Multivariate logistic regression: Risk factors for low KGR (<7%/week)

Parameter	OR	95% Cl		p value
		Lower	Upper	
Age (years)	1.016	0.976	1.058	0.436
Charlson Comorbidity Index	0.909	0.756	1.093	0.312
sFLR-pre-Step 1 (%)	5.876	0.032	1069.9	0.505
Interstage Complication Index	0.985	0.965	1.005	0.147
BMI [kg/m^2]	1.182	1.023	1.367	**0.024**
SMI [cm^2/m^2]	0.597	0.408	0.875	**0.008**

4.1.4 Operative characteristics of ALPPS-Step-1 and interstage complications

First stage operative parameters showed no significant difference between the two groups regarding KGR. Furthermore, interstage complications such as bile leak, bleeding and infection were not significantly different between the two groups (Table 3). Interestingly, interstage PHLF was 20% for low KGR compared to 7% with a high KGR (p=0.112). Regarding the volumetric analysis, the preoperative FLR was comparable between groups. Not surprisingly, a much higher and faster hypertrophy of the FLR can be seen for the group with the KGR of >7%/week, which also had a much shorter time between the two steps (**Table 4**).

Table 3 - Operative characteristics and interstage complications after Step-1

	Low KGR <7%/week		**High KGR >7%/week**		**p value**
Operative Characteristics					
OR time (min), median (IQR)	212	(163-275)	227	(180-307)	0.540
Blood loss (ml), median (IQR)	0	(0-700)	0	(0-650)	0.783
Biliodigestive anastomosis, n (%)	3	(4,9)	1	(3,6)	0.773
Pringle, n (%)	7	(11,9)	3	(10,7)	0.875
Clearance of FLR, n (%)	35	(57)	14	(48)	0.418
Classic split, n (%)	23	(38)	14	(48)	0.340
Partial, n (%)	22	(36)	11	(38)	0.158
Hybrid, n (%)	15	(25)	4	(14)	0.240
Interstage complications					
Interstage PHLF, n (%)	12	(20)	2	(7)	0.112
Grade A	2	(3)	1	(3)	0.357
Grade B	3	(5)	0	(0)	-
Grade C	7	(12)	1	(3)	-
Bile leak, n (%)	5	(8)	3	(10)	0.738
Bleeding, n (%)	5	(8)	5	(17)	0.212
Infection, n (%)	9	(12)	5	(17)	0.452
No Step II, n (%)	10	(16)	2	(7)	0.215

4.1.5 Operative characteristics of ALPPS Step-2 and postoperative complications

Regarding the extent of resection, blood loss and complexity of the case (Pringle, vascular reconstruction, biliary reconstructions, biliodigestive anastomosis) no differences were observed (**Table 5**). However, surgery time was shorter in patients with a high KGR (p=0.015).

The post-operative outcome showed a significantly lower rate of minor complications in patients with a high KGR (p=0.034), and no major complications or deaths occurred in this group. On the other hand, patients with a low KGR were more likely to be affected by post-operative bleeding (p=0.033). Between the two groups, the overall complication index, bile leak, surgical site infections and 90-day-mortality were comparable.

Table 4 - Volumetric Analysis

	Low KGR <7%/week		**High KGR >7%/week**		**p value**
sFLR pre-Step I (%), median (IQR)	20	(16-29)	21	(16-29)	0.986
sFLR pre-Step II (%), median (IQR)	34	(28-38)	39	(33-53)	**0.002**
Absolute growth (ml), median (IQR)	190	(112-247)	308	(235-375)	**<0.001**
Relative growth (%), median (IQR)	55	(31-83)	89	(64-124)	**<0.001**
Degree of hypertrophy (%), median (IQR)	11	(8-15)	18	(16-23)	**<0.001**
Time duration (weeks), median (IQR)	4	(2-8)	1	(1-2)	**<0.001**

Table 5 - Operative characteristics of ALPPS Step-2 and postoperative complications

