Risk Adjustment in ALPPS Is Associated With a Dramatic Decrease in Early Mortality and Morbidity

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Objective: To longitudinally assess whether risk adjustment in Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) occurred over time and is associated with postoperative outcome.

Background: ALPPS is a novel 2-stage hepatectomy enabling resection of extensive hepatic tumors. ALPPS has been criticized for its high mortality, which is reported beyond accepted standards in liver surgery. Therefore, adjustments in patient selection and technique have been performed but have not yet been studied over time in relation to outcome.

Methods: ALPPS centers of the International ALPPS Registry having performed ≥10 cases over a period of ≥3 years were assessed for 90-day mortality and major interstage complications (≥3b) of the longitudinal study period from 2009 to 2015. The predicted prestage 1 and 2 mortality risks were calculated for each patient. In addition, questionnaires were sent to all centers exploring center-specific risk adjustment strategies.

Results: Among 437 patients from 16 centers, a shift in indications toward colorectal liver metastases from 53% to 77% and a reverse trend in biliary tumors from 24% to 9% were observed. Over time, 90-day mortality decreased from initially 17% to 4% in 2015 ($P = 0.002$). Similarly, major interstage complications decreased from 10% to 3% ($P = 0.011$). The reduction of 90-day mortality was independently associated with a risk adjustment in patient selection ($P < 0.001$; OR: 1.62; 95% CI: 1.36–1.93) and using less invasive techniques in stage-1 surgery ($P = 0.019$; OR: 0.39; 95% CI: 0.18–0.86). A survey indicated risk adjustment of patient selection in all centers and ALPPS technique in the majority (80%) of centers.

Conclusions: Risk adjustment of patient selection and technique in ALPPS resulted in a continuous drop of early mortality and major postoperative morbidity, which has meanwhile reached standard outcome measures accepted for major liver surgery.

Keywords: ALPPS, colorectal liver metastases, less invasive ALPPS variants, outcome, risk adjustment, two-stage hepatectomy

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Associating Liver Partition and Portal vein Ligation for Staged Hepatectomy (ALPPS) is a novel 2-stage hepatectomy variant that combines portal vein occlusion and parenchymal transection at the first stage.[1,2] The major advantage of this procedure is an exceptionally fast liver growth compared with ''conventional'' 2-stage hepatectomies[3–6] enabling a higher resectability rate.[7] The initial enthusiasm for the procedure has been consistently challenged due to the high reported morbidity and mortality labeling this procedure as a high-risk operation.[7] Some hepatobiliary centers have therefore discontinued performing this operation.

Many surgical procedures including liver surgery have experienced unfavorable outcomes in the beginning, which was followed by continuous improvement with more careful patient selection and technical refinement. Previous reports on ALPPS, most of them with a small number of patients, reveal a wide range of early postoperative mortality ranging from 1% to 25%.[8–13] All of these studies are mainly reporting morbidity and mortality rates of pooled populations and outcome studies of ALPPS over time are lacking.

Therefore, the aim of the present study was to analyze whether adjustments in patient selection, ALPPS technique, and interstage management occurred and whether those were associated with change of morbidity and mortality over time. For this purpose, we

designed a longitudinal cohort study based on identified centers of the International ALPPS Registry meeting the inclusion criteria.

METHODS

Study Design

The present ALPPS cohort study is composed of data derived from the International ALPPS Registry. The registry was set up in 2012 and is co-ordinately maintained by the Department of Surgery, University of Zurich, Switzerland, approved by the Cantonal Ethics Committee of Zurich (KEK 2013-0326) and is registered at ClinicalTrials.gov (NCT01924741). The registry serves as a data platform to prospectively collect the worldwide experience of this procedure using a web-based data capture system secuTrial (Interactive System, Berlin, Germany). Using a longitudinal study design, the objective of the study was to investigate whether risk adjustment and technical modifications occurred over time and whether those changes had an impact on early outcome including morbidity and mortality. The study was approved by the Scientific Committee of the ALPPS Registry on May 18, 2016 (http://www.alpps.net/?q=node/82). Registry data were exported for the current analysis on August 29, 2016. Questionnaires were sent to all centers exploring center-specific risk adjustment strategies.

Definition of the Study Population

In an attempt to longitudinally monitor the effect of risk adjustment over time, only ALPPS centers entering $\geq$10 cases over a duration $\geq$3 years were considered for the study population. Patients of eligible centers who were captured in the International ALPPS Registry until December 31, 2015 were included in the analysis. All centers fulfilling the inclusion criteria were approached (i) to provide missing data commonly observed in registries, (ii) to provide detailed information on procedure-related technique not captured in the registry (eg, technical variants[14]), and (iii) to disclose their individual strategy of risk adjustment for ALPPS over time using a survey questionnaire (Table 1).

Risk Adjustment and Outcome Measures

Primary outcome measures were 90-day mortality after stage 1 surgery as well as major interstage and poststage 2 complications ($\geq$3b) as a global performance metrics of procedure-related morbidity over time starting from the first registered cases in 2009 until the end of 2015.

Secondary outcome measures included comorbidities (Charlson comorbidity index, cardiovascular disease, chronic obstructive pulmonary disease, diabetes, and renal disease), size and growth of the future liver remnant [standardized future liver remnant (sFLR), future liver remnant/bodyweight, sFLR increase, Δ sFLR], concomitant resections, interstage interval defined as time period between stage 1 and stage 2 surgery, liver failure using Model of End-stage Liver Disease score and International Study Group of Liver Surgery criteria, laboratory tests at poststage-1 day 5 and prestage-2, feasibility of stage 2, and length of intensive care unit and hospital stay.

