Prediction of Mortality After ALPPS Stage-1

An Analysis of 320 Patients From the International ALPPS Registry

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Objectives: The aim of this study was to identify predictors of 90-day mortality after Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS), available after stage-1, either to omit or delay stage-2.

Background data: ALPPS is a two-stage hepatectomy for patients with extensive liver tumors with predicted small liver remnants, which has been criticized for its high mortality rate. Risk factors for mortality are unknown.

Methods: Patients in the International Registry undergoing ALPPS from April 2011 to July 2014 were analyzed. Primary outcome was 90-day mortality. Liver function after stage-1 was assessed using the criteria of the International Study Group for Liver Surgery (ISGLS) after stage-1 among others. A multivariable model was used to identify independent predictors of 90-day mortality.

Results: Three hundred twenty patients registered by 55 centers worldwide were evaluated. Overall 90-day mortality was 8.8% (28/320). The predominant cause for 90-day mortality was postoperative liver failure in 75% of patients. Fourteen percent of patients developed liver failure according to ISGLS criteria already after stage-1 ALPPS. Those and patients with a model of end-stage liver disease (MELD) score more than 10 before stage-2 were at significantly higher risk for 90-day mortality after stage-2 with an odds ratio (OR) 3.9 [confidence interval (CI) 1.4–10.9, $P = 0.01$] and OR 4.9 (CI 1.9–12.7, $P = 0.006$), respectively. Other factors, such as size of future liver remnant (FLR) before stage-2 and time between stages, were not predictive.

Conclusions: This analysis of the largest cohort of ALPPS patients so far identifies those patients in whom stage-2 ALPPS surgery should be delayed or even denied. These findings may help to make ALPPS safer.

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Disclosure: The authors of this manuscript have no conflicts of interest to disclose as described by the *Annals of Surgery*.

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

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ISSN: 0003-4932/14/26105-0821
DOI: 10.1097/SLA.0000000000001450

Keywords: hepatectomy, liver neoplasms, liver regeneration, portal vein (qualifier surgery)

(*Ann Surg* 2015;262:780–786)

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) is a novel two-stage hepatectomy that induces rapid growth of the liver remnant in primarily nonresectable liver tumors by combining transection of the liver with portal vein ligation.[1,2] The procedure was initially developed to avoid liver failure by rapid volume enhancement of the future liver remnant (FLR), but high mortality rates have been reported. This has led to an ongoing debate about the safety of ALPPS.

The international ALPPS registry monitors feasibility and safety of ALPPS. The first analysis of 202 patients in January 2014 reported a 90-day mortality of 9% and a liver failure rate of 9%. The majority of registered deaths were due to liver failure, but an analysis of the risk factors for mortality was unsuccessful due to the low event rate.[3]

The majority of deaths and the development of posthepatectomy liver failure (PHLF) occur after the completion hepatectomy in stage-2. The goal of the current study is to identify risk factors, which may help clinicians to avoid adverse outcomes before performing stage-2. Although the high feasibility rate is considered to be the major strength of ALPPS by many, the two stages also allow a delay or even cancellation of stage-2, if the risk is too high or may be modified.

MATERIAL AND METHODS

Study Design and Study Setting

This observational study is based on data from the international ALPPS registry. It is administered by the Clinical Trials Center at the University of Zurich and approved by the Ethics Committee of the Canton of Zurich, Switzerland, and is registered at Clinicaltrials.gov (NCT01924741). Centers enter patient data using the web-based SECUTRIAL clinical trials software. Data entry is monitored through a query and answer system maintained by a dedicated study nurse. A request submitted to study postoperative mortality and liver failure was made by the authors and approved by the Scientific Committee of the ALPPS registry on August 14, 2014. Data export and analysis was performed in October 2014.

Participants

Patients were consented to have their data entered into the International Registry according to requirements of local ethics committees. All patients entered by centers between the inception of the registry on October 1, 2012 and September 30, 2014 were eligible in this analysis. Patient data were screened for complete

outcome data, that is, patient follow-up at least 90 days after stage-2 with information about death or survival of the patients as well as information about postoperative liver function.

Variables

Data on patient demographics, tumor type and prior therapy, comorbidities, histology, volumetry, and procedure details were extracted. Volumetric data were entered on the basis of imaging performed in each center. Standardized total liver volume (sTLV) was calculated according to the Vauthey formula.[4]

Main outcome measure of this study was 90-day mortality in a multivariable analysis of clinically modifiable risk factors. Any death occurring during the postoperative 90-day period in the presence of at least one of the liver failure criteria was considered a liver-related mortality.