	Low KGR <7%/week		High KGR >7%/week		p value
Operative Characteristics					
OR time (min), median (IQR)	182	(140-262)	139	(110-182)	**0.015**
Blood loss (ml), median (IQR)	750	(0-1450)	250	(0-1000)	0.287
Biliodigestive anastomosis, n (%)	1	(1,6)	1	(4)	0.828
Pringle, n (%)	6	(12)	2	(8)	0.634
Vascular reconstructions, n (%)	6	(12)	1	(4)	0.253
Right hepatectomy, n (%)	13	(26)	4	(15)	0.312
Trisectionectomy, n (%)	38	(74)	22	(85)	-
Outcome					
Complications, n (%)					
None (grade 0)	37	(68)	13	(54)	0.222
Minor (grade II-IIIa)	12	(22)	11	(45)	**0.034**
Major (grade IIIb-IV)	3	(5)	0	(0)	0.238
Death (V)	2	(3)	0	(0)	0.339
CCI, mean (SD)	29.6	(20,9-60,0)	28.6	(0-51,8)	0.569
Bile leak, n (%)	7	(14)	8	(31)	0.074
Postoperative bleeding, n (%)	20	(39)	4	(15)	**0.033**
Surgical site infection, n (%)	12	(24)	11	(42)	0.089
Acute Kidney Injury, n (%)	11	(18)	6	(21)	0.763
Posthepatectomy liver failure, n (%)	16	(31)	2	(7)	**0.020**
Grade A	2	(3)	0	(0)	0.173
Grade B	3	(5)	0	(0)	-
Grade C	11	(18)	2	(7)	-
Hospital stay, median (IQR)	12	(7-24)	13	(7-19)	0.969
90-day mortality, n (%)	7	(14)	2	(8)	0.436

4.2 Interstage Renal Function during Associating liver partition and portal vein ligation for staged hepatectomy

4.2.1 Study Population and Demographics

A total of 705 patients who underwent ALPPS were included in this analysis from the ALPPS registry, and 7.5% (n=53) had interstage RI. Patients with interstage RI had more comorbidities such as myocardial infarction, cerebral vascular disease, diabetes, and liver disease, and were also older than patients without RI (66 years (55-71) vs. 60 years (52-67)). The incidence of CRLM was lower (43% vs. 69%, p=0.002), but higher for hepatocellular carcinoma, intrahepatic and perihilar cholangiocarcinoma in the interstage RI group (**Table 6**). Correspondingly, neoadjuvant chemotherapy was used less in the interstage RI group. The incidence of kidney disease was higher in patients with interstage-RI (p<0.001), but the preoperative GFR was similar between the two groups.

Table 6 - Preoperative Demographics for interstage-RI

	No RI (n=652)	**Interstage-RI (n=53)**	**p value**
Females, n (%)	254 (39)	17 (32)	0.379
Age (years), median (IQR)	60 (52-67)	66 (55-71)	**0.018**
BMI, median (IQR)	25.0 (22.7-28.0)	25.5 (22.2-27.8)	0.803
Myocardial infarction, n (%)	22 (4)	5 (9)	**0.032**
Cerebral vascular disease, n (%)	19 (3)	5 (9)	**0.017**
Diabetes, n (%)	65 (10)	10 (19)	**0.048**
Liver disease, n (%)	65 (11)	12 (23)	**0.008**
Renal disease, n (%)	10 (2)	5 (7)	**<0.001**
GFR (ml/min), median (IQR)	93 (80-103)	91 (81-104)	0.968
Chemotherapy, n (%)	413 (65)	20 (38)	**<0.001**
Diagnosis, n (%)			
CRLM	439 (69)	23 (43)	**0.002**
HCC	78 (12)	10 (19)	-
IHCC	42 (7)	4 (8)	-
PHC	25 (4)	6 (11)	-
NET	13 (2)	2 (4)	-
Other	40 (6)	8 (15)	-

4.2.2 Operative characteristics of ALPPS-Step-1 and interstage course

The interstage RI group had a longer duration of stage 1 surgery and a higher proportion of hepaticojejunostomies. In addition, fresh frozen plasma (FFP) and platelets were used more frequently in this group (23% vs. 11%, p=0.008 and 6% vs. 1%, p=0.012, respectively). The use of packed red blood cells (PRBC) was not significant (22% vs. 30%, p=0.160), but there was a trend towards interstage RI (**Table 7**).

