Original Article

Optimization of ALPPS stage II timing with the APRI/ALBI score—an international, multicenter cohort study

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Background: Primarily unresectable liver tumors may be approached by the Associating Liver Partition and Portal vein Ligation for Staged Hepatectomy (ALPPS) procedure. Post-hepatectomy liver failure (PHLF) poses the most significant risk factor for poor outcomes. The AST-to-platelets ratio index (APRI)/albumin-to-bilirubin index (ALBI) score has been proposed as an easy and routinely available score to monitor liver function. Here, we explored the predictive capability of the APRI/ALBI score to determine PHLF and perioperative morbidity to help determine the optimal timing of the 2nd stage of ALPPS.

Methods: Based on the international multicenter ALPPS registry, patients from 2012 to 2020 with an available APRI/ALBI score were included. Postoperative outcomes (clinically relevant PHLF B + C, 90-day mortality, and severe morbidity (≥ Clavien-Dindo 3b) after ALPPS stage II were assessed. The APRI/ALBI score was monitored perioperatively, and the predictive value was evaluated using logistic regression and

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receiver operating characteristics. Performance of APRI/ALBI score was compared to the ALPPS futility risk score in this cohort study.

Results: Overall, 464 patients from 16 participating centers were included. Clinically relevant PHLF (B + C) was observed in 7.5% of patients, of which 63% ultimately died. After stage I, the APRI/ALBI score gradually recovered. The pre-stage II APRI/ALBI score significantly predicted clinically relevant PHLF [area under the curve (AUC) =0.78; P<0.001], 90-day mortality (AUC =0.67; P=0.002), and severe morbidity (AUC =0.65; P<0.001). Three clinically relevant APRI/ALBI score risk groups were defined: clinically relevant PHLF occurred in 3.1% in the low-, 8.7% in the intermediate-, and 28.0% in the high-risk groups. 90-day mortality was 6.8% in the low-, 15.9% in the intermediate-, and 19.4% in the high-risk groups. Integrated assessment of the established futility risk score in combination with the APRI/ALBI score documented further increased predictive potential for clinically relevant PHLF (AUC 0.81; P<0.001).

Conclusions: The APRI/ALBI score allows for simple and dynamic liver function recovery monitoring after the first ALPPS stage. Inadequate recovery of the APRI/ALBI score until ALPPS stage II was associated with PHLF B + C, 90-day mortality, and severe morbidity. With the proposed risk model, optimized timing of the second stage of ALPPS may further increase the safety of this procedure.

Keywords: Associating Liver Partition and Portal vein Ligation for Staged Hepatectomy (ALPPS); AST-to-platelets ratio index (APRI); albumin-to-bilirubin index (ALBI); post-hepatectomy liver failure (PHLF); timing

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Introduction

Surgery remains the cornerstone for curative treatments of primary and secondary liver tumors. Many of these tumors are initially unresectable due to extensive spread, thus leading to insufficient future liver remnant (FLR). ALPPS (Associating Liver Partition and Portal vein Ligation for Staged Hepatectomy) is a surgical option for patients with inadequate FLR. It involves a two-stage procedure, including surgical portal vein closure and parenchyma transection with various modifications to achieve FLR augmentation. This is followed by completion hepatectomy one or two weeks later (1). However, in its early stages, this procedure carried high rates of morbidity and mortality due to underestimation of its impact on liver physiology and regeneration. As time passed, this shortcoming improved through careful patient selection and a better understanding of the technical details of the procedure. The most common indication for ALPPS remains bilobar colorectal cancer liver metastases (CRLM) that cannot be cleared with a single surgical procedure (2). Common issues after extensive surgery, like ALPPS, include post-hepatectomy liver failure (PHLF), major morbidity and mortality (3). PHLF after ALPPS occurs with an incidence of 7% to 20% and can lead to mortality rates as high as 50% (3-6). The risk of PHLF increases with liver parenchyma damage. It is also associated with chemotherapy-associated liver injury (CALI), especially in extensively pre-treated colorectal

Highlight box

Key findings

- AST-to-platelets ratio (APRI)/albumin-to-bilirubin index (ALBI) score predicts the risk of post-hepatectomy liver failure (PHLF) B + C before Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) stage II leading to optimal stage II timing and improved perioperative risk profile.