Secondary outcomes included four different definitions of PHLF:

(1) *50–50* criteria are considered positive when the prothrombin time index is less than 50% (≈ International normalized ratio (INR) ≥1.7) and serum bilirubin is more than 50 micromol/L (≈2.9 mg/dL) on postoperative day 5, predicting a mortality of 50%.[5]
(2) $_{DAY5}$*bil>7 criterion* is considered positive when bilirubin is more than 7 mg/dL in noncirrhotic, noncholestatic patients on day 5 after surgery. The $_{DAY5}$*bil>7 criterion* is different but close to the $_{PEAK}$bil>7 criterion published by Mullen et al.[6] The Mullen criterion had to be modified because in the ALPPS registry, only bilirubin levels at postoperative day 5 are recorded and a peak value cannot be assessed.
(3) *International Study Group for Liver Surgery (ISGLS*) criteria are positive when INR *and* bilirubin were above the normal cut-off as defined by the local laboratory on day 5 after liver resection.[7] Because the registry data relate to many different local laboratory standards, we set an INR of 1.3 and bilirubin of more than 20 micromol/L (≈1.2 mg/dL). Biliary complications did not exclude patients from being positive for liver failure, as in the published definition.[7]
(4) *Clinicians' assessment criterion* is positive, when clinicians entering the data into the registry checked of the box ''yes'' after the question if patients, according to their clinical judgment, developed PHLF.

Postoperative complications were recorded by clinicians in the registry as the highest complication grade occurring after each stage using the Clavien-Dindo classification.[8,9]

All patients, who died within 90 days after ALPPS, were listed and analyzed in detail according to the following five categories: (1) demographic factors age and tumor type;[3] (2) liver function, assessed by histology and the presence of cholestasis; (3) surgical severity factors, assessed by blood transfusion and duration of surgery;[3] (4) liver function after stage-1 by ISGLS criteria and MELD score; and (5) sFLR prior to stage-2. Outcomes are assessed by the presence of any of the four above-listed liver failure criteria, the most severe complication, the direct cause leading to death, and the root cause according to the judgment of the authors according to a methodology widely used to investigate adverse events in health care.[10]

Bias and Study Size

Patients with incomplete outcomes data were excluded, introducing a reporting and incomplete reporting bias whereby patients with negative outcome are either not getting reported at all or are in the excluded group of patients.[11] An on-site auditing to avoid such biases is currently not available in the registry.

Quantitative Variables and Statistical Methods

Data were expressed using means and standard deviation (SD) for normally distributed, and median and interquartile ranges (IQRs) for skewed data. In univariate analyses, *P* values less than 0.05 were considered significant. Multivariable binary logistic regression analyses were performed with the endpoint 90-day mortality using backward elimination removing variable until all have individual *P* values are less than 0.10. All covariates with significant correlations in univariate analysis or those with clinical importance were included in the analysis. Covariates representing competing risks were selected by choosing the covariate that is clinically most important and modifiable. Receiver-operating characteristic curves (area under the curve, AUC) and the area under the AUC curve (c-statistic) were used to find discrimination thresholds. All statistical analyses were performed using SPSS version 22 for Mac (IBM Corp, Armonk, NY).

RESULTS

Participants

During the study period, 73 centers entered patient data on 406 patients undergoing ALPPS. Eighty-six patients (21%) had to be excluded due to missing information on 90-day mortality, either because 90 days after surgery were not reached or because centers, despite repeated requests, failed to complete this information (Supplementary Figure 1, http://links.lww.com/SLA/A878). In 320 patients, 90-day survival and liver function data were available and confirmed.

Descriptive Data

The characteristics of the study population are provided in Table 1. The mean age was 60 years, and 72% of patients suffered from colorectal liver metastases. The majority of patients with colorectal liver metastases underwent chemotherapy.

Causes of the Mortality After ALPPS

Supplementary Table 1, http://links.lww.com/SLA/A877 lists all 28 patients who died within 90 days after ALPPS. The table displays the known risk factors for poor outcomes defined so far. In only five patients, the sFLR before stage-2 was less than 0.3. PHLF was the most common complication in patients and septic shock the most common direct cause of death. Errors in patient selection and liver function assessment were the two most common root causes for patient mortality.

Association of Liver Failure and Mortality

Three hundred fifteen out of 320 patients (98.4 %), who underwent ALPPS stage-1, reached stage-2 resection, while five patients did not (Supplementary Table 2, http://links.lww.com/SLA/A877). The 90-day mortality of the 315 patients, who underwent both stages, was 8.8%. The 90-day mortality for all patients with CLRM was 5%. The table illustrates the incidence of liver failure after ALPPS stage-2. Nine percent experienced liver failure after stage-2 by *50–50 criteria*, 7% by $_{DAY5}$Bili> *7criteria*, and 30% by *ISGLS criteria* after stage-2. $_{DAY5}$Bili> *7 criteria* had the highest accuracy with a positive predictive value of 33% and a negative predictive value of 94% for 90-day mortality. Liver failure by the same three criteria was a rare event after ALPPS stage-1 in 1%, 2%, and 14% of patients positive for 50–50% criteria, $_{DAY5}$Bili>7 criteria, and ISGLS criteria, respectively.

For patients, who fulfilled 50-50, DAY5Bil >7 and ISGLS criteria, 90-day mortality was 23%, 28% and 18%, respectively. Twenty-one of the twenty-eight 90-day mortalities after ALPPS (75%) were positive for one of the liver failure criteria and were considered to be liver-related 90-day mortalities.