An increase in major complications (5% vs. 28%) and interstage mortality (1% vs. 8%, p<0.001) was seen in the interstage-RI group. Interstage PHFL was 13% (n=7) in the Interstage-RI group and 1% in the control group (p<0.001).

In terms of volumetric analysis, there were no differences between the two groups in sFLR pre-stage-1 and pre-stage-2, and no differences in kinetic growth rate (**Table 8**).

Table 7 – Operative characteristics of ALPPS-Step-1 and interstage course

	No RI (n=652)	Interstage-RI (n=53)	p value
Operation time (min), median (IQR)	300 (215-370)	360 (300-500)	**<0.001**
Hepaticojejunostomy, n (%)	9 (1)	4 (8)	**0.001**
Laparoscopic, n (%)	29 (5)	4 (8)	0.362
Transfusion, n (%)			
PRBC	142 (22)	16 (30)	0.160
FFP	69 (11)	12 (23)	**0.008**
Platelets	8 (1)	3 (6)	**0.012**
Additional Procedure, n (%)			
Overall	103 (18)	16 (36)	**0.004**
Gastrointestinal Resection	34 (33)	5 (31)	0.093
Liver Ablation/Wedge	57 (55)	6 (38)	-
Vascular	4 (4)	3 (18)	-
Other	8 (8)	2 (13)	-
Complications, n (%)			
None	426 (71)	17 (34)	**<0.001**
Minor (≤3a)	140 (23)	10 (20)	-
Major (≥3b)	28 (5)	19 (38)	-
Death	6 (1)	4 (8)	-
Renal failure (≥4a), n (%)	1 (0)	7 (14)	**<0.001**
Interstage PHLF, n (%)	8 (1)	7 (13)	**<0.001**
No Stage-2, n (%)	16 (3)	5 (9)	**0.004**

Table 8 - Volumetric Analysis

	No RI (n=652)	Interstage-RI (n=53)	p value
sFLR Stage 1 (%), median (IQR)	21 (15-27)	22 (16-27)	0.930
sFLR Stage 2 (%), median (IQR)	36 (28-45)	35 (29-48)	0.681
Total Gain (%), median (IQR)	15 (10-21)	14 (10-20)	0.778
Ratio Gain, median (IQR)	1.67 (1.42-2.00)	1.63 (1.47-1.82)	0.676

4.2.3 Operative characteristics of ALPPS Step-2 and postoperative complications

Regarding operative factors, such as operation time and extend of resection, were similar between the two groups. After stage 2 (**Table 9**), major complications (≥3b) and mortality increased (12% vs. 16% and 8% vs. 38%) for interstage-RI. The incidence of PHFL showed a trend towards interstage-RI, but was not significant (15% vs 7%, p=0.057). PRBC, FFP and platelets were used more frequently in patients with interstage-RI and the time between the two stages was comparable.

4.2.4 Renal Recovery and Renal Impairment after Stage-2

After the second stage, 62 out of 621 patients (10%) developed RI, and 41% of the cases with interstage RI recovered before stage 2 and had the same sCr value as before stage 1. In spite of this, the mortality rate after stage 2 was high in this group (27%). Mortality after stage 2 increased to 39% in patients with interstage-RI and elevated sCr values (59%) up to stage 2. The interval between the stages was 16 days (11-26) in patients with renal recovery compared to 9 days (7-12) in patients with elevated sCr values up to stage-2 (p=0.005). There were no differences between these groups in the remaining patient and operative characteristics. In patients with normal renal function between the stages, 9% (n=53) developed a de novo RI after stage 2. Most of these patients had no complications (59%). However, mortality after stage 2 was high (25%).

The 520 patients who did not develop RI after either stage 1 or stage 2 represent 85% of all patients who completed stage 2 and had a perioperative mortality of 6.6%.