Risk adjustment was tested by calculating the predicted prestage 1 and 2 mortality risks[15] for each patient incorporating age, tumor entity, interstage complications $\geq$3b, and prestage 2 serum bilirubin and creatinine[15] (Supplementary Table 1, http://links.lww.com/SLA/B310). The analysis was performed for the periods $\leq$2011, 2012, 2013, 2014, and 2015. Furthermore, the development of technical refinements of the ''classical'' ALPPS procedure[14] toward less invasive ALPPS variants (''technically modified ALPPS''), including portal vein embolization (PVE)-ALPPS, Partial ALPPS, Laparoscopic ALPPS, Tourniquet ALPPS, and Mini-ALPPS was longitudinally analyzed (Supplementary Table 2, http://links.lww.com/SLA/B310). The combination of at least 2 of the latter variants was summarized as ''combined modification.''

TABLE 1. Survey With Response of 16/16 (100%)

Survey Questions	n	%
Was patient selection adjusted? (yes/no)	16/16	100/0
Patient selection was adjusted for:		
Age	10	63
Tumor entity	14	88
Risk assessment before surgery*	8	50
Liver function testing	10	63
Timing of stage 2	11	69
Was ALPPS technique modified over time? (yes/no)	12/4	75/25
Did risk adjustment or technique improve safety of ALPPS? (yes/no)	16/16	100/0

*Refers to following parameters: ALPPS risk score (n = 1), ASA (n = 2), ECOG (n = 1), frailty (n = 1), BMI (n = 1), cardiopulmonary reserve (n = 3).

ASA indicates American Society of Anesthesiologists Score; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group Score.

Statistical Analysis

Descriptive Statistics and Univariate Analysis

Data were expressed using median and interquartile range for continuous and absolute number (%) for categorical variables. Longitudinal trends between the years of ALPPS performed were calculated using Spearman's ρ correlation for continuous variables and Kendalls τ for categorical variables. In preparation for multivariate analysis on 90-day mortality and major interstage complications, variables of interest were tested using Kruskal–Wallis test for continuous and χ^2 square test for categorical variables. Only clinically useful parameters selected in a discussion between biostatistician and clinician were included in regression analysis avoiding automatic variable selection. P values $\leq$ 0.05 were considered statistically significant.

Multivariate Logistic Regression Analysis

Variables, which showed a statistically significant change over time, were considered for regression analysis. Parameters, which were hypothesized to reduce 90-day mortality and major interstage complications were subsequently split into 2 categories: (1) variables representing risk adjustment (prestage-1 and prestage-2 risk) and (2) variables representing the technical refinement of the procedure. The influence of the respective variables was quantified using odds ratio (OR) and 95% confidence interval (CI). Calibration of regression models was assessed using the Hosmer–Lemeshow test.

All statistical analyses were performed using IBM SPSS Statistics version 22 for Macintosh (IBM Corporation, Armonk, NY).

RESULTS

Study Population With Improved Data Quality

Of 836 registered patients from 123 centers, 16 centers (13%) were identified meeting the inclusion criteria (at least 10 cases over a period of $\geq$3 yr), providing a total of 437 patients for analysis. Percent of data completeness of registry-captured variables has been significantly increased from 86% (75%–94%) at the time of registry data export to 97% (92%–99%) after approaching all centers. In addition, new information on technical aspects of ALPPS variants, which did not exist in the registry, was collected reaching 99% of data completeness.

Participating centers were mainly located in Europe (n = 11), followed by Asia (n = 2), South America (n = 2), and North America

(n = 1). A median number of 26 (17–35) patients per center were enrolled over a median period of 5 years (4–5 yr). Eleven of 16 (69%) centers started ALPPS in the early period (≤2011) and 5 centers (31%) in 2012. ALPPS procedures were annually distributed with 48 (11%), 103 (24%), 101 (23%), 105 (24%), and 79 (18%) for the annual periods ≤2011, 2012, 2013, 2014, and 2015 (Supplementary Table 3, http://links.lww.com/SLA/B310).

Survey Exploring Center-specific Risk Adjustment Strategies

Before analysis, all centers participated in a survey exploring center-specific risk adjustment strategies (Table 1). All centers (n = 16) stated that they adjusted patient selection over time for age (63%), risk assessment before surgery (50%), liver function testing (63%), and timing of stage-2 surgery (69%). The majority of centers (75%) modified their surgical ALPPS technique.

Longitudinal Improvement of Procedure-related Safety

Study population characteristics are presented in Table 2, and operative characteristics in Table 3. Over time, there was a significant decrease in the annual 90-day mortality rate ($\tau = -0.124$; $P = 0.002$) starting from 17% in the early period (≤2011) to 3.8% in 2015 (Fig. 1A). This development was parallelly accompanied by a steady reduction of the annual overall ($\tau = -0.151$; $P < 0.001$) and major ($\tau = -0.102$; $P = 0.011$) interstage complication rates with 78% and 10% for the period ≤2011 versus 56% and 3% for 2015 (Fig. 1B, Table 4).

In the same line, the prestage-2 ALPPS risk model as a measure of interstage performance revealed a substantial decrease over time from a mean of 11.6% to 3.1% ($\rho = -0.260$; $P < 0.001$; Fig. 1A). Interstage serum bilirubin and international normalized ratio levels, Model of End-stage Liver Disease, as well as intensive care unit stay significantly decreased over time (Table 4).