What is known and what is new?

- The preoperative APRI/ALBI score is a PHLF predictor in single-stage liver resection.
- This study is the first to evaluate the APRI/ALBI performance in the ALPPS setting with the aim to optimize stage II timing.

What is the implication, and what should change now?

- Optimized stage-II timing can lead to less postoperative morbidity, especially a reduction of clinically relevant PHLF B + C.
- The APRI/ALBI score during the interstage phase of ALPPS can help optimize the timing of stage II. This score improves over time until it reaches an optimal value (<–0.95), with the lowest possible associated PHLF B + C incidence of 3%.

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cancer (CRC) patients receiving more than six cycles of chemotherapy (7).

On a pathomolecular level, liver regeneration between the first and the second ALPPS stage (interstage phase) is crucial for the success of the 2nd stage. Major morbidity and mortality usually occur after stage II, which highlights the need to optimally assess liver function in the interstage phase (8). The optimal interstage phase duration has yet to be defined and presumably varies significantly between individual patients. Pre-stage II assessment is usually performed by computed tomography (CT) or magnetic resonance imaging (MRI) volumetry and liver function tests such as maximum liver function capacity (LiMAx), hepatobiliary iminodiacetic acid (HIDA), or indocyanine green (ICG) as suggested by the E-AHPBA-ESSO-ESSR Innsbruck guidelines on preoperative liver function assessment (9). Limitations of these assessments lie in the limited availability and associated costs of these tests and that they often consume significant amounts of time and resources.

To address the issue of liver dysfunction in different scenarios, the AST-to-platelets ratio index (APRI) was proposed in 2003 and has since evolved from a predictor of fibrosis/cirrhosis to a predictor of PHLF in the setting of liver surgery (10,11). Another score, the albumin-to-bilirubin index (ALBI), was proposed in 2015 to assess the liver function of HCC patients (12). A combined score of these two indices (i.e., APRI/ALBI) reflects liver parenchyma damage and hepatocyte function and was first assessed as a preoperative PHLF predictor in 2019 (13). This score demonstrated good preoperative predictive performance for PHLF and 30-day mortality in a large international cohort of patients undergoing liver resection (13-15). Importantly, the APRI/ALBI score has been applied to dynamically monitor liver function recovery after an injury such as chemotherapy (13). Accordingly, we hypothesized that the APRI/ALBI score might allow dynamic and cost-efficient monitoring of liver function and its recovery to optimize the timing of the 2nd stage of ALPPS. We aimed to define APRI/ALBI cut-offs to define different risk categories for PHLF after ALPPS to propose a clinically useful model. We present this article in accordance with the STROCSS reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-617/rc).

Methods

Study design

The ALPPS registry database was initiated in 2011 and prospectively collects data on ALPPS cases. The Department of Visceral- and Transplant Surgery of the University Hospital Zurich, Switzerland maintains the database. Patients were entered after signing their respective written informed consent forms. This study was approved by the Cantonal Ethics Committee of Zurich (KEK 2013-0326; ClincialTrials.gov NCT01924741). The study was performed in accordance with the Declaration of Helsinki and its subsequent amendments (16). This study is designed as a retrospective cohort study. Data extraction and analysis were conducted after project approval by the ALPPS steering committee in 2023. Data were extracted from the ALPPS Registry on 15th March 2023. Consecutive patients were considered with any indication for ALPPS after discussing the clinical, laboratory and radiology investigations in a multidisciplinary tumor board. Center inclusion criterion was a minimum of 10 ALPPS cases, and of the 42 contacted centers, 16 centers agreed to participate in the study. These centers were contacted to supply missing laboratory parameters. Data input was closed in October 2023. Finally, the APRI/ALBI score was calculated for each patient.