TABLE 1. Main Characteristics of 320 Patients in the ALPPS Registry 2012–2014

Variable of Interest	All Patients (n = 320)
Age, mean (±SD)	60 (±12.4)
Median (IQR)	61 (IQR 53–68)
Sex, female/male, number (%)	124/196 (39%/61%)
Ethnic origin, white, number (%)	299 (93%)
Asian, number (%)	13 (4%)
Other, number (%)	8 (3%)
Tumor type, CRLM, number (%)	228 (72%)
Non-CRLM	26 (8%)
HCC, number (%)	32 (10%)
IHCC, number (%)	13 (4%)
PHCC, number (%)	14 (4%)
GBCA, number (%)	7(2%)
Charlson index (1–14),* mean (±SD)	7.2 (±1.9)
Median (IQR)	7 (IQR 6–9)
Histological abnormalities,† data available (100%)	188 (100%)
Macro-steatosis, number (%)	60 (32%)
Macro-steatosis, number (%)	16 (9%)
Fibrosis	51 (27%)
SOS	37 (20%)
Chemotherapy before ALPPS, data available	308 (100%)
Overall patients with chemotherapy	209 (67%)
CLRM patients, data available	203 (100%)
Patients with CLRM who had chemotherapy, number (%)	203/217 (94%)
Patients with other tumors than CRLM with chemotherapy	6 (2%)
sFLR before stage-1, mean (±SD)‡	0.21 (±0.15)
Median (IQR)	0.21 (0.12–0.27)
Number of patients with starting sFLR <0.15 (%)	49 (15%)
sFLR before stage-2, mean (±SD)	0.4 (±0.13)
Median (IQR)	0.4 (0.31–0.46)
Time between stages, days, mean (±SD)	14.1 (±11.2)
Median (range)	10 (5–70)
Procedure duration stage-1, minutes, mean (±SD)	325 ± 117
Median (IQR)	310 (259–390)
RBC transfusion during either stage, data available	312 (100%)
Yes	106 (34%)
No	206 (66%)
Kinetic growth in sFLR/week, mean (±SD)	0.16 (±0.14)
Median (IQR)	0.13 (0.07–0.20)
Year in which ALPPS was performed	
2011, number (%)	35 (10%)
2012, number (%)	133 (42%)
2013, number (%)	115 (36%)
2014, number (%)	37 (12%)
Experience of center performing ALPPS	
Low volume (<10 procedures) number of patients/centers	157 (49%) in 9 centers
High volume (≥10 procedures) number of patients/number of centers	163 (51%) in 46 centers

"Data available" refer to the number of patients in the registry with complete information about the respective variable.

*Charlson index is a validated method to quantify comorbidities.

†Several histologic abnormalities may be present in one patient.

‡Kinetic growth was assessed in sFLR per week, as customary.[21]

CRLM indicates colorectal liver metastases; GBCA, gallbladder carcinoma; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; NCLRM, noncolorectal liver metastases; PHCC, perihilar cholangiocarcinoma; sFLR, standardized future liver remnant according to Vauthey et al.[4]

Preoperative Laboratory Tests Prior to Stage-2 and Mortality

Figure 1 shows the predictive value of laboratory tests for 90-day mortality before stage-2 ALPPS. Figure 1 A and C show that bilirubin and creatinine levels before stage-2 were strong predictors of mortality after stage-2. INR before stage-2 showed no significant association (Fig. 1B). Increase of bilirubin between stage-1 and 2 was also a significant predictor (Fig. 1D). Using the MELD score to combine all three laboratory values yielded the highest AUC of 0.73 [confidence interval (CI) 0.60–0.86]. The best cut-off giving weight to sensitivity and specificity was a MELD score of at least 10 (Fig. 1E) resulting in an AUC of 0.79 (CI 0.67–0.92) for liver-related mortality (Fig. 1F).

Multivariate Analysis of Mortality ISGLS Criteria After Stage-1 and Meld Score Before Stage-2

Liver failure after stage-1 and MELD score were entered into a multivariate model encompassing factors known or suspected to affect outcomes after ALPPS to adjust for confounders (Fig. 2). Age, primary liver tumors, operative time more than 5 hours during stage-1, and the administration of red blood cell (RBC) transfusions during either stage were significant predictive risk factors for 90-day mortality. In addition, patients who met ISGLS criteria for PHLF after stage-1 had an adjusted odds of 3.9 (CI 1.4–10.9) and patients with a MELD score at least 10 MELD before stage-2 had an adjusted odds of 90-day mortality of 4.9 (CI 1.9–12.7). Charlson score, sFLR before stage-2, sex, center volume, and time between stages had no significant impact on outcome in the model.