Liver volumetric measures before stage-2 such as sFLR and future liver remnant/bodyweight ratio changed toward smaller volumes over time (Table 4). Liver mass gain, as measured by Δ sFLR, also slightly decreased over time (Table 4). Interestingly, a prolongation of the interstage interval (10 d in the early period ≤2011 vs 14 d in 2015) was noted (Table 4). This development and the increasingly use of functional liver tests indicate a more cautious progression to stage-2 surgery. Failure to reach stage-2 surgery slightly increased over time with a borderline significance ($\rho = 0.051$; $P = 0.467$; Table 4). Of note, causes of mortality did not change significantly over the years. For the periods ≤2011, 2012, 2013, 2014, and 2015 liver failure occurred in 3, 5, 7, 3, and 2 cases ($\tau = 0.084$, $P = 0.507$), death of sepsis/infection in 8, 7, 6, 5, and 1 cases ($\tau = -0.219$, $P = 0.070$), cardiac death in 0, 2, 1, 0, and 0 cases ($\tau = -0.064$, $P = 0.420$), and other causes of death in 0, 5, 2, 2, and 0 cases ($\tau = 0.007$, $P = 0.951$). Due to the fact, that death of liver failure or sepsis/infection is in some cases difficult to distinguish, in 8 patients cause of death was categorized for both.

TABLE 2. Study Population

Parameter	Completeness (%) Before	After	≤2011	2012	2013	2014	2015	Correlation	*P*
Demographics									
Age, yr	96	100	63 (54–71)	62 (53–70)	63 (56–70)	62 (52–71)	59 (49–65)	−0.107	0.026
Sex; male, n, %	98	100	29 (60)	59 (57)	72 (71)	62 (59)	49 (62)	0.011	0.809
BMI, kg/m^2	97	100	25 (23–28)	26 (23–28)	27 (24–29)	25 (23–29)	25 (23–29)	−0.017	0.726
Tumor									
CRLM, n, %	94	99	27 (53)	62 (59)	75 (75)	76 (73)	61 (77)	0.127	0.003
Biliary tumor, n, %	94	100	12 (24)	21 (20)	14 (14)	17 (16)	7 (9)	−0.107	0.013
HCC, n, %	90	99	1 (2)	10 (9)	7 (7)	5 (5)	3 (4)	−0.040	0.311
Other, n, %	94	99	11 (21)	13 (12)	4 (4)	6 (6)	8 (10)	−0.104	0.039
Comorbidities									
Charlson comorbidity index	—	100	6 (2–6)	6 (3–8)	6 (4–7)	6 (4–7)	6 (4–6)	0.021	0.665
Cardiovascular disease, n, %	98	100	17 (35)	42 (41)	44 (44)	32 (31)	20 (25)	−0.093	0.026
COPD, n, %	98	100	2 (4)	1 (1)	3 (3)	4 (4)	2 (3)	0.015	0.728
Diabetes, n, %	98	100	4 (8)	11 (11)	8 (8)	13 (13)	4 (5)	−0.022	0.594
Renal disease, n, %	98	100	3 (6)	2 (2)	1 (1)	1 (1)	0 (0)	−0.100	0.048
Liver baseline characteristics									
sFLR	88	95	0.23 (0.16–0.29)	0.24 (0.17–0.30)	0.22 (0.17–0.26)	0.23 (0.19–0.28)	0.21 (0.16–0.26)	−0.033	0.502
FLR/BW	88	96	0.37 (0.27–0.52)	0.37 (0.28–0.49)	0.37 (0.29–0.48)	0.36 (0.29–0.45)	0.31 (0.25–0.48)	−0.081	0.097
Bilobar tumor, n, %	—	98	25 (52)	67 (65)	63 (64)	71 (71)	55 (71)	0.095	0.030
Chemotherapy*, n, %	98	100	20 (74)	56 (90)	69 (92)	69 (91)	58 (95)	0.112	0.043
Steatohepatitis, n, %	48	74	7 (22)	7 (10)	9 (12)	11 (14)	8 (12)	−0.024	0.645
Fibrosis, n, %	46	76	7 (21)	12 (16)	14 (19)	18 (22)	10 (14)	−0.015	0.759
Macrosteatosis, n, %	45	75	6 (18)	23 (31)	20 (28)	22 (28)	17 (25)	0.003	0.959
Serum Creatinine, mg/dL	82	92	0.84 (0.60– 0.98)	0.78 (0.65–0.90)	0.84 (0.70–0.92)	0.81 (0.70–0.90)	0.81 (0.62–0.95)	0.000	0.996
Serum Bilirubin, mg/dL	91	98	0.60 (0.40–0.98)	0.64 (0.41–0.90)	0.50 (0.40–0.78)	0.50 (0.36–0.70)	0.50 (0.32–0.70)	−0.219	<0.001
INR	86	91	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	−0.018	0.719
MELD	76	84	7 (6–8)	6 (6–8)	7 (6–8)	6 (6–7)	6 (6–7)	−0.066	0.203

Continuous variables presented as median and interquartile range (IQR), correlation with Spearmans ρ; categorical variables presented as count and percent (%), correlation with Kendalls τ.

*Refers to CRLM only.

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; FLR/BW, future liver remnant/bodyweight; INR, international normalized ratio; MELD, Model of End-stage Liver Disease.