Table 9 – Interstage-RI on operative Characteristics of Stage-2 and postoperative complications

	No RI (n=636)	Interstage-RI (n=48)	p value
Operation time	150 (113-210)	171 (125-193)	0.534
Resection Type, n (%)			
Right Hepatectomy	192 (36)	19 (53)	0.234
Extended right Hepatectomy	302 (57)	17 (47)	-
Left Hepatectomy	13 (2)	0 (0)	-
Extended left Hepatectomy	16 (3)	0 (0)	-
Other	8 (2)	0 (0)	-
Transfusion, n (%)			
PRBC	131 (21)	19 (40)	**0.002**
FFP	55 (9)	9 (19)	**0.021**
Platelets	4 (1)	2 (4)	**0.011**
Complications, n (%)			
None	237 (42)	9 (20)	**<0.001**
Minor (≤3a)	215 (38)	12 (27)	-
Major (≥3b)	71 (12)	7 (16)	-
Death	48 (8)	17 (38)	-
PHLF, n (%)	40 (7)	6 (15)	0.057
Renal impairment	53 (9)	8 (21)	**0.023**
Renal failure	22 (4)	9 (20)	**<0.001**
Interstage Interval (days), median (IQR)	12 (8-16)	11 (7-19)	0.490

4.2.5 Identification of Risk Factors for Interstage-RI and Mortality after Stage-2

In the multivariate analysis, an age of more than 67 years, a prolonged operation time of more than 5 hours and an additional procedure contributed as independent risk factors for interstage-RI (Table 10). Individual preoperative and interstage-stage risk factors for mortality after stage 2 are shown in **Table 11**. Age over 67 years, interstage complications ≥3b and use of PRBC during stage 2 were independent risk factors. Interstage-RI was not (p=0.07).

Table 10 - Multivariate Analysis of Independent Preoperative and Intraoperative Risk Factors for Development of Interstage Renal Impairment

Parameter	OR	95% CI		p value
Cases in Analysis: 565 (80%)		Lower	Upper	
Liver Disease	2.27	0.93	5.56	0.07
Aspirin	1.62	0.62	4.20	0.32
GFR <60ml/min	1.48	0.33	6.71	0.61
PRBC	1.21	0.59	2.48	0.60
Age over 67 years	3.42	1.76	6.62	**<0.001**
OR Time over 5h	2.40	1.14	5.03	**0.02**
Additional Procedure	2.34	1.15	4.74	**0.02**

Table 11 - Multivariate Analysis of Independent Preoperative and Interstage Risk Factors for Mortality after Stage-2

Parameter	HR	95% CI		p value
Cases in analysis: 436 (64%)		Lower	Upper	
Interstage Renal Impairment	1.74	0.96	3.15	0.07
Additional Procedure	1.34	0.90	2.00	0.15
Extended Resection	1.08	0.77	1.51	0.65
Biliary Tumour	1.04	0.61	1.79	0.87
Interstage Complications ≥3b	2.34	1.36	4.02	**0.002**
PRBC (Stage 2)	2.21	1.57	3.12	**<0.001**
Age over 67 years	1.96	1.39	2.76	**<0.001**

4.3 Acute Kidney Injury after Associating liver partition and portal vein ligation for staged hepatectomy

4.3.1 Study Population and Preoperative Characteristics

During the study period, 147 extended hepatectomies were performed. One patient had to be excluded due to missing data. Therefore, 146 extended hepatectomies were used for further analysis. The cohort comprised of 60 ALPPS procedures (41.1%), 31 extended

left hepatectomies (21.2%), and 55 extended right hepatectomies (37.7%). AKI occurred in 20.5% of all cases. Out of 31 extended left hepatectomies, only one patient (3.2%) developed AKI, while out of 55 extended right hepatectomies, 16 patients (30.2%) developed AKI. The incidence of AKI among the 60 ALPPS patients was 21.7% (n=13).

4.3.2 Risk Factors for Acute Kidney Injury and Mortality

The multivariate analysis with preoperative und intraoperative parameters is shown in **Table 12**. Independent risk factors for the development of an AKI are age above 70 years, preexisting chronic kidney disease and the ALPPS-Procedure. **Table 13** shows risk factors for mortality and highlights that AKI is the only risk factor for mortality in this study.