ALPPS Outcomes Stratified by Risk Groups

Figure 3 A to F shows the incidence of the three outcomes: (1) complications of Clavien-Dindo grade at least IIIA, (2) liver failure according to ISGLS criteria, and (3) 90-day mortality for the subgroups of patients stratified by risk factors analyzed in this study: Age, tumor types, ISGLS criteria after stage-1, and MELD score before stage-2 stratify to different outcomes in this univariate analysis, while sFLR volume before stage-2 and center experience do not. Mortality was 14% for patients older than 60 years, 71% and 36% for patients with gallbladder cancer and cholangiocarcinoma, respectively, 20% for patients who fulfilled ISGLS criteria after stage 1, and 22% for patients with a MELD score more than 10 before stage 2.

DISCUSSION

This analysis of the International ALPPS registry demonstrates that occurrence of liver failure according to the ISGLS criteria after stage 1 and a MELD score at least 10 before stage-2 are independent predictors of 90-day mortality, in addition to previously defined risk factors. Both predictors identify a high-risk population and may be used to guide the surgeon when or even whether stage-2 should be performed. The findings of this study imply that the stage-2 operation might be deferred as long as the MELD score is at least 10.

The main goal of this study was to provide a useful and easy applicable tool to identify those patients after stage-1 operation who are at a higher risk for death after stage-2 operation. Global liver function between stages is crucial for success and failure of this novel and complex procedure. ISGLS criteria and MELD score reflect the excretory and synthetic liver function and we observed that liver function is significantly compromised by portal vein ligation and parenchymal transection. Directing the entire blood flow through the small liver remnant at stage-1 causes liver failure by ISGLS criteria in 14% of patients after ALPPS stage-1. This study suggests that

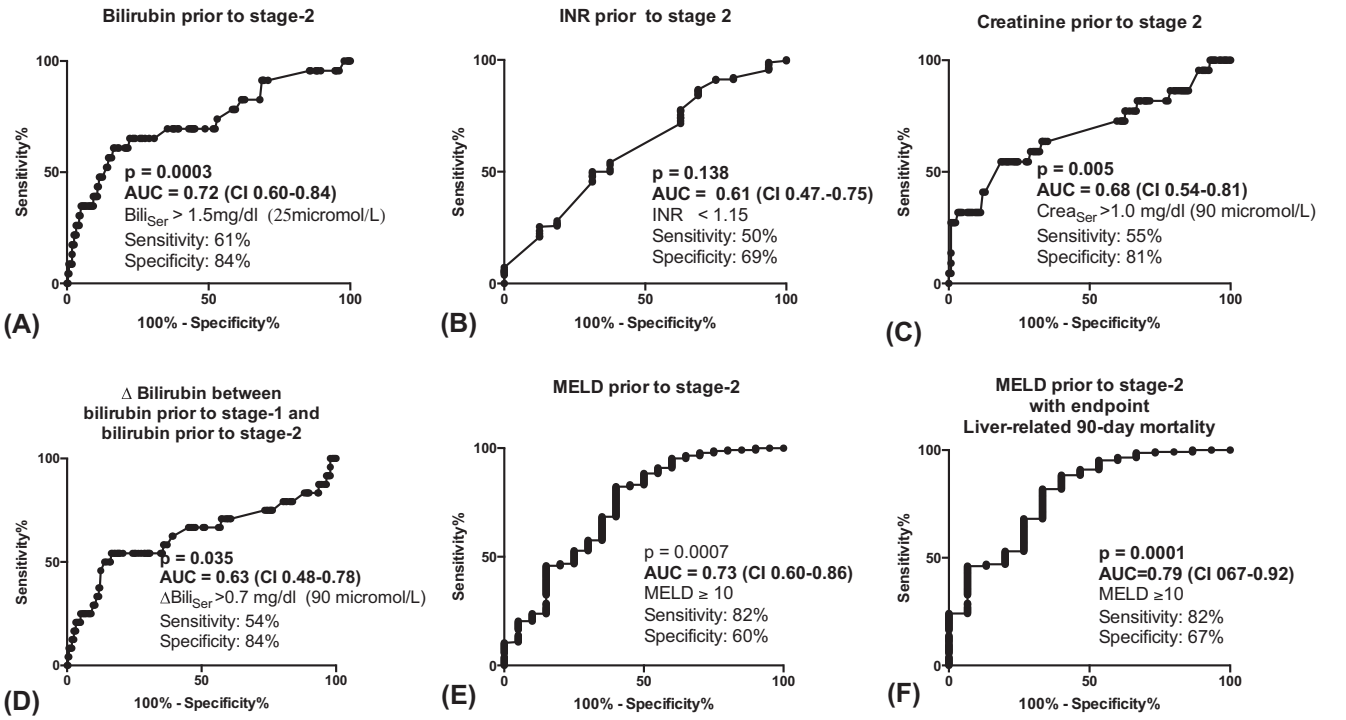

FIGURE 1. Receiver-operating characteristic curves (ROC) for routine laboratory tests predicting 90-day mortality after ALPPS. A, Serum bilirubin levels at baseline before stage-2; *P*, level of significance, AUC, area under the curve; cut-off value giving equal weight to sensitivity and specificity. B, I levels before stage-2, with no statistically significant correlation. C, Serum creatinine before stage-2. D, Difference between serum bilirubin before stage-1 and serum bilirubin before stage-2. E, MELD (model of end-stage liver disease encompassing bilirubin INR and creatinine) before stage-2 as a predictor of 90-day mortality. F, MELD before stage-2 as a predictor of liver-related 90-day mortality, using *death due to liver failure* as an endpoint.