Outcome parameters

The study's primary aim was to investigate the prediction of PHLF with the APRI/ALBI score after ALPPS stage I and II. A previously published formula was used to calculate the APRI/ALBI score as a continuous variable with negative and positive values. Four blood parameters were recorded at several perioperative time points: aspartate aminotransferase (AST), platelet (PT), albumin, and bilirubin (13,14). These parameters were sampled the day prior, the first and third day after each ALPPS stage I and II. Generally, higher score numbers indicate worse liver function. PHLF was assessed and graded according to the International Study Group of Liver Surgery (ISGLS) criteria (17). Morbidity and mortality were documented within the first 90 postoperative days and classified according to the Clavien-Dindo classification, while major complications were defined as grade Clavien-Dindo 3b or higher (18). Intraoperative blood loss was categorized

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into low (101–600 mL), moderate (601–1,000 mL), and high (>1,000 mL). Furthermore, the PHLF prediction ability of the APRI/ALBI score was compared to the previously published ALPPS risk score (19). This score assesses the futility (=90-day mortality) of ALPPS surgery based on different parameters: (I) tumor type and age ≥67 years as independent predictors of futility before stage I; (II) major complications, bilirubin, and creatinine for the futility of stage II. In addition, the predictive value for PHLF of a combined model, including ALPPS futility risk score and APRI/ALBI, was determined based on Youden's index and in line with previously published data from this research group (13,20).

Inclusion and exclusion criteria

Patients were included if 18 years or older. Indication for ALPPS surgery was discussed within the MDT board. The underlying tumor entity was not restricted. All patients signed the written informed consent for the surgical intervention. Exclusion criteria included unresectable disease, pregnancy, and no given consent. Patients were treated at different centers, and upon their consent, their data was provided to the international multicentric ALPPS registry, of which the data extraction was performed for this study. Patients did not receive financial compensation or priority in clinical treatment if they participated in this registry. Patients were continuously recruited from the respective international participating centers.

Intervention

ALPPS surgery involves a two-stage treatment with the ultimate aim to clean the liver of all tumors. This technique is applied if the FLR is deemed too small. During the first stage, the portal vein to the to-be-removed liver lobe is tied, and the parenchyma is dissected to a certain degree. After achieving adequate hypertrophy, stage II can be completed by removing the previously deportalized liver lobe. This procedure is one of the most complex liver surgery procedures and was first proposed in 2012. Special fellowship training helps to surmount the learning curve. Postoperatively, particular emphasis needs to be put on PHLF as this is a known complication after extensive liver surgery.

Statistical analysis

The APRI-ALBI score was calculated using the formula provided in the supplemental data (Figure S1). The data distribution was represented as median and interquartile range. The APRI/ALBI scores between different time points were tested using the Friedman rank-based and pairwise post-hoc Conover tests with Bonferroni correction (R package PMCMRplus) on complete profiles. Logistic regression analyses and receiver operating characteristics were performed for different outcome parameters (PHLF B + C, PHLF A–C, severe morbidity, and 90-day mortality) and the APRI/ALBI score as a predictor variable (R package ROCR, pROC). The area under the curve (AUC) was used as a predictive value, and P values were calculated using the Wilcoxon rank sum test (R package verification). The APRI/ALBI score cut-off calculation was based on the maximal Youden Index and maximal F1-score [high negative predictive value (NPV)], and based on these two cutoffs, three PHLF risk groups were observed. Logistic regression analyses were performed to determine whether interstage days (ISD) had predictive power for PHLF. Linear regression analyses have been conducted to detect an association between ISD and APRI/ALBI scores pre-stage II. We also performed logistic regression and ROC analyses for ALPPS futility risk scores from stages I and II. Additionally, a combined model, including the ALPPS futility risk score II and the APRI/ALBI score pre-stage II, was used to predict the PHLF B + C outcome based on the following formula: *RISK_SCORE1<-0*CRLM+1*NONCRLM_NONBILIARY+2*BILIARY+3*AGE_67Y andRISK_SCORE2<-0.66*SCORE1+1.2* STAGE_I_COMPL_3B+1.5*log10(10x Bili in mg/dL)+1.7*log10 (10x Crea in mg/dL)*. We used a two-sided Fisher's exact test and a two-sided Wilcoxon rank sum test to compare various parameters and clinical characteristics between patients with PHLF (B + C) and those with no liver dysfunction. P values <0.05 were considered significant. The statistical analysis was conducted using SPSS version 24 (IBM Inc., Armonk, NY, USA) and the software environment R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient demographics