TABLE 3. Operative Characteristics

Parameter	Completeness (%) Before	After	≤2011	2012	2013	2014	2015	Correlation	P
"Classic" ALPPS*, n, %	—	100	33 (69)	69 (66)	75 (74)	71 (68)	38 (48)	−0.102	0.021
Technically modified ALPPS, n, %	—	100	15 (31)	35 (34)	26 (26)	34 (32)	41 (52)	0.098	0.027
One modification, n, %	—	100	14 (29)	31 (30)	18 (18)	29 (28)	24 (30)	0.004	0.928
Combined modification† (>1), n, %	—	100	1 (2)	4 (4)	8 (8)	5 (5)	17 (22)	0.173	<0.001
PVE-ALPPS, n, %	—	99	6 (13)	4 (4)	11 (11)	7 (7)	8 (10)	0.015	0.741
Partial ALPPS, n, %	—	99	5 (10)	10 (10)	13 (13)	20 (20)	28 (36)	0.180	<0.001
Tourniquet ALPPS, n, %	—	99	5 (10)	19 (18)	9 (9)	8 (8)	5 (6)	−0.096	0.024
Laparoscopic ALPPS stage 1, n, %	77	99	1 (2)	3 (3)	1 (1)	0 (0)	6 (8)	0.055	0.319
Laparoscopic ALPPS stage 2, n, %	—	100	1 (2)	3 (3)	1 (1)	2 (2)	6 (8)	0.068	0.188
Mini-ALPPS, n, %	—	99	0 (0)	0 (0)	0 (0)	2 (2)	8 (10)	0.180	0.001
Rescue ALPPS, n, %	—	99	6 (13)	4 (4)	9 (9)	11 (11)	2 (3)	−0.029	0.480
Stage 1									
Concomitant resections, n, %	—	99	7 (15)	14 (14)	8 (8)	8 (8)	5 (6)	0.087	0.048
Colorectal resections, n, %	—	99	2 (4)	5 (5)	11 (11)	7 (7)	4 (5)	0.013	0.742
Gastric/bowel resections, n, %	—	99	3 (6)	1 (1)	2 (2)	1 (1)	1 (1)	−0.058	0.250
Pancreatic resections, n, %	—	99	1 (2)	4 (4)	0 (0)	1 (1)	0 (0)	−0.083	0.066
Cleaning of the FLR, n, %	40	99	19 (40)	58 (55)	53 (53)	57 (55)	52 (67)	0.101	0.018
Operation time, min	81	99	331 (268–480)	330 (240–330)	317 (241–420)	300 (216–405)	320 (225–433)	−0.060	0.211
Pringle, n, %	53	95	15 (34)	22 (22)	31 (32)	23 (23)	21 (30)	−0.005	0.919
Transfusion, n, %	95	100	12 (25)	21 (20)	20 (20)	18 (17)	6 (8)	−0.111	0.007
Stage 2									
Concomitant resections, n, %	—	100	1 (2)	2 (2)	2 (2)	2 (2)	3 (4)	0.030	0.527
Colorectal resections, n, %	—	100	1 (2)	1 (1)	0 (0)	2 (2)	2 (3)	0.033	0.525
Gastric/bowel resections, n, %	—	98	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0.032	0.318
Pancreatic resections, n, %	—	98	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	−0.005	0.399
Operation time, min	66	95	156 (120 – 213)	150 (120–200)	155 (110 – 218)	153 (115 – 213)	175 (116 – 259)	0.038	0.444

Continuous variables presented as median and interquartile range (IQR), correlation with Spearmans ρ; categorical variables presented as count and percent (%), correlation with Kendalls τ.

*Refers to the initially described procedure (REF 1,2).

†Combination of at least 2 of the following 5 ALPPS variants.

Adjustment in Patient Selection Is Associated With Reduced Early Mortality

The prestage-1 risk model of the ALPPS Risk Score[15] was used as a standardized measure of patient selection for ALPPS upfront. A significant shift toward younger patients (63 yr in ≤2011 to 59 yr in 2015) as well as toward colorectal liver metastases (CRLM) (53% in ≤2011 to 77% in 2015) with concomitant decline in biliary tumors (24% in ≤2011 to 9% in 2015) was observed (Fig. 1C, Table 2). These changes in age and indications are also reflected in a significant annually drop of the mean predicted pre-stage-1 mortality risks (24% in ≤2011 vs 9% in 2015; $\rho = -0.168$; $P < 0.001$) (Fig. 1A).

Of note, CRLM patients in the later periods were more likely to undergo chemotherapy than in the earlier periods suggesting a more cautious management in terms of response to chemotherapy (Table 2).

Multivariate logistic regression analysis identified the pre-stage 1 risk model to be independently associated with a decline in 90-day mortality ($P < 0.001$; OR: 1.62; 95% CI: 1.36–1.93; Supplementary Table 4, http://links.lww.com/SLA/B310). The Hosmer–Lemeshow test revealed a stable model fit ($P = 0.429$).

Less Invasive ALPPS Techniques Are Associated With Improved Safety

Technically modified ALPPS procedures were independently developed to reduce invasiveness of stage 1 surgery aiming to improve safety. Over time, there was significantly increased use of less invasive ALPPS variants ($\tau = 0.098$; $P = 0.027$), including PVE-ALPPS, Partial ALPPS, Laparoscopic ALPPS, Tourniquet ALPPS, and Mini-ALPPS with a corresponding decline of "classic" ALPPS cases ($\tau = -0.102$; $P = 0.021$) (Fig. 1D, Table 3). In 2015, less invasive variants represented the half of all ALPPS cases (52%) of which partial ALPPS was the most frequently performed variant (68%).