Table 12 - Multivariate Analysis for Acute Kidney Injury

Parameter	**OR**	**95% CI**		**p value**
		Lower	**Upper**	
HCC	1.954	0.433	8.820	0.384
Extended Right Hepatectomy	1.127	0.719	2.891	0.417
Preoperative FLR <30%	0.999	0.350	2.848	0.998
Age ≥70 years	7.212	2.705	19.226	**<0.001**
Chronic Kidney Disease	5.072	1.101	23.372	**0.037**
ALPPS	18.569	1.866	184.837	**0.013**

Table 13 - Multivariate Analysis for Survival

Parameter	**HR**	**95% CI**		**p value**
		Lower	**Upper**	
Age ≥75 years	1.760	0.866	3.578	0.118
Extended Right Hepatectomy	0.835	0.492	0.992	0.852
ALPPS	1.181	0.807	1.641	0.857
PHLF	1.289	0.604	2.752	0.512
AKI	2.059	1.104	3.838	**0.023**

4.3.3 ALPPS and the development of postoperative AKI

ALPPS patients who developed an AKI after step-2 had a complicated interstage course. The mean interstage CCI was 23,9 compared to 10,0 (p=0,020). The type of parenchymal split (classic, partial or hybrid) had no impact on AKI. Liver volumetric analysis revealed that AKI patients had a lower future liver remnant (FLR before step-1 and before step-2). However, the kinetic growth rate (%/week) was comparable between the groups. After step-2 the complications and incidence of PHLF were higher in the AKI group. There was no difference in perioperative mortality.

Table 14 – ALPPS and postoperative AKI

	No AKI (n=47)	**AKI (n=13)**	**p value**
Interstage Complications			
None, n (%)	34 (72)	5 (39)	0.052
Interstage CCI, Mean (SD)	10.0 (17.3)	23.9 (21.1)	**0.020**
Days between Steps, Median (IQR)	21 (15-35)	37 (26-49)	0.090
sFLR pre-Step-1 (%), Median (IQR)	20 (16-27)	16 (12-23)	**0.040**
sFLR pre-Step-2 (%), Median (IQR)	35 (30-39)	29 (26-33)	**0.012**
KGR (%/week), Median (IQR)	6.4 (3.8-11.5)	5.5 (2.1-7.6)	0.183
Type of Split, n (%)			
Classic	23 (49)	6 (46)	
Partial	16 (34)	5 (39)	0.956
Hybrid	8 (17)	2 (15)	
Complications after Step-2, n (%)			
Minor (≤3a)	25 (53)	1 (8)	**0.003**
Major (≥3b)	22 (47)	12 (92)	-
Death (V)	5 (11)	2 (15)	0.637
CCI, Mean (SD)	32.7 (28.9)	67.6 (23.8)	**<0.001**
Posthepatectomy Liver Failure	7 (15)	5 (39)	0.060

5 Discussion

Liver resection for benign or malignant tumours is often the only curative option, but is still associated with significant morbidity and mortality [3, 12]. Developments and improvements in this field made liver resection a safe procedure in experienced centres [14]. In particular, several risk factors associated with a serious outcome have been identified [15]. In recent years, sarcopenia and postoperative acute kidney injury have been identified as playing a role in the development of complications after liver resection [21–23, 57, 60].

Patients with sarcopenia undergoing hepatobiliary surgery have demonstrated an increase in morbidity and mortality after major liver surgery in patients with CRLM and HCC [21–23]. It has also been associated with a smaller estimated total liver volume [24] and adverse effects in combination with other severe diseases [25–29].