A total of 464 patients from 16 international centers were included. The median age was 61 [20–83] years and 274 patients were male (59%). ALPPS was mainly performed for CRLM (54%), HCC (12%) and CCC (10%). The pre-stage

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I median sFLR was 384 [158–1,081] mL or 24% (10–55%). The median BMI was 25.4 [15–58] kg/m^2. Concerning ALPPS stage I, from the 464 patients, 6 (1.3%) did not proceed to stage II due to tumor progression in five cases and one death due to abdominal bleeding with consecutive cardiac failure. Thirteen patients (2.8%) underwent stage I laparoscopically. In contrast, the rest underwent an open stage I procedure. The median interstage interval was 13 [4–751] days. Regarding stage II, the median intensive care unit (ICU) stay after stage II was 2 [0–70] days. Severe complications after stage II occurred in 75 patients (16%), with biliary fistulas (11%), postoperative hemorrhage (13%), acute kidney injury (11%), and PHLF (14%) being the most frequent ones. Overall, 90-day mortality was 8% (*Table 1*).

Perioperative APRI/ALBI dynamics

From preoperative value –2.36 (–2.59 to –2.0), the APRI/ALBI score increased on the first day after stage I [4.41 (1.87 to 30.9)] in all included patients, followed by a plateau until the third postoperative day [1.2 (–0.43 to 6.9)], decreasing to pre-stage II value [–1.13 (–2.15 to –0.1)]. After a median interstage interval of 13 [4–751] days, the preoperative stage II score was higher than the pre-stage I score (median scores pre-stage I –2.36 and pre-stage II –2.07; P<0.001). The post-stage II score (day 1) was lower than the post-stage I score [0.23 (–0.86 to 2.4) *vs.* 4.41 (1.87 to 30.9)] (*Figure 1A*). During the interstage phase, the APRI/ALBI score decreased over time by a median daily decrease of 0.067 (range, 0.011–0.068) (*Figure 1B*).

PHLF after ALPPS

PHLF B + C after the 2nd ALPPS stage occurred in 35 patients (7.5%). Patients with PHLF B + C were older {66 [27–81] years} compared to non-PHLF patients {59 [20–83] years} (P=0.003). Furthermore, no significant differences in sex, BMI, or associations with liver parenchyma pathology were seen. Patients with PHLF B + C versus non-PHLF showed no differences in tumor entity distribution. However, patients with PHLF B + C had a higher Model for End-Stage Liver Disease (MELD) score before surgery (PHLF B + C: 15 *vs.* non-PHLF: 14, P=0.006). The median interstage period was similar, with 14 days for PHLF B + C versus 13 days for the non-PHLF group (P=0.75). More patients died in the PHLF B + C group (63% *vs.* 4%; P<0.001). The median length of stay (LOS) and ICU LOS were significantly longer after stage II in the PHLF B + C group versus non-PHLF (LOS: 30 *vs.* 12 days, P<0.001; ICU LOS: 13 *vs.* 2 days, P<0.001) (*Table 1*).