Independently of patient selection using the prestage 1 risk model, multivariate regression analysis showed that less invasive ALPPS variants were associated with decreased 90-day mortality rates ($P = 0.019$; OR: 0.39; 95% CI: 0.18–0.86; Supplementary Table 4, http://links.lww.com/SLA/B310). When the variable "year of ALPPS performed" was included into the regression model, the analysis revealed that the year of ALPPS performed did not significantly affect the outcome ($P = 0.085$; Supplementary Table 4, http://links.lww.com/SLA/B310). This implies that improved outcome of less invasive variants is not exclusively a result of a potential learning curve bias of early cases.

Adjustment in Patient Selection and ALPPS Technique Results in Improved Interstage Complication Profile

To further investigate why patient selection and technical refinement of stage 1 surgery translates into a dramatic decrease of early mortality, we tested whether this finding was accompanied by a parallel reduction of major interstage complications. Both overall ($\tau = -0.151$; $P < 0.001$) and major ($\tau = -0.102$; $P = 0.011$) interstage complications significantly declined over time (Fig. 1B). Multivariate regression analysis demonstrated that a

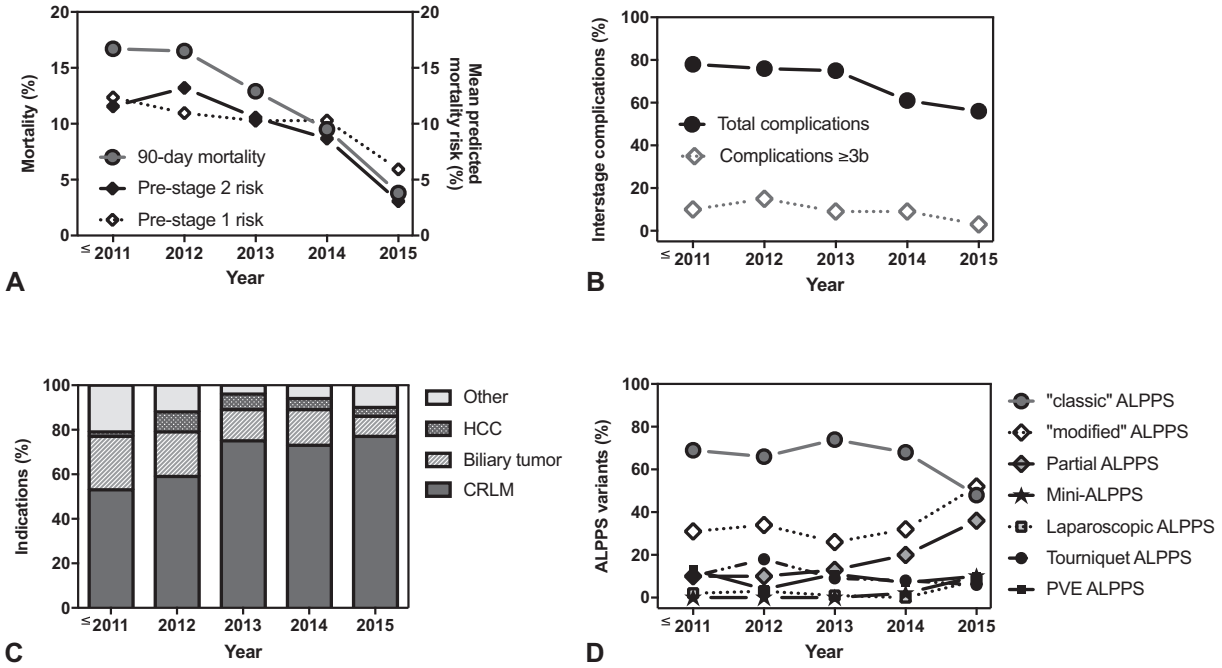

FIGURE 1. Decline of ALPPS associated 90-day mortality (A). Mortality rates significantly improved from 16.7%, 16.5%, 12.9%, 9.5%, to 3.8% in the respective years ≤2011, 2012, 2013, 2014, and 2015 ($P = 0.009$). Reduction of early mortality over time was associated with a gradual decline of the mean predicted prestage 1 and prestage 2 mortality risks indicating risk reduction. Prestage 1 and prestage 2 mortality risks were calculated for each patient according to the previously published ALPPS risk formula[15] using the variables age, tumor entity, interstage complications ≥3b, and prestage 2 serum bilirubin and creatinine. Mean predicted risks dropped in the prestage 1 model from 12.4%, 11.0%, 10.3%, 10.3%, to 6.0% ($P < 0.001$) and in the prestage 2 model from 11.6%, 13.2%, 11.0%, 8.6% to 3.1% ($P < 0.001$) in the annual periods ≤2011, 2012, 2013, 2014, and 2015. Total and major interstage complications dropped from 78% to 56% ($P = 0.001$), and 10% to 3% ($P = 0.020$) in the periods ≤2011 and 2015 (B). Indications for ALPPS significantly changed over time with an increase in CRLM and a decline in biliary tumors (C). (D) This illustrates the technical development of ALPPS over time. PVE-ALPPS, Partial ALPPS, Laparoscopic ALPPS, Tourniquet ALPPS, and Mini-ALPPS were categorized as ''modified ALPPS'' as opposed to ''classic'' ALPPS as initially described.[1,2] In 2015, 52% were modified ALPPS as compared with 31% in ≤2011. Partial ALPPS was the most common technical modification, representing 68% of all technically modified ALPPS.

reduction of prestage 1 risk, which reflects patient selection, is associated with a decrease in major interstage complications ($P = 0.011$; OR 1.26, 95% CI 1.06–1.51; Supplementary Table 4, http://links.lww.com/SLA/B310). Furthermore, less invasive ALPPS variants were associated with a reduction of major interstage complications ($P = 0.035$; OR 0.40; 95% CI 0.17–0.94; Supplementary Table 4, http://links.lww.com/SLA/B310), underlining the impact of less invasive techniques on favorable interstage course.

