The ALPPS Procedure: Impact of Kinetic Growth Rate and Renal Function

PhD thesis

Tim Reese

Károly Rácz Doctoral School of Clinical Medicine
Semmelweis University

Supervisor: Karl J. Oldhafer, MD, Ph.D
Official reviewers: Attila Szíjártó, MD, Ph.D
Åsmund Fretland, MD, Ph.D

Head of the Complex Examination Committee:
Gábor Varga, Ph.D, D.Sc

Members of the Complex Examination Committee:
Miklós Sárdy, MD, Ph.D
András Folyovich, MD, Ph.D
János Vág, DMD, Ph.D
György Losonczy, MD, Ph.D,D.Sc

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1 Introduction

Liver resection is an essential component in a multidisciplinary approach for curative treatment of various primary and secondary liver malignancies and benign liver lesions. However, it is associated with postoperative morbidity and mortality. According to current literature, morbidity rates remain around 20-45%, with mortality rates at 2-4%. Risk factors for morbidity and mortality can be categorized into preoperative, intraoperative, and postoperative parameters.

The main preoperative risk factors include age, comorbidities and liver-related factors such as cirrhosis, or preoperative chemotherapy. Sarcopenia is a condition characterized by generalized skeletal muscle disorder that results in loss of muscle mass and function, and it is primarily caused by the aging process. Recent studies on sarcopenia indicate a higher incidence of morbidity and mortality following major liver surgery in patients with colorectal liver metastasis (CRLM) and hepatocellular carcinoma (HCC). Recent research has shown that sarcopenia has a negative impact on hypertrophy following portal vein embolization (PVE).

Prolonged operative time, open surgery, major hepatectomies, and blood loss including transfusions are the most common intraoperative parameters associated with an impaired postoperative outcome. It is well known that minor liver resections have lower morbidity rates compared to major liver resections (>3 segments).

When the future liver remnant (FLR) after resection, is too little and the risk for a posthepatectomy liver failure (PHLF) is too high, there are several hypertrophy-procedures available. An approach is the Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure. During the first step the right portal vein is ligated, and the parenchyma is dissected in the future resection line. In the interstage-phase the FLR increases in size. The second step – the major hepatectomy – is performed with a sufficient FLR, otherwise the risk of PHLF and postoperative mortality increases. Despite the critique of ALPPS, most comparative studies showed similar results regarding complications, completion rate or long-term outcome.

In healthy liver, a minimum FLR volume of 25-30% is necessary to reduce the risk of PHLF. In a damaged liver (e.g. due to cirrhosis or chemotherapy), the required FLR can vary between 30-50%. The rate of hypertrophy can vary among individual patients. Several studies have analysed different factors that can influence the FLR, such as hepatic steatosis, a high BMI, previous infections, and neoadjuvant chemotherapy, which have been associated with a decreased liver hypertrophy following PVE.

The kinetic growth rate (KGR) is an essential parameter for monitoring hypertrophy after major liver resection. It indicates the percentage increase per week of the FLR. However, there is limited information available on the factors that influence KGR.

Acute kidney injury (AKI) occurs in approximately 8-15% of cases after liver resection, with a higher incidence in major hepatectomy compared to minor hepatectomy. The occurrence of AKI is associated with increased morbidity and mortality following liver resection. There are different mechanisms for developing AKI after liver resection: large blood loss during resection with intraoperative hemodynamic changes leading to renal hypoperfusion, and postoperative liver dysfunction or failure leading to hepatorenal syndrome. The main risk factor for AKI remains the complexity of liver resection. Parameters such as blood loss or operation duration are often surrogate markers for the extent or complexity of liver surgery. Most studies investigating risk factors for AKI have included minor and major hepatectomy, and therefore risk factors are often related to the extent of resection. Additionally, no study has included ALPPS. Given the long operative time, high blood loss, and high morbidity associated with the procedure, it is reasonable to assume an increased incidence of AKI.

2 Objectives

Study #1 – The aim of this study was to investigate the impact of the kinetic growth rate within the ALPPS procedure and to determine a cut off value of KGR to develop PHLF.

Study #2 – The aim of this study was to perform an investigation of renal function in the interstage interval of ALPPS. 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 investigate the impact of AKI on the perioperative outcome after ALPPS. This study investigates whether ALPPS is a risk factor for AKI in a cohort of patients at high-risk (extent of the liver resection including patients undergoing ALPPS).

3 Methods

3.1 Patient selection and databases

For study #1, all patients undergoing ALPPS at the Department of Hepatobiliary Surgery of Asklepios Hospital Barmbek, Hamburg from 01/2010 until 12/2020 were included. For study #3, the study period was from January 2010 to May 2018, and included patients who underwent extended right hepatectomy, extended left hepatectomy or ALPPS to investigate differences in AKI incidence.