stage-1 ALPPS might be considered as a liver function 'stress test' and patients who develop liver failure after stage-1 are not good candidates to proceed with stage-2 within the 1 week typical for classical ALPPS. By taking these factors into account, a considerable proportion of the mortality after ALPPS stage-2 may be preventable.

Although more sophisticated liver function tests such as intraoperative ICG,[12] mebrofenin scintigraphy (HIDA),[13] and LiMAX[14] test may be more specific in assessing liver function than routine laboratory parameters, such tests require special devices and are not routinely available in many centers.[15] The advantage of the ISGLS criteria and MELD score is that both are readily available and easily accessible in all hepatobiliary centers worldwide. Although the MELD score is normally used to estimate the survival probability of patients with end-stage liver disease on the liver transplant waiting list, the criterion of MELD score at least 10 immediately before stage-2 had a good discriminatory power with a *c*-statistic of 0.79.

Another important finding of the study is that any bilirubin more than 2 mg/dL or 37 micromol/L before stage-1 or stage-2 as well as any increase in bilirubin levels between the baseline level before stage-1 and the baseline level before stage-2 are also relevant predictors of mortality. In the present multivariate model, we did not include bilirubin more than 2 mg/dL or 37 micromol/L before stage-1, as the few patients with elevated bilirubin before stage-1 had perihilar cholangiocarcinoma (PHCC) or IHCC and including both bilirubin more than 2 mg/dL and more than 37 micromol/L before stage-1 and tumor type would have resulted in two competing variables in the model. Our previous recommendations regarding primary tumors,[3,16] which are also observed by this study, appropriately address the negative impact of cholestasis before stage-1 associated with a 33% mortality risk. Therefore, surgeons should be cautious in the presence of hyperbilirubinemia also before stage-1, when classical ALPPS is considered as a resection strategy.

The present analysis demonstrates that the early enthusiasm for ALPPS-induced rapid hypertrophy led to overemphasis of liver volume in predicting future liver function. Assessing liver function between stages using routine laboratory tests now appears more critical to decide at what time patient should undergo stage-2 ALPPS. The current analysis demonstrates that the vast majority of patients (86%) tolerate rapid hypertrophy without developing liver dysfunction after stage-1. The remaining 14% of patients may simply require longer recovery after stage-1 and may not tolerate stage-2 ALPPS. The reportedly high complication and mortality rates may well be related to the undue use of stage-2 in most patients irrespective of compromised liver function 1 week after stage-1. This study analyzed a larger cohort of patients than prior studies on two-stage hepatectomies and helps to refine criteria to select those ALPPS patients who are not candidates for classic ALPPS.

The analysis also demonstrates that previously described[3] risk factors for complications, namely, (1) age, (2) tumor type, (3) duration of stage-1 surgery, and (4) intraoperative blood transfusions, are also risk factors for mortality. The impact of age and tumors type as indications of ALPPS on outcomes has been stressed in the first registry analysis of risk factors for complications at least IIIB and is again striking in the current analysis of outcomes. ALPPS should be used with utmost caution in patients older than 60 years and for indications other than metastatic liver tumors. However, among the