DISCUSSION

This longitudinal cohort study demonstrated for the first time that risk adjustment in patient selection, and technical modifications toward less invasive ALPPS procedures, and interstage management occurred over time. These changes resulted in a continuous drop of early mortality and major postoperative morbidity, which has meanwhile reached standard outcome accepted for major liver surgery.

ALPPS has initiated hot debates on its safety and efficacy among experienced hepatobiliary surgeons with opposite attitudes of advocating or refusing this procedure.[7] One major drawback of this procedure is the high early mortality rate, which was reported in initial series between 10% and 20%.[9,11–13,16] Even a recent ALPPS registry analysis looking at centers with ≥5 registered patients found an overall 90-day mortality rate of 9%.[15] Today, these data need to be put in perspective since 5 years have passed since the inaugural description of ALPPS[1,2] and 8 years since the first recorded cases in the ALPPS registry. However, previous ALPPS studies analyzed only pooled data of entire time periods[10,15,17] but longitudinal observation studies, which are focused on change in patient characteristics and outcome over time, are generally rare in surgical mortality studies[18] and have not yet been reported in ALPPS. To monitor changes or adjustments over time, a longitudinal study design requires a minimum length of observation period as well a minimum number of ALPPS cases performed within this period. To consider these requirements, we included only centers, which reported at least 10 cases over a minimum period of 3 years.

The central observation of the study is the dramatic decrease in early mortality after ALPPS. The unacceptable 90-day mortality rate of 17% in the early pioneer period steadily improved to 4% in 2015. This favorable development represents a major milestone for ALPPS that now compares with the standard outcome accepted for major liver surgery[7,19] To study which factors are the main contributors for this development, we dissected the analysis into 3 categories looking at adjustment of patient selection, technical modification, and interstage management.

TABLE 4. Interstage and Poststage 2 Course

Parameter	Completeness (%) Before	After	≤2011	2012	2013	2014	2015	Correlation	*P*
Interstage course									
sFLR	87	95	0.36 (0.30–0.45)	0.41 (0.33–0.49)	0.36 (0.30–0.45)	0.37 (0.30–0.44)	0.35 (0.29–0.42)	−0.116	0.019
sFLR increase, %	80	91	84 (43–113)	74 (50–107)	77 (43–101)	61 (39–93)	82 (45–117)	−0.053	0.288
Δ sFLR	81	92	0.28 (0.17–0.40)	0.27 (0.20–0.42)	0.27 (0.17–0.34)	0.21 (0.15–0.30)	0.26 (0.17–0.31)	−0.128	0.010
FLR/BW	77	95	0.65 (0.48–0.86)	0.69 (0.53–0.85)	0.66 (0.54–0.75)	0.57 (0.48–0.73)	0.58 (0.46–0.72)	0.154	0.002
Interstage interval, d	80	94	10 (7–14)	11 (8–17)	12 (9–17)	11 (8–15)	14 (10–21)	0.128	0.009
Lab tests day 5									
Serum bilirubin, mg/dL	91	99	0.80 (0.50–1.45)	0.82 (0.53–1.75)	0.76 (0.60–0.86)	0.67 (0.47–1.21)	0.60 (0.40–0.90)	−0.151	0.002
Serum creatinine, mg/dL	77	92	0.70 (0.57–0.90)	0.69 (0.60–0.97)	0.71 (0.60–0.85)	0.67 (0.50–0.80)	0.70 (0.58–0.80)	−0.083	0.097
INR	88	93	1.1 (1.0–1.2)	1.2 (1.0–1.3)	1.1 (1.0–1.3)	1.1 (1.0–1.3)	1.1 (1.0–1.2)	−0.042	0.395
MELD	72	86	9 (7–11)	9 (7–12)	8 (7–10)	8 (7–11)	8 (6–10)	−0.083	0.108
ISGLS	88	97	2 (4)	14 (14)	12 (12)	17 (17)	6 (8)	0.020	0.612
Lab tests prestage 2									
Serum bilirubin, mg/dL	91	97	0.70 (0.40–1.10)	0.80 (0.50–1.20)	0.73 (0.40–1.14)	0.60 (0.40–0.90)	0.50 (0.30–0.70)	−0.221	<0.001
Serum creatinine, mg/dL	82	91	0.70 (0.60 -0.80)	0.72 (0.58–0.89)	0.76 (0.60–0.86)	0.66 (0.58–0.80)	0.70 (0.60–0.84)	−0.044	0.386
INR	86	91	1.1 (1.0–1.2)	1.1 (1.0–1.3)	1.2 (1.0–1.3)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	−0.091	0.069
MELD	75	84	8 (6–9)	8 (7–11)	8 (7–11)	8 (6–9)	7 (7–9)	−0.128	0.014
Liver function testing*, n, %	—	99	11 (21)	25 (24)	20 (20)	31 (30)	30 (39)	0.103	0.021
Interstage complications, n, %	84	97	36 (78)	77 (76)	64 (65)	62 (61)	43 (56)	−0.151	<0.001
Interstage complications ≥3b, n, %	99	100	5 (10)	15 (15)	9 (9)	9 (9)	2 (3)	−0.102	0.011
ICU stay, d	71	99	1 (1–3)	2 (1–5)	1 (1–3)	1 (1–3)	1 (1–2)	−0.166	0.001
Stage 2 not performed, n, %	98	100	1 (2)	3 (3)	0 (0)	2 (2)	4 (5)	0.051	0.467
Poststage 2 course									
Complications stage 2, n, %	71	97	37 (77)	66 (66)	74 (73)	67 (67)	46 (61)	−0.062	0.158
Complications stage 2 ≥3b, n, %	71	97	15 (31)	30 (30)	21 (21)	29 (29)	19 (25)	−0.027	0.538
ICU stay, d	69	75	2 (0–4)	2 (1–4)	1 (0–4)	1 (0–4)	1 (0–2)	−0.142	0.010
Hospital stay, d	73	83	11 (7–34)	10 (7–21)	12 (7–24)	12 (7–22)	12 (8–19)	0.006	0.910

Continuous variables presented as median and interquartile range (IQR), correlation with Spearmans ρ; categorical variables presented as count and percent (%), correlation with Kendalls τ.