To assess renal function during the ALPPS procedure (study #2), data were collected from the International ALPPS Registry (www.alpps.net) from 2010 to 2018 (NCT01924741). If preoperative serum creatinine (sCr) levels were not available, patients were excluded. 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.

3.2 Data and definitions

PHLF was defined according to the International Study Group of Liver Surgery (ISGLS). In the ALPPS-Registry, PHLF is defined according to the 50-50 criteria. All complications that occurred after liver resection were graded using the Clavien-Dindo Classification and cumulated with the Comprehensive Complications Index (CCI).

According to the Kidney Disease: Improving Global Outcome (KDIGO) definition, AKI was characterised as an increase of serum creatinine by ≥ 0.3 mg/dL within 48 hours postoperative or an increase of serum creatinine to ≥ 1.5 times of the preoperative baseline. In the ALPPS-Registry study, sCr values were entered on the 5th postoperative day, therefore interstage renal impairment (RI) was defined as an increase of serum-creatinine on the 5th postoperative day of ≥0.3mg/dl or ≥1.5x compared to the preoperative value.

3.3 Volumetric measurements and Sarcopenia muscle index

On preoperative computed tomography scans the FLR was manually outlined on axial planes and calculated with Advantage Workstation 4.1.2 (GE Healthcare). For Sarcopenia, the area of both psoas major muscles was measured of the preoperative computer tomography at the 3rd lumbar vertebra, 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].

3.4 Statistical analysis

Continuous variables are reported as median (interquartile range, IQR) or mean (standard deviation) as appropriate, and proportions are presented as numbers with percentages. Categorical data was compared using the Pearson $\chi 2$ test, while continuous variables were compared using the Mann–Whitney U or Student's t-test as appropriate. An area under the curve measurement was performed to calculate a cut-off value for KGR for PHLF. For the multivariate analysis, we conducted a backward stepwise logistic regression to determine the independent risk factors. A p-value of less than 0.05 was considered statistically significant. We performed statistical analysis using IBM SPSS statistical software v23© or v25© for Mac.

4 Results

4.1 Kinetic Growth Rate

Ninety patients underwent ALPPS, which contained 62 patients with CRLM (69%), 10 with non-colorectal-non-neuroendocrine liver metastasis (11%), eight with HCC (9%), seven with intrahepatic cholagiocarcinoma (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.

4.1.1 Cut-off value calculation of Kinetic Growth Rate

The calculations of the area under the curve indicate that a KGR of 7% per week or more is necessary to significantly reduce the incidence of PHLF. In the group with a KGR below 7%, 16 patients (31%) experienced PHLF, while only two patients (7%) with a higher KGR experienced PHLF (p=0.02). The sensitivity was 88%, and the specificity was 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 patients' characteristics (**Table 1**). The kidney function was also comparable between both groups.

Table 1 - Preoperative 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
Diabetes mellitus, n (%)	8	(13)	1	(4)	0.166
Kidney disease, n (%)	4	(6)	0	(0)	0.166
GFR (ml/min), median (IQR)	89	(75-90)	88	(82-90)	0.647
SMI, 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 cm2/m2 (4.8 - 6.7), whereas patients with high KGR (>7%/week) had an SMI of 6.9 cm2/m2 (5.8 - 7.5) (p=0.017). SMI was the only preoperative factor showing a statistically significant difference between both groups. In the multivariate logistic regression analysis, an elevated BMI (p=0.021) and a decreased SMI (p=0.008) were the only independent risk factors for a low KGR.

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

Operative parameters of the step-I showed no differences between the two groups regarding KGR. Additionally, interstage complications were not significantly different between the two groups. Notably, interstage PHLF was 20% for low KGR compared to 7% with a high KGR (p=0.112).

Regarding volumetric analysis, the preoperative FLR was comparable between groups. A much higher and faster hypertrophy of the FLR can be seen for the group with the KGR of >7%/week.

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. However, surgery time was shorter in patients with a high KGR (p=0.015).

The postoperative outcome (Table 2) showed a lower rate of minor complications in patients with a high KGR (p=0.034), and no major complications or deaths occurred in this group. However, patients with a low KGR had a higher rate of post-operative bleeding (p=0.033).

In addition, neither KGR nor Sarcopenia had no effect on the occurrence of AKI after ALPPS resection.