Interestingly, we observed that pre-stage II volumetry could not predict PHLF B + C (AUC =0.55, P=0.22). Further, we did not observe a difference in the baseline pre-stage I APRI/ALBI score in patients with or without PHLF B + C (PHLF B + C: –2.38 *vs.* non-PHLF: –2.24; P=0.08). On postoperative day (POD) 1 and POD 3 APRI/ALBI values after stage I were also not different between the two cohorts (POD 1 PHLF B + C: 4.39 *vs.* non-PHLF: 4.46; P=0.11; POD 3 PHLF B + C: 0.81 *vs.* non-PHLF: 1.95; P=0.17). In contrast, the pre-stage II APRI/ALBI scores were significantly higher in the PHLF B + C cohort (PHLF B + C: –0.78 *vs.* non-PHLF: –1.61; P=0.002). Also, the post-stage II POD 1 and POD 3 scores were highly different between the two cohorts (POD 1 PHLF B + C: 0.877 non-PHLF: –0.27; P<0.001; POD 3 PHLF B + C: –0.11 *vs.* non-PHLF: –0.78; P<0.001).

Prediction of PHLF and morbidity with the APRI/ALBI score

With the APRI/ALBI score, a model was calculated and predicted PHLF B + C before stage II with an AUC of 0.775 (P<0.001). Further, the score was able to predict major morbidity preoperatively following stage II (AUC =0.646, P<0.001) as well as 90-day mortality after stage II (AUC =0.674, P=0.002) (*Figure 2*).

While no overall significant predictive potential between ISD and PHLF was observed, PHLF appeared to cluster in the earlier ISD (<10 days) with a cumulative incidence of 16.1% compared to later interstage periods (12.9% for 11–20 ISD and 9.1% for 21–30 ISD) (*Table 2*).

PHLF risk groups according to the APRI/ALBI score

Three clinically relevant APRI/ALBI score intervals were defined by two cut-offs in relation to PHLF incidence after stage II. These three risk groups had cumulative PHLF B + C incidences of 3.13% in the low-, 8.7% in the intermediate-, and 28% in the high-risk groups. The proposed algorithm depicts these risk groups in the graph, translating into a clinical recommendation (*Figure 3*). Also, 90-day mortality was 6.8% in the low-, 15.9% in the intermediate-, and 19.4% in the high-risk groups. In the low-risk group, pre-stage II APRI/ALBI scores were lower than the cut-off of –0.95, which excluded PHLF B + C with a NPV of 0.97. In the high-risk group, pre-stage II APRI/

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Table 1 Patient demographics

Variable	Overall (n=464)	PHLF B + C (n=35)	Non-PHLF (n=429)	PHLF groups P value
Age (years), median (range)	61 (20 to 83)	66 (27 to 81)	59 (20 to 83)	0.003
Sex (male), n [%]	274 [59]	21 [60]	253 [62]	0.86
BMI (kg/m^2), mean (range)	25 (15 to 59)	26.8 (19 to 41)	25.9 (15 to 59)	0.18
Liver tumor, n [%]				0.057
CRLM	250 [54]	20 [57]	230 [54]	
Hepatoma	54 [12]	5 [14]	49 [11]	
Biliary tumor	46 [10]	7 [20]	39 [9]	
Other	43 [9]	2 [6]	41 [10]	
NA	71 [15]	1 [3]	70 [16]	
Liver baseline characteristics				
Pre-step I sFLR (mL), median (range)	384 (158 to 1,082)	369 (164 to 618)	391 (158 to 1,082)	0.06
Steatohepatitis, n [%]	32 [7]	4 [19]	28 [14]	0.524
Fibrosis, n [%]	58 [13]	7 [30]	51 [27]	0.81
Macrosteatosis, n [%]	81 [17]	11 [46]	70 [35]	0.37
SOS, n [%]	22 [5]	1 [6]	21 [12]	0.70
CASH, n [%]	17 [4]	0 [0]	17 [10]	0.37
Pre-step II lab parameters				
Creatinine (mg/dL), mean (range)	0.71 (0.26 to 2.6)	1.00 (0.41 to 2.6)	0.82 (0.26 to 2.6)	0.005
Bilirubin (mg/dL), mean (range)	0.1 (0.1 to 31.7)	1.42 (0.20 to 14.0)	0.82 (0.10 to 31.7)	0.11
INR, mean (range)	1.03 (0.76 to 2.7)	1.04 (0.85 to 1.5)	1.06 (0.76 to 2.7)	0.26
MELD score, median (range)	12 (3 to 38)	15 (7 to 29)	14 (3 to 38)	0.006
APRI + ALBI scores				
Pre stage I, median (IQR)	−2.36 (−2.59 to −2.0)	−2.24 (−2.59 to −1.5)	−2.38 (−2.70 to −2.0)	0.09
Stage I POD1, median (IQR)	4.41 (1.87 to 30.9)	4.46 (2.09 to 30.9)	4.39 (1.87 to 11.5)	0.11
Stage I POD3, median (IQR)	1.2 (−0.43 to 6.9)	1.95 (−0.18 to 6.9)	0.81 (−0.43 to 3.5)	0.18
Pre stage II, median (IQR)	−1.13 (−2.15 to −0.1)	−0.78 (−1.69 to −0.1)	−1.61 (−2.15 to −1.0)	0.002
Stage II POD1, median (IQR)	0.23 (−0.86 to 2.4)	0.87 (0.40 to 2.4)	−0.27 (−0.86 to 0.5)	<0.001
Stage II POD3, median (IQR)	−0.42 (−1.21 to −0.4)	−0.11 (−0.45 to 0.7)	−0.78 (−1.21 to −0.4)	<0.001
ALPPS stage II parameters				
Median interstage days	13	14	13	0.75
Stage II LOS (d), median (days)	13 (0 to 113)	30 (1 to 93)	12 (0 to 113)	<0.001
Stage II ICU (d), median (days)	2 (0 to 70)	13 (2 to 70)	2 (0 to 59)	<0.001
90-day mortality, n [%]	38 [8]	22 [63]	16 [4]	<0.001
Severe morbidity, n [%]	75 [16]	29 [83]	46 [11]	<0.001