*Refers to hepatobiliary scintigraphy, indocyanine green, or LiMAx testing.

ICU indicates intensive care unit; INR, international normalized ratio; ISGLS, International Study Group of Liver Surgery criteria; MELD, Model for End-stage Liver Disease.

Patient selection is one of the key principles for improving outcome in surgery.[20] In the present study, a significant age shift to younger patients as well as a shift toward more colorectal liver metastases and less biliary tumors were characteristic changes over time. The decline of the mean predicted prestage 1 risk of early mortality,[15] which incorporates both variables age and tumor type, illustrates that the risk was lowered by adjusting age and tumor indication over time. These observations go along with the results of the survey where the majority of centers stated that risk adjustment in patient selection was performed for age and tumor indication (Table 1). Independently of the present study, age has been reported as crucial factor for mortality in ALPPS[15,17] and many centers have also observed favorable outcomes for CRLM[8,17,21] but inferior results for biliary tumors.[9,17,22] Another important observation of this study was the decreasing proportion of ALPPS patients with cardiovascular disease. Although prevalent cardiovascular disease was not an element of the prestage 1 risk prediction model,[15] the negative impact of this comorbidity on postoperative outcome has been well documented in major liver surgery[23] and might be also a contributing factor of risk adjustment in the present study.

Several technical modifications of the ALPPS operation have been developed which include the variants[14,24] PVE-ALPPS,[25] Partial ALPPS,[26,27] Laparoscopic ALPPS,[28] Tourniquet ALPPS,[29] and Mini-ALPPS.[30] All variants have in common less invasive stage 1 surgery aiming to avoid major interstage complications and to improve safety of the procedure. Despite the less invasiveness, rapid hypertrophy is not considerably impaired in ALPPS variants compared with the classical procedure.[8,27,30] In the present study, we observed a trend of increasingly performed ALPPS variants and a concurrent decrease of classical procedures (Fig. 1D). In accordance with this observations, the majority of centers stated in the survey that ALPPS technique has been modified over time (Table 3). Although comparing studies suggest superior outcome for less invasive techniques,[8,27,30] none of them could statistically demonstrate that less invasiveness is associated with reduced early mortality, mainly due to the small sample and event size. We therefore tested in the present cohort whether less invasive ALPPS is independently associated with 90-day mortality and demonstrated for the first time that less invasiveness is an independent risk factor for reduced mortality (Supplementary Table 4, http://links.lww.com/SLA/B310). Since regression analysis was controlled for the year of ALPPS performed, the novel finding of reduced mortality appears not to be superimposed by a potential learning curve bias and is rather a inherent characteristic of the less invasive procedure itself. The observed lower interstage complication rate in less invasive techniques might be also an additional contributing factor for lower mortality observed in modified ALPPS (Supplementary Table 4, http://links.lww.com/SLA/B310).

Following stage 1 surgery, greatest attention needs to be directed to the interstage course. In our study, interstage management was evaluated by the length of the interstage interval as well as liver function tests and occurrence of complications during the interstage course. The importance of an uneventful interstage course in terms of normal renal and hepatic function as well as avoidance of complications has been repeatedly reported.[13,15,17] As demonstrated in our study, interstage complications are mainly influenced by patient selection and ALPPS technique while interstage renal and hepatic function might be modified by extending the interstage interval until both organ functions reach normal range.[15,17] The observed prolongation of the interstage interval was accompanied by increasingly used liver function testing in our study. This implies the importance of liver function tests for guiding safe progression with stage 2

surgery.[31,32] Furthermore, the adjustments of interstage management is also partially mirrored by the decreasing prestage 2 mortality risk over time since 3 of 4 variables of the prestage 2 risk model are interstage measures such as interstage major complications, prestage 2 serum bilirubin and creatinine.[15]

The strength of this study is the transformation of a registry-based cohort into an international prospectively collected, ALPPS cohort with a longitudinal study design. This process led to a significant improvement in data quality and completeness (Tables 2–4). Further strength of this study is related to gathering of new data on ALPPS technique, which were not captured by the registry. This allowed including technical modifications in the analysis. In addition, an independently undertaken survey on risk adjustment accompanied the statistical findings of the longitudinal study. However, this study has also shortcomings, which are associated with voluntary data entry potentially leading to reporting bias. To minimize this problem, centers were individually approached to provide their entire ALPPS experience and avoid missing data.

In conclusion, this longitudinal study demonstrates that risk adjustment of patient selection, ALPPS technique, and interstage management resulted in improved outcome of ALPPS over time, which now compares with standard outcome accepted for major liver surgery. Despite these remarkable results, there is still room for continuous improvement in ALPPS for procedure-related safety and oncological outcome.