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

	Low KGR <7%/week		**High KGR >7%/week**		**p value**
Complications, n (%)					
Grade II-IIIa	12	(22)	11	(45)	**0.034**
Grade IIIb-IV	3	(5)	0	(0)	0.238
Grade V	2	(3)	0	(0)	0.339
Bile leak, n (%)	7	(14)	8	(31)	0.074
Bleeding, n (%)	20	(39)	4	(15)	**0.033**
AKI, n (%)	11	(18)	6	(21)	0.763
PHLF, n (%)	16	(31)	2	(7)	**0.020**
90-d mortal., n (%)	7	(14)	2	(8)	0.436

4.2 Interstage Renal Function

4.2.1 Study Population and Demographics

From the ALPPS-registry, 705 patients who underwent ALPPS were included in this analysis, and 7.5% (n=53) had interstage RI. Patients with interstage RI had had a higher incidence such as diabetes, myocardial infarction, and liver disease (Table 3). The incidence of pre-existing kidney disease was higher in patients with interstage-RI ($p<0.001$), but the median preoperative GFR was similar between the two groups.

Table 3 - Preoperative Demographics for interstage-RI

	No RI		Interstage-RI		p value
Females, n (%)	254	(39)	17	(32)	0.379
Age (years), median (IQR)	60	(52-67)	66	(55-71)	**0.018**
Diabetes, n (%)	65	(10)	10	(19)	**0.048**
Renal disease, n (%)	10	(2)	5	(7)	**<0.001**
GFR (ml/min), median (IQR)	93	(80-103)	91	(81-104)	0.968

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

The interstage RI group had a longer operation time of stage-1, higher proportion of hepaticojejunostomies, fresh frozen plasma (FFP) and platelets (Table 4). An increase in major complications (5% vs. 36%) 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.

Table 4 – Operative characteristics of Step-1 and interstage course

	No RI		Interstage-RI		p value
Operation time (min), median (IQR)	300	(215-370)	360	(300-500)	**<0.001**
Hepaticojejunostomy, n (%)	9	(1)	4	(8)	**0.001**
FFP, n (%)	69	(11)	12	(23)	**0.008**
Platelets, n (%)	8	(1)	3	(6)	**0.012**
Complications, n (%)					
Grade 0	426	(71)	17	(34)	**<0.001**
Grade II-IIIa	140	(23)	10	(20)	**-**
Grade IIIb-IV	28	(5)	19	(36)	**-**
Grade V	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**

4.2.3 Operative characteristics of ALPPS Step-2 and postoperative complications

After stage 2 (Table 5), major complications (≥3b) and mortality increased (38% vs. 16% and 8% vs. 12%) for patients with interstage-RI. PRBC, FFP and platelets were used more frequently in patients with interstage-RI.

Table 5 – Operative Characteristics of Stage-2 and postoperative complications

	No RI		Interstage-RI		p value
Complications, n (%)					
Grade 0	237	(42)	9	(20)	**<0.001**
Grade II-IIIa	215	(38)	12	(27)	-
Grade IIIb-IV	71	(12)	7	(16)	-
Grade V	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**
Interval (days), median (IQR)	12	(8-16)	11	(7-19)	0.490

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. Despite this, the mortality rate after stage 2 was high in this group. Mortality after stage 2 increased to 39% in patients with interstage-RI and elevated sCr values (59%) up to stage 2. 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%.

4.2.5 Risk factors for Interstage-RI and Mortality

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. Individual preoperative and interstage-stage risk factors for mortality after stage 2 are age over 67 years, interstage complications ≥3b and use of PRBC during stage 2. Interstage-RI was not ($p=0.07$).

4.3 Acute Kidney Injury

4.3.1 Study Population and Incidence of AKI

During the study period, 146 extended hepatectomies were included for further analysis. The cohort consisted of 60 ALPPS (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 and out of 55 extended right hepatectomies, 16 patients (30,2%) developed AKI. The AKI incidence within 60 ALPPS patients was 21,7% (n=13).

4.3.2 Risk Factors for Acute Kidney Injury and Mortality

Independent risk factors for the development of an AKI was age above 70 years, preexisting chronic kidney disease and the ALPPS-Procedure. AKI was the only risk factor for mortality after extended liver resection or ALPPS in this study.

4.3.3 ALPPS and the development of postoperative AKI

ALPPS patients who developed an AKI after step-2 had a complicated interstage course (Table 6). 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 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 6 – ALPPS and postoperative AKI

	No AKI (n=47)		AKI (n=13)		p value
Interstage CCI, Mean (SD)	10.0	(17.3)	23.9	(21.1)	**0.020**
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**
Complications after Step-2, n (%)					
Grade II-IIIa	25	(53)	1	(8)	**0.003**
Grade IIIb-IV	22	(47)	12	(92)	-
Grade V	5	(11)	2	(15)	0.637
Posthepatectomy Liver Failure	7	(15)	5	(39)	0.060

5 Conclusion

Liver resection for benign or malignant tumours is a safe procedure in experienced centres with decreased morbidity and mortality rates. Risk factors, such as sarcopenia and postoperative acute kidney injury, associated with serious outcomes have been identified. It is important to consider these factors when assessing the development of complications after liver resection.