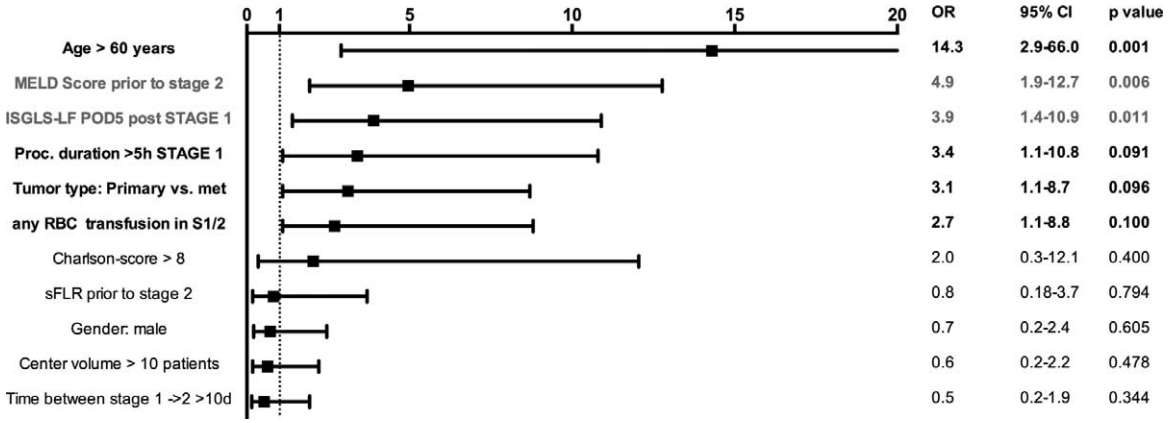

FIGURE 2. Multivariable model of risk factors for 90-day mortality. Adjusted odd ratios and *P* values are shown in a multivariable model with the endpoint 90-day mortality. Backward elimination was used until all factors have individual *P* values <0.10. MELD, model of end-stage liver disease; ISGLS LF POD 5 poststage-1, liver failure by criteria of the International Study group for Liver Surgery 5 days after stage-1; procedure duration >5 h stage-1, duration of the ALPPS procedure in stage-1 of more than 5 hours; tumor type, primary liver tumor (intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, hepatocellular carcinoma, gallbladder tumor) versus metastatic liver tumors (colorectal liver metastases, noncolorectal liver metastases); any RBC transfusion in S1/2: any need for red blood cell transfusion in either stage; Charlson score > 8: Charlson comorbidity index greater than 8; sFLR before stage-2 size of the standardized future liver remnant as calculated by the Vauthey formula; Center volume > 10 patients, centers with more than 10 patients performed and completely entered were considered to be high volume centers; time between stages >10 days, time period between the 2 stages of ALPPS of more than 10 days

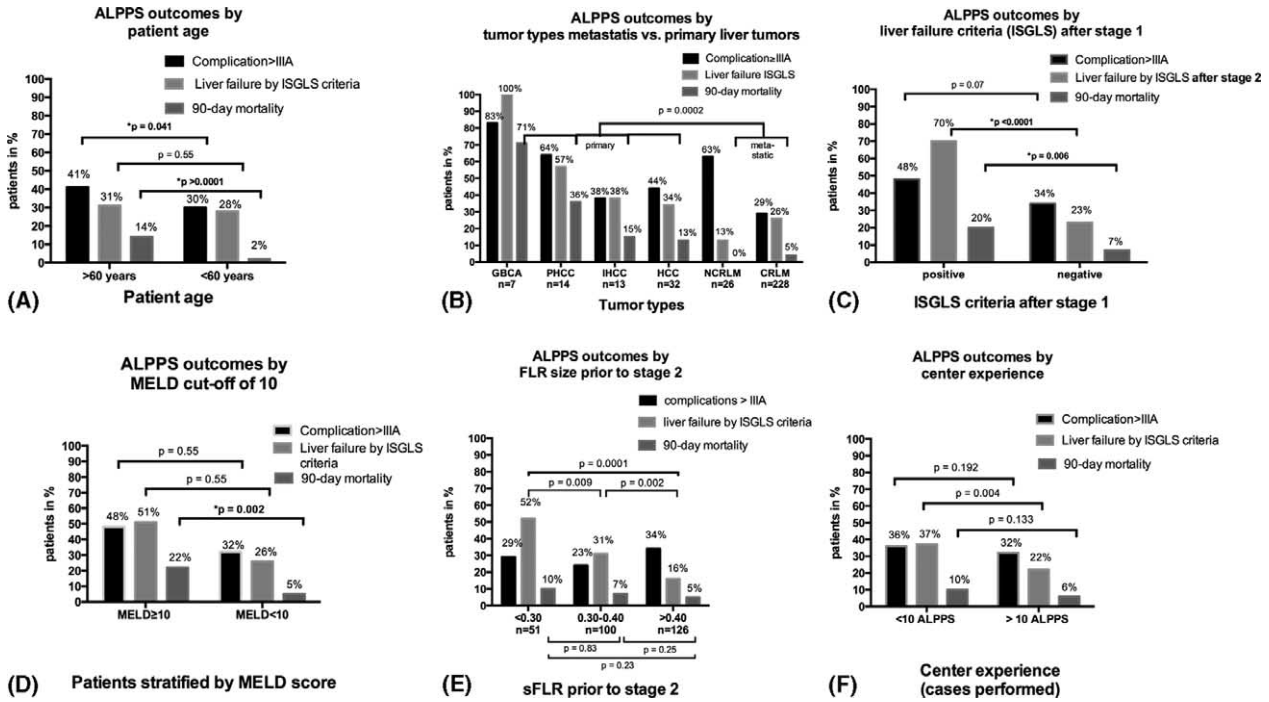

FIGURE 3. Predictors of outcome in ALPPS. A, Age ≥60 years is a predictor of 90-day mortality after ALPPS. B, The 90-day mortality in patients with colorectal liver metastases (CRLM) was 4%, with noncolorectal liver metastases (NCLRM) 0%, and the 90-day mortality in patients with primary liver tumors is markedly higher. C, International study group for liver surgery (ISGLS) criteria for liver failure after stage-1 are predictors of liver failure after stage-2 and 90-day mortality. D, Model of end-stage liver disease (MELD) ≥10 is a predictor of 90-day mortality after ALPPS. E, The size of the liver remnant before stage-2 (standardized future liver remnant-sFRL according to Vauthey et al[4]) has no impact on complications and 90-day mortality, but the incidence of liver failure after stage-2 decreases with progressively larger sFLR. F, Complications and mortality are equivalent between low and high volume centers, but liver failure is less common in high volume centers.