The overall cohort characteristics are depicted on the left. Group comparisons between PHLF B + C and non-PHLF patients on the right. ALBI, albumin-to-bilirubin index; ALPPS, Associating Liver Partition and Portal vein Ligation for Staged Hepatectomy; APRI, AST-to-platelets ratio; APRI + ALBI, AST-to-platelets ratio index & albumin-to-bilirubin index; AST, aspartate transferase; BMI, body mass index; CASH, chemotherapy-associated steatohepatitis; CRLM, colorectal cancer liver metastases; HCC, hepatocellular carcinoma; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; LOS, length of stay; MELD, Model of End-Stage Liver Disease; NA, not available; PHLF, post-hepatectomy liver failure; POD, postoperative day; sFLR, standardized future liver remnant; SOS, sinusoidal obstruction syndrome.

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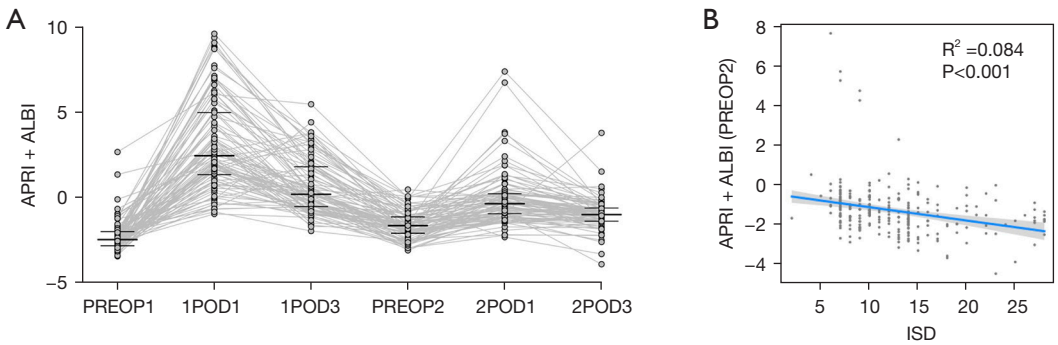


Figure 1 Perioperative APRI/ALBI dynamics. (A) Perioperative score dynamics with increases after each ALPPS step followed by a decrease. A significant difference between pre-step I and pre-step II scores was observed. Other significant differences are highlighted as well. (B) APRI/ALBI score decreases over time in the interstage phase. ALBI, albumin-to-bilirubin index; ALPPS, Associating Liver Partition and Portal vein Ligation for Staged Hepatectomy; APRI, AST-to-platelets ratio; ISD, interstage days; POD, postoperative day; PREOP, preoperative day.