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DISCUSSANTS

Pål-Dag Line (Oslo, Norway):

Thank you for the privilege and opportunity to evaluate this important paper about improvements in patient selection and management in ALPPS and the impact on early morbidity and mortality. First, one of the weaknesses of longitudinal studies is that it may be difficult to detect causal relationships. You have evaluated changes over time by correlation analysis. Subtle changes over time do not always imply an underlying relationship. Did you ever consider an alternative design with treatment period/year as a grouping variable, and if so, would this alter the statistical approach? Second, it is difficult to me to assess the significance of less invasive ALPPS separately from the learning curve and clinical experience gained throughout the study period. Therefore, from the authors perspective, what is the most important factor to improve outcomes in ALPPS; patient selection, interstage management or ALPPS technique (classical vs technically modified)?

Third, liver failure and sepsis remain the most important causes of death following ALPPS. Do the authors have any information regarding liver function testing in the fatal group in particular and whether interstage interval length was different from the other patients? Fourth, regarding the operative characteristics and ALPPS variants as given in Table 3: Why is rescue ALPPS listed as a separate category together with classical and technical modified ALPPS?

Response from Henrik Petrowsky (Zurich, Switzerland):

Thank you Prof. Line for reviewing our manuscript and I really appreciate your interesting and important questions that I would like to answer point by point. Your first question arises the concern that the observational findings of our study do not necessarily detect causal relationships. Therefore, an important part of our study was to conduct a multivariant analysis, in which various risk factors that influence outcome of ALPPS were controlled. We also included the variable treatment period. Statistical observations over time is one important element but the multivariant analysis identified less invasiveness, as well as patient selection using the prestage 1 risk score as independent predictors regardless in which year ALPPS was performed. I think we could clearly demonstrate that both risk factors are independent predictors independently of the year that also explains risk adjustment.

In your second question, you mentioned that it is difficult to assess the significance of less invasive ALPPS separately from the learning curve. This is an important question and I would like to refer to my previous reply and our multivariant regression analysis. I agree with you that a certain effect of the learning curve on outcome cannot be excluded but as mentioned before we controlled our regression analysis for the year of ALPPS was performed. Despite this approach, less invasive ALPPS technique was an independent predictor of improved outcome regardless of the year when ALPPS was performed. Another independent predictor was prestage 1 risk, which reflects patient selection. We put all the important and significant variables of the uni-variant analysis into the multi-variant analysis including interstage variables, but they did not come out as significant. It might be that patient selection influences a favorable interstage outcome. I think that patient selection as well as the use of less invasive stage 1 surgery is probably the most important factor, which resulted in improved outcome.

Next, you asked whether liver function testing and interstage interval were different for the fatal and nonfatal group. Yes, indeed we looked at these variables and, interestingly, there was no significant difference between both groups. In your next question you asked why rescue ALPPS has been listed as a separate category. The simple purpose to do so was to provide the reader with figures in which ALPPS was performed for portal vein embolization failure. I think, this is an important information to be included in the manuscript.

Christiane Bruns (Cologne, Germany):

Thank you very much for this presentation. I have 2 questions: You nicely demonstrated that modifications of the ALPPS procedure, in particular less invasive ALPPS procedures, led to a reduction of mortality. I am curious to know, how much future liver remnant you gain with less invasive ALPPS procedures? Is this less invasive ALPPS procedure really necessary or could the anticipated liver resection also be performed without the less invasive ALPPS procedure? You definitely decrease morbidity with less invasive ALPPS procedures, have you also looked at the oncological outcome of those patients receiving the less invasive ALPPS compared to patients who received more invasive ALPPS procedures for instance the recurrence free survival in patients with colorectal liver metastases? Furthermore, have you compared the morbidity and mortality of patients after the mini-ALPPS and reduced ALPPS procedures to patients receiving 2-stage hepatectomy if this is possible?

Response from Henrik Petrowsky (Zurich, Switzerland):

Thank you, Prof. Bruns for your important questions. We looked into these things and we found that the group of modified procedures had no major disadvantage in terms of hypertrophy. Even by partial transection, you achieve almost what you gain with complete transection. Hypertrophy is not the only critical part of ALPPS. How much the future liver remnant is instrumented another important factor for the indication of ALPPS. Interstage complications might delay stage 2 surgery and start of chemotherapy. Therefore, it is important that you improve the interstage course so that these patients don't get any complications and can proceed to stage 2 surgery. To address your question of oncological outcome and comparison to 2-stage hepatectomy, we did not look into these topics.

Antonio Pinna (Bologna, Italy):

Nice presentation. Quick questions. First, how do you explain a better outcome, due to the fact that the functional volume liver remnant is actually less overtime in the study. I would like to know how do you explain if the volume is not increasing as much as in the original group, and how can we have a better outcome?

And my second question is, would it be nice to compare morbidity and mortality outcome between classical ALPPS and all the group of modified ALPPS to have a better clue, if this is the right technique for extended liver disease or rather this technique is just comparable to a single stage large hepatectomy?

Response from Henrik Petrowsky (Zurich, Switzerland):

Thank you Prof. Pinna for your relevant questions. Let me first address your questions on volume increase and outcome. Volume increase is necessary, but probably not the most critical factor for the risk of mortality as we also have demonstrated in our previous ESA paper on the ALPPS risk score where the degree of hypertrophy was not a significant predictor of early mortality. As I outlined in my previous comments to Prof. Line, appropriate patient selection and lowering interstage complications by using less invasive techniques are probably the 2 most important key elements for improved outcome. I agree with you, it would be terrific study looking into all less invasive groups in comparison with the classical procedure. We tried to look into whether we can split up the different less invasive groups but the numbers were too small.