This is the inaugural research to investigate the impact of KGR during ALPPS surgery and its correlation with sarcopenia. The study unambiguously demonstrates that the frequency of PHLF substantially rises at a KGR less than 7%/week, whereas sarcopenia constitutes a notable risk factor for a low KGR. It is acknowledged that a diminished KGR carries a substantial risk of PHLF, leading to increased morbidity and mortality following ALPPS [37]. Moreover, the KGR constitutes a measure to forecast postoperative complexities and fatality [54], although a decisive threshold was yet to be established. Other studies indicate that sarcopenia leads to decreased liver hypertrophy after PVE [21, 30]. Our study confirms the impact of sarcopenia on liver regeneration in ALPPS patients, with SMI and BMI identified as the only preoperative factors that influence KGR. Patients with a low sarcopenia index and a high BMI commonly suffer from malnutrition, resulting in impaired nutritional and physical status. These factors have been known to affect liver regeneration and subsequently surgical outcomes [76]. Sarcopenia and BMI are factors that can be positively affected by resistance exercise, leading to enhanced strength and performance [77]. However, the insufficient future liver remnant could be due to the pathophysiological background of the disease making it unclear if exercise alone can lead to the desired outcome.

Before ALPPS, an accurate preoperative evaluation of the patient is essential, and sarcopenia is a novel parameter that should be incorporated in this assessment. The patient can be encouraged and guided to lose weight and exercise to increase the skeletal muscle

index before or during neoadjuvant chemotherapy to ensure a better recovery. Recent research indicates that prehabilitation prior to hepatobiliary surgery can significantly decrease complications and enhance surgical outcomes. [78]. A study in rodent showed that physical prehabilitation can enhance liver regeneration and mitochondrial function after ALPPS [70]. However, it has not been established that exercise alone can prevent PHLF.

While the outcomes of this research are considerable, it is not advisable to solely rely on SMI as a predictor for FLR growth. It should be employed alongside various clinical factors and other current liver function tests, including the indocyanine green clearance test (ICG-green), the maximum liver function capacity (LiMAx), and the hepatobiliary iminodiacetic acid scan (HIDA-scan) [79, 80], to assess the regenerative ability.

Another risk factor for severe outcome after liver resection is an increase in serum creatinine after liver resection, defined as an acute kidney injury. With the extent of liver resection (major resection or extended resection), the risk of an AKI increases [56, 58, 59].

Overall, studies that included minor and major resections show an incidence of AKI of about 15% [56, 59, 60]. Postoperative AKI has not been described in patients who underwent extended hepatectomy, including ALPPS. Especially the analysis of renal function between the two surgical steps has not been performed. This insight could inform patient selection and management strategies to mitigate AKI.

For further analysis of the role of renal function and its impact on the outcome after ALPPS, a comprehensive registry study was carried out. The results showed that patients who experienced interstage-RI demonstrated significantly higher interstage and post-stage-2 mortality rates. Notably, patients who recovered renal function before stage-2 mortality still faced a 27% mortality rate. These findings suggest that it is vital to protect the renal function of older patients undergoing ALPPS, and whenever feasible, additional resections should be avoided. The reported incidence of interstage renal injury (RI) in ALPPS may be an underestimation of the true occurrence of acute renal injury.

An interstage-RI during stage-2 is linked to an increased requirement for transfusions, as well as more significant complications that contribute to a high mortality rate of 38%. A prediction model for futile outcomes of ALPPS has identified raised creatinine levels before stage-2 as a crucial predictive factor [38]. In this cohort, nearly 40% of patients

with interstage-renal impairment (RI) recovered and had normal serum creatinine (sCr) levels before stage-2. However, these patients exhibited better postoperative survival rates compared to those without recovery. Patients who experienced renal recovery also had a longer interstage interval. This implies that patients with interstage-RI may derive benefits from a longer interstage interval. Although interstage-RI is not a contraindication for stage-2 per se, a prolonged interstage interval should be considered. In cases of persistent RI, stage-2 should be avoided.

However, if ALPPS is a contributing risk factor for postoperative AKI has not yet been shown. The current study included high-risk patients undergoing extended liver resections, with an incidence of 21% similar to another study that reported a 19% incidence in patients undergoing extended resection [63]. This study was conducted solely in extended liver resections to reduce the major risk factor for AKI, which is parenchymal loss. Nevertheless, the incidence of AKI was found to be highest among patients after extended right hepatectomy. On the other hand, the distribution of AKI was comparable in the ALPPS group. This assumes that a larger FLR and the previous FLR regeneration in ALPPS patients might have a protective effect on the renal system.