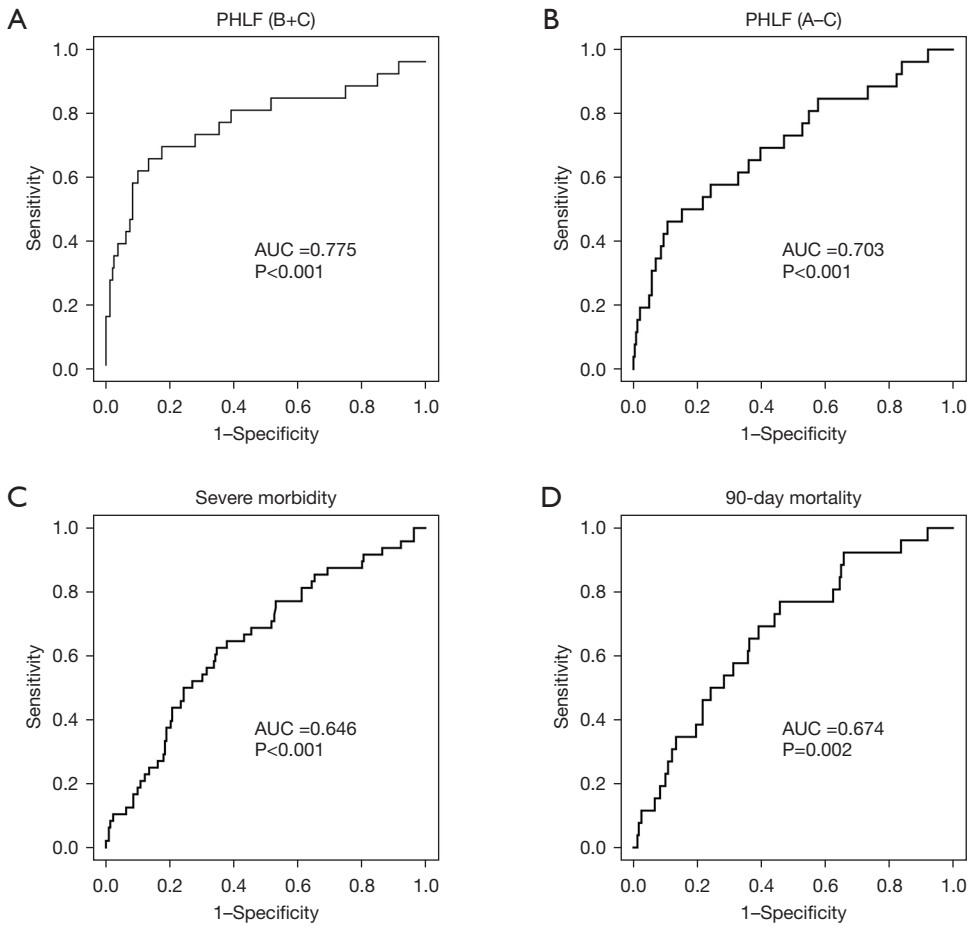


Figure 2 Predictive potential of pre-step II APRI/ALBI given as AUCs for primary outcome variables. (A) PHLF B + C. (B) PHLF A–C. (C) Severe morbidity. (D) 90-day mortality. ALBI, albumin-to-bilirubin index; APRI, AST-to-platelets ratio; AUC, area under the curve; PHLF, post-hepatectomy liver failure.