Patients with sarcopenia who undergo hepatobiliary surgery have demonstrated higher morbidity and mortality rates following major liver surgery for both CRLM and HCC. Sarcopenia has also been linked to a smaller estimated total liver volume and negative outcomes when combined with other severe illnesses.

This research investigates the impact of KGR during ALPPS surgery and its correlation with sarcopenia. The study demonstrates that the frequency of PHLF increases when KGR is less than 7% per week, whereas sarcopenia is a notable risk factor for a low KGR. Further studies have shown that sarcopenia can lead to a decrease in liver hypertrophy after PVE. Our study confirms the impact of sarcopenia on liver regeneration in ALPPS patients. Patients with a low sarcopenia index commonly experience malnutrition and impaired physical status, which can negatively affect liver regeneration and surgical outcomes. Resistance exercise has been shown to improve sarcopenia and enhance strength. Before undergoing ALPPS, it is essential to conduct an objective preoperative evaluation of the patient, which should include the incorporation of sarcopenia as a novel parameter. Recent research suggests that prehabilitation before hepatobiliary surgery can significantly reduce complications and improve surgical outcomes. Additionally, a rodent study demonstrated that physical prehabilitation can enhance liver regeneration and mitochondrial function following ALPPS. Although the outcomes of this research are significant, it is not recommended to rely solely on SMI as a predictor for FLR growth. It should be used in conjunction with various clinical factors and other current liver function tests to evaluate the regenerative ability.

Acute kidney injury is another risk factor for severe outcome after liver resection. With the extent of liver resection (major resection or extended resection), the risk of an AKI increases. Studies that included minor and major resections show an incidence of AKI of about 15%. However, this study was investigated in a cohort of high-risk patients who underwent extended hepatectomy, including ALPPS to lower the bias regarding parenchymal loss. Especially the analysis of renal function between the two surgical steps has not been performed, which could impact management strategies to mitigate AKI.

The study results indicate that patients who experienced interstage-RI had significantly higher interstage and post-stage-2 mortality rates. Therefore, it is crucial to protect the renal function of patients undergoing ALPPS. A prediction model for futile outcomes of ALPPS has also identified elevated creatinine levels before stage-2 as a crucial predictive factor. In this cohort, almost 40% of patients with interstage-RI recovered and had normal sCr levels before stage 2. Those patients had better postoperative survival rates compared to those who did not recover. In addition, they had a longer interstage interval. Therefore, an interstage-RI is not necessarily a contraindication for stage-2, it is important to consider a prolonged interstage interval. But in cases of persistent RI, it is advisable to avoid stage-2.

However, it has not been demonstrated whether ALPPS is a risk factor for postoperative AKI. Our study included patients undergoing extended liver resections, with an AKI incidence comparable with other studies for extended resections. Nevertheless, the incidence of AKI was found to be highest among patients undergoing extended right hepatectomy and not in the ALPPS group. This assumes that the greater FLR and the previous FLR regeneration in ALPPS patients can have a protective effect on the renal system. In contrast to that finding, the multivariate analysis revealed that ALPPS is a significant independent risk factor for AKI. The ALPPS procedure contributes to a higher risk of AKI due to having two operations under general anaesthesia and a short interstage time. The current literature extensively discusses the implications of interstage management and its associated complications on the outcome of ALPPS. Therefore, the primary objective of the initial step in ALPPS is the reduction of complications to decrease postoperative morbidity and AKI. In cases with a challenging interstage course, lengthening the duration between steps may be a possible approach to limit or prevent post-step-2 AKI. Patients with AKI had a smaller FLR before undergoing the ALPPS procedure. It is crucial to have an adequate FLR before ALPPS to reduce the risk of AKI, not only after ALPPS but also after conventional liver resection. The incidence of PHLF was higher among the AKI cohort compared to those with normal postoperative kidney function. As AKI occurs within the first 48 hours of surgery and PHLF is indicative of laboratory changes at least five days after surgery, AKI may serve as an early indicator for PHLF. This warrants changes in patient observation and management.

In conclusion, our studies demonstrate that a KGR below 7% per week after ALPPS is associated with an increased risk of postoperative morbidity and sarcopenia is a contributing risk factor in such patients. However, it does not necessarily imply that sarcopenia independently leads to a worse outcome. In the context of the ALPPS procedure, postoperative AKI is associated with severe outcomes and may serve as an early warning sign for PHLF. Both a low FLR and the ALPPS procedure remain risk factors for AKI. The interstage management during ALPPS significantly affects the postoperative outcome, and a prolonged time interval or abandoning stage-2 can have a detrimental effect.

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