group of primary liver tumors, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHCC) had a more favorable complication profile and lower rates of liver failure and mortality than PHCC and gallbladder carcinoma (GBCA). Therefore, if ALPPS is to be conservatively used in primary liver tumors, IHCC or HCC may be among better indication and further explorations in this direction may be justified. Although this analysis attempts to give a guideline on how to prevent mortality after stage 2 by assessment of liver function and delay of stage 2, indications for ALPPS stage 1 should remain fairly restrictive, as stage 1 ALPPS may, once performed, significantly compromise quality of life and access to chemotherapy.

Duration of stage 1 (3) and intraoperative blood transfusions (4) are likely markers of severity and complexity of the surgical procedure. The search for technical modifications of the procedure with less invasive surgery as documented by the innovations hybrid-ALPPS,[17] ALTPS,[18] RALPP,[19] or partial-ALPPS[20] reflects the clinicians' awareness that classical ALPPS might be too much surgery for some patients.

The large cohort of patients from 73 centers in 49 different countries hopefully presents a large sample of all ALPPS patients operated worldwide. The collaborative effort for data collection allowed performing a robust analysis on small differences in potential outcome predictors. However, a registry based on voluntary reporting has limitations due to a potential reporting bias,[11] resulting in underreporting of unfavorable outcome and mortality. Despite efforts from our side, data entry could not be completed to include outcome data in 65 patients, which represent 20% of the entire study population. Despite this limitation, the risk factor analysis per se, which is based on large sample, can provide enough useful information to clinicians to help to reduce mortality in the future. Another limitation of this study is related to the design of the registry with reporting serum bilirubin values at day 5 after each stage. Therefore, the exact use of the originally described $_{\text{PEAK}}$*bil>7 criteria* was not possible. We modified the $_{\text{PEAK}}$*bil>7 criterion* to the$_{\text{DAY5}}$*bil >7 mg/dl criterion*. Despite this, the DAY5bil >7 has the highest accuracy to predict mortality after ALPPS:

In conclusion, ISGLS-defined liver failure at day 5 after stage-1 and MELD score at least 10 immediately before stage-2 are independent predictors of poor outcome after ALPPS stage-2. Both criteria identify high-risk patients for mortality and enable the surgeon to decide when to proceed to or when to defer the stage-2 operation. This recommendation may be easily applicable and hopefully make ALPPS safer.

ACKNOWLEDGMENTS

We acknowledge the contribution of Sabine Kern, RN, and Michael Linecker, MD, from the Department of Surgery, University Hospital Zurich for data acquisition and monitoring.

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DISCUSSANTS

D. Cherqui (Paris, France):

The main results are that either post-stage 1 liver failure according to ISGLS or pre-stage 2 MELD higher than 10 points predicted mortality. The authors suggest delaying or canceling stage 2 in the presence of one of these interstage criteria. This is useful information. I have a few comments and questions. First, 86 cases (21%) had to be excluded due to missing data. It is not clear how many were really missing data and how many had just not reached 90-day follow-up. This is inherent to registry data as acknowledged by the authors. In any case, mortality rates reported here should be considered the minimal estimate of mortality, as at least some of the missing cases include fatalities. Second, in this study, sFLR before stage 2 was not a predictor of 90-day mortality. As the main cause of mortality is liver failure, this finding suggests dissociation between volume and function. A highly publicized feature of ALPPS is rapid interstage hypertrophy. As ALPPS as well as portal vein

embolization (PVE) are mainly indicated on the basis of insufficient estimated FLR before major resection, this observation requires additional comments. Third, ISGLS grade is sensitive to minor variations and has a low specificity. This suggests that minor changes in liver function after stage 1 may have a major impact. It is striking that bilirubin more than 2 mg/dL has a higher impact than liver volume (IU for bilirubin is μmol/L not mmol). Fourth, despite the fact that the present study focused on interstage liver function, previously described risk factors were confirmed, that is, age, tumor type, durations of stage 1 surgery, and transfusions. Two are related to patient selection, which was found to be the root cause in 14 of 28 deaths. I read in the supplement Table 1, http://links.lww.com/SLA/A877.

Age more than 60 years was associated with a 14-fold increased mortality. This is a limitation of ALPPS, as a large proportion of patients requiring liver resection for cancer are more than 60. Next, 90-daymortality after ALPPS for biliary cancer was 47% (gallbladder cancer 71%, perihilar cholangcarcinoma 36%).

These are unacceptable figures. These latter pathologies have inherent limitations: preoperative hyper-bilirubinemia, bile bacterial contamination with stents, and need for hilar dissection (RPV ligation) in the exact area wherein the tumor is located. Is it time to call biliary cancer a contraindication to ALPPS?