The multivariate analysis showed that ALPPS is an independent risk factor for AKI, in addition to CKD and age over seventy. The ALPPS procedure provides a higher risk of AKI due to having two operations under general anaesthesia and a short interstage time. Although the type of parenchymal split did not affect the risk for AKI, patients suffering from a complicated interstage course had a greater chance of developing AKI after the second step. The current literature extensively discusses the implications of interstage management and its associated complications on the outcome of ALPPS [38, 39, 42, 81]. Thus, the primary objective of the initial step in ALPPS is the mitigation and elimination of complications to decrease postoperative morbidity and AKI. In patients with a challenging interstage course, lengthening the duration between steps may be a possible approach to limit or prevent post-step-2 AKI.

One of the most important factors that influence the development of an AKI is the FLR. Patients with AKI had a lower preoperative FLR. It is essential to have a sufficient FLR before ALPPS to reduce the risk of AKI, not exclusively after ALPPS but also after conventional liver resection [62, 63]. A small FLR can cause small-for-size-syndrome or PHLF, which can lead to hepatorenal syndrome [60]. The occurrence of PHLF was

greater among the AKI cohort in contrast to those with regular postoperative kidney function. As AKI transpires within the initial 48 hours of surgery and PHLF is illustrative of laboratory variations five days at least after surgery, the existence of AKI may be considered as a premature indicator for PHLF which warrants alterations in patient observation and management.

The perioperative mortality in the present study aligns with newest research that reports a mortality rate of 16% following an extended resection [82]. Nevertheless, the incidence of AKI leads to a substantial perioperative mortality rate of 30%. It is currently uncertain whether AKI is due to the liver resection itself caused by a systemic inflammatory response syndrome or represents an indirect marker for a complicated postoperative course [60].

6 Conclusions

To summarise, the studies presented demonstrate that a KGR below 7% per week is linked to increased postoperative morbidity risk, and in such patients, sarcopenia can act as a contributing risk factor. However, it does not imply that sarcopenia independently results in a worse outcome. For individuals at higher risk undergoing ALPPS, early sarcopenia assessment is beneficial in identifying potential PHLF indicators.

During ALPPS procedure, postoperative AKI is linked to severe outcomes and may serve as an early warning for PHLF. A low FLR and the ALPPS procedure continue to be risk factors for AKI. The management in-between stages during ALPPS significantly influences the postoperative outcome, and a prolonged time interval or abandoning stage-2 can have a detrimental effect.

7 Summary

Introduction: Despite the significant advancements in surgical techniques, posthepatectomy liver failure (PHLF) continues to present a challenge. For complex scenarios such as a small future liver volume, the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) resection method has been the subject of extensive investigation. The kinetic growth rate (KGR) is a measure of liver growth that is normalised to time. In the context of portal venous embolization, a low KGR is associated with an elevated risk of PHLF. Acute kidney injury (AKI) is an additional risk factor for adverse outcomes following liver resection. However, both factors were not examined in a cohort who underwent ALPPS. This complex procedure may be associated with a high risk of AKI, and the effect of sarcopenia has not been described.

Objectives: To evaluate the effect of KGR for ALPPS patients and to assess the impact of sarcopenia on liver regeneration and AKI on postoperative outcome. Additionally, to determine whether impaired renal function influences outcomes.

Methods: A patient cohort from the Division of Hepatobiliary and Pancreatic Surgery undergoing ALPPS were analysed to investigate the impact of KGR and acute kidney injury. Detailed interstage renal function was assessed using the ALPPS registry.

Results: Area under the curve calculation indicated that a significant reduction in the incidence of PHLF requires a KGR of >7%/week. An increased body mass index (BMI) ($p=0.021$) and sarcopenia ($p=0.008$) were identified as the only independent risk factors for a reduced KGR. Additionally, it was demonstrated that renal dysfunction between the stages during and after ALPPS leads to a complicated second stage and a complex postoperative course characterised by a mortality rate of 38%. Furthermore, it was found that this effect could be reduced by 27% following renal recovery. The incidence of AKI after ALPPS was associated with a complication rate greater than IIIb of 92% and a mortality rate of 15% compared to 47% and 11% for patients without AKI, respectively.

Conclusion: A KGR <7%/week is associated with an elevated risk of postoperative morbidity. In these patients, sarcopenia serves as a contributing risk factor. Following the ALPPS procedure, postoperative AKI is linked to severe outcomes and may function as an early warning for PHLF. A low FLR and the ALPPS procedure persist as risk factors for AKI. The management of ALPPS between stages significantly impacts postoperative outcomes.

7.1 Összefoglaló

Bevezetés: A sebészeti technikák jelentős fejlődése ellenére a hepatektómia utáni májelégtelenség (PHLF) továbbra is kihívást jelent. Az olyan komplex esetekben, ahol a maradék májtérfogat (FLR), ezáltal a májfunkció elégtelen, egy modern speciális műtéti technika „Associating Liver Partition and Portal vein ligation for Staged hepatectomy" (ALPPS) nyújthat segítséget, mely rendkívül rövid idő alatt képes elegendő májnövekedést elérni a tervezett reszekció biztonságos elvégzéséhez. A kinetikus növekedési ráta (KGR) a máj növekedésének időhöz viszonyított mérőszáma. Az alacsony KGR a PHLF megnövekedett kockázatával jár együtt. Az akut vesekárosodás (AKI) a májreszekciót követő kedvezőtlen kimenetel további kockázati tényezője. Azonban mindkét tényezőt nem kutatták olyan kohorsz vizsgálatban, ahol ALPPS műtéten átesett betegek szerepeltek. Az ALPPS az AKI magas kockázatával járhat együtt, továbbá a szarkopéniának a folyamatban betöltött szerepe még nem került leírásra.

Célkitűzések: A KGR hatásának értékelése ALPPS betegek esetében, valamint a szarkopénia májregenerációra és az AKI posztoperatív kimenetelre gyakorolt hatásának felmérése.

Módszerek: A Hepatobiliáris és Pancreas Sebészeti Osztály ALPPS műtéten átesett betegcsoportja került elemzésre a KGR és az akut vesekárosodás hatásának vizsgálata céljából. Az ALPPS-regiszter segítségével értékeltük a perioperatív vesefunkciót.

Eredmények: A PHLF előfordulásának jelentős csökkenéséhez >7%/hét KGR szükséges. A BMI és a szarkopénia volt az egyetlen független kockázati tényezője a csökkent KGR-nek. Továbbá kimutatásra került, hogy az ALPPS szakaszai alatti és közötti veseelégtelenség bonyolult második műtéthez és szövődményes posztoperatív lefolyáshoz vezet, amelyet 38%-os mortalitási arány jellemez. Ez a kedvezőtlen hatás a vesefunkció helyreállítását követően 27%-kal csökkenthető. Az AKI előfordulása az ALPPS után 92%-os >IIIb morbiditási arányhoz és 15%-os mortalitási arányhoz társult, szemben az AKI nélküli betegek 47%-os és 11%-os értékével.

Következtetés: A KGR <7%/hét a posztoperatív morbiditás megnövekedett kockázatával jár. Ezekben a betegekben a szarkopénia járulékos kockázati tényezőként szolgál. Az ALPPS eljárást követően a posztoperatív AKI súlyos kimenetelhez kapcsolódik, és a PHLF korai figyelmeztető jeleként működhet. Az ALPPS szakaszok közötti AKI kezelése jelentősen befolyásolja a posztoperatív kimenetelt.

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9 Bibliography of the candidate's publications

9.1 Articles providing the basis of the doctoral thesis

1. **Reese, T.**; Fard-Aghaie, M.H.; Makridis, G.; Kantas, A.; Wagner, K.C.; Malagó, M.; Robles-Campos, R.; Hernandez-Alejandro, R.; de Santibañes, E.; Clavien, P.-A.; Petrowsky, H.; Linecker, M.; Oldhafer, K.J.
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