Response From E. Schadde (Zurich, Switzerland):

Thank you for those questions, Prof. Cherqui. First, indeed, there was a 20% dropout in the last analysis. We tried hard to get these data and I agree with you that this is a minimum figure. We had the opportunity to look at a national database on ALPPS recently and mortality figures were double as high as we are reporting in the International Registry. It would be reasonable to assume that this is the case in the worldwide experience as well, but these are the limitations that we acknowledged in the paper.

Second, minor changes in laboratory values after stage-1 ALPPS predict adverse outcomes. This was an interesting finding that we were not prepared for when we designed the analysis. We do think that there is a decrease in liver function after stage-1 ALPPS that is different than what we would expect in the setting of an auxiliary arterialized part of the liver. Recent data on LiMAx testing of patients undergoing ALPPS from the group in Berlin, Germany, as well as the recent data from the group in Lille, France, show this as well. There is a decline in liver function after stage 1 that we should take seriously, and this is the main message of our study. Third, the question about volume versus function is important. Obviously, it will be necessary to evaluate not just volume but function and, if possible, using regional liver function tests. It is unclear whether this is going to be HIDA scanning or whether there is going to be a magnetic resonance imaging (MRI) methodology. This is not only true for ALPPS but also for any procedure wherein you do extended liver resections. The last issue: We agree that the mortality of ALPPS for primary liver tumors is prohibitive. We recommend avoiding the classical ALPPS in these patients, but perhaps we can use a modification on ALPPS associated with a decreased risk of poor outcome.

J. Figueras (Girona, Spain):

Congratulations for this excellent presentation and thank you for helping us to better understand the mechanism of liver failure in the ALPPS procedure. In fact, we did a retrospective analysis of our cases, and we arrived to the same conclusions. First, the indications. This is an operation mostly for liver metastases. Second one, the age; the liver hypertrophy in old patients is poorer. The third one, hyper-bilirubinemia after the first procedure. You mention that if bilirubin is higher than the normal levels, we should wait before doing the second procedure. We found two additional risk factors. One is the association of surgery of the primary tumor with the first procedure and the reverse approach. What do you think about these two risk factors?

Response From E. Schadde (Zurich, Switzerland):

Thank you Prof. Figueras. In our multivariate model, we did not look at those two risk factors, that is, complex ALPPS with an associated procedure during the first stage and the reverse approach. This ought to be done by other groups. Actually, in the ALPPS registry, there are several groups, who have approval from the scientific committee for a variety of analyses. We did not want to pack everything into the current analysis.

F. Pruvot (Lille, France):

Thank you Dr. Schadde for this presentation. According to the preliminary report of the French series about 70 patients, we have shown, as you suggested, that interstage failure was a determinant factor for poststage 2 morbidity and mortality, but in our work using scintigraphy we demonstrated a paradox. The reason of the insufficiency during the interstage is not the failure of the future remnant liver, but rather the failure of the whole liver, and specifically of the ligated livers, wherein liver function is depressed. Do you think in your registry you have the clinical basis of these hypotheses?

Response From E. Schadde (Zurich, Switzerland):

Yes, indeed, I think that our findings go exactly in parallel with what you show in your most recent study on HIDA scanning.

C. Bruns (Magdeburg, Germany):

Thank you very much for the great presentation. My question is, because you did not mention it, what about the impact of chemotherapy on the two different steps of ALPPS? Did you collect the data if liver function is compromised after the first step of ALPPS when chemotherapy is administered and does it impact mortality? Furthermore, I believe it is much more important to develop a score predicting the outcome with respect to mortality and morbidity before step 1 of the ALPPS procedure to pre-estimate the liver function of the FLR instead of developing a score to predict which patient after step 1 will or will not be able to proceed to step 2 of the ALPPS procedure.

What is your recommendation to do with those patients who are at risk for developing liver failure after step 1 before step 2 and which treatment will be offered to patients that cannot proceed to step 2 based on the scoring system? You mentioned a delay of step 2, but what will be the next step if you have to delay step 2 further on?

Response From E. Schadde (Zurich, Switzerland):

Thank you for those questions, Professor Bruns. I'll take that last question first. So, what do you do for those patients? Our suggestion is to wait until their liver function is normalized. We have several patients in the registry who underwent ALPPS and lived with a split liver without getting completely resected. When ALPPS was developed, we focused on the high feasibility, but perhaps we should get away from the idea that we need to get to the second stage in every patient. We may accept a certain failure, and 97% reaching the second stage is probably too much. This might cost patient lives. As far as your second question about chemotherapy is concerned, we put it into the model and it was not a significant risk factor. Regarding the question about the usefulness of the score, we used the ISGLS and the MELD score after stage 1 because we found that stage 1 ALPPS was a liver function test in its own right. Certainly, it would be a good idea to develop a comprehensive risk score with data exclusively before stage 1, and Drs. Clavien and Petrowsky in Zurich are underway to develop such a score.