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Table 2 Calculated risk groups according to pre-step II APRI/ALBI score

Variables	Time	Low risk*	Intermediate risk**	High risk***
PHLF (B + C)	Overall	192 (3.1)	46 (8.7)	32 (28.1)
	ISD <10	61 (3.3)	22 (9.1)	17 (29.4)
	10≥ ISD ≤19	105 (1.9)	20 (10.0)	13 (30.8)
	19< ISD <29	26 (7.7)	4 (11.2)	2 (33.1)
90-day mortality	Overall	191 (6.8)	44 (15.9)	31 (19.4)
	ISD <10	61 (3.3)	20 (10.0)	16 (18.8)
	10≥ ISD ≤19	104 (5.8)	20 (20.0)	13 (23.1)
	19< ISD <29	26 (19.2)	4 (25.0)	2 (28.5)

Data are presented as n (%). Cut-offs: *, <–0.95; **, –0.95 to –0.37; ***, >–0.37. ALBI, albumin-to-bilirubin index; APRI, AST-to-platelets ratio; PHLF, post-hepatectomy liver failure; ISD, interstage days.

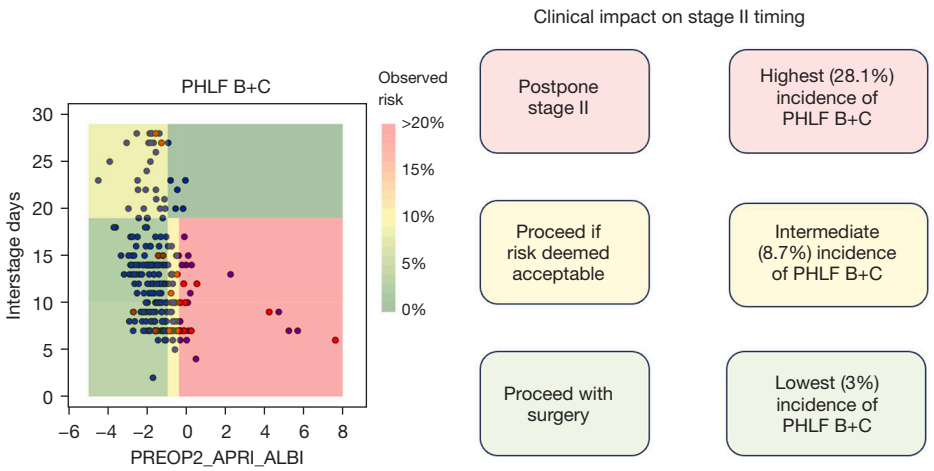


Figure 3 Proposed algorithm to determine timing of stage II based on the PHLF B + C risk according to the pre-step II APRI + ALBI score. ALBI, albumin-to-bilirubin index; APRI, AST-to-platelets ratio; AST, aspartate transferase; PHLF, post-hepatectomy liver failure.

ALBI score higher than –0.37 had a sensitivity of 0.47 and specificity of 0.91 for clinically relevant PHLF with a false positive rate of 9% (positive predictive value 0.281).

APRI/ALBI score and the ALPPS risk score

In addition to the APRI/ALBI score, the established ALPPS futility risk score was calculated. We observed that the pre-stage I and the pre-stage II ALPPS risk score were both significant in predicting PHLF B + C (pre-stage I score AUC 0.69, P<0.001; pre-stage II score AUC 0.801, P<0.001, *Figure 4A*). In a next stage, logistic regression revealed that a combined model of the ALPPS risk score with our pre-stage II APRI/ALBI score further improved the diagnostic accuracy of the APRI/ALBI score (P= combined APRI/ALBI and ALPPS risk score PHLF B + C AUC =0.814, P<0.001; severe morbidity AUC =0.684, P<0.001; 90-day mortality AUC =0.812, P<0.001; *Figure 4B-4D*). Figure S2 provides details on the APRI/ALBI score, the ALPPS risk score, and the combined model.

Discussion

The results of this international multicenter cohort study show that the APRI/ALBI score can reliably predict the risk of PHLF B + C, major morbidity, and 90-day mortality before ALPPS stage II. Three risk cohorts were identified based on the pre-stage II APRI/ALBI score: a high-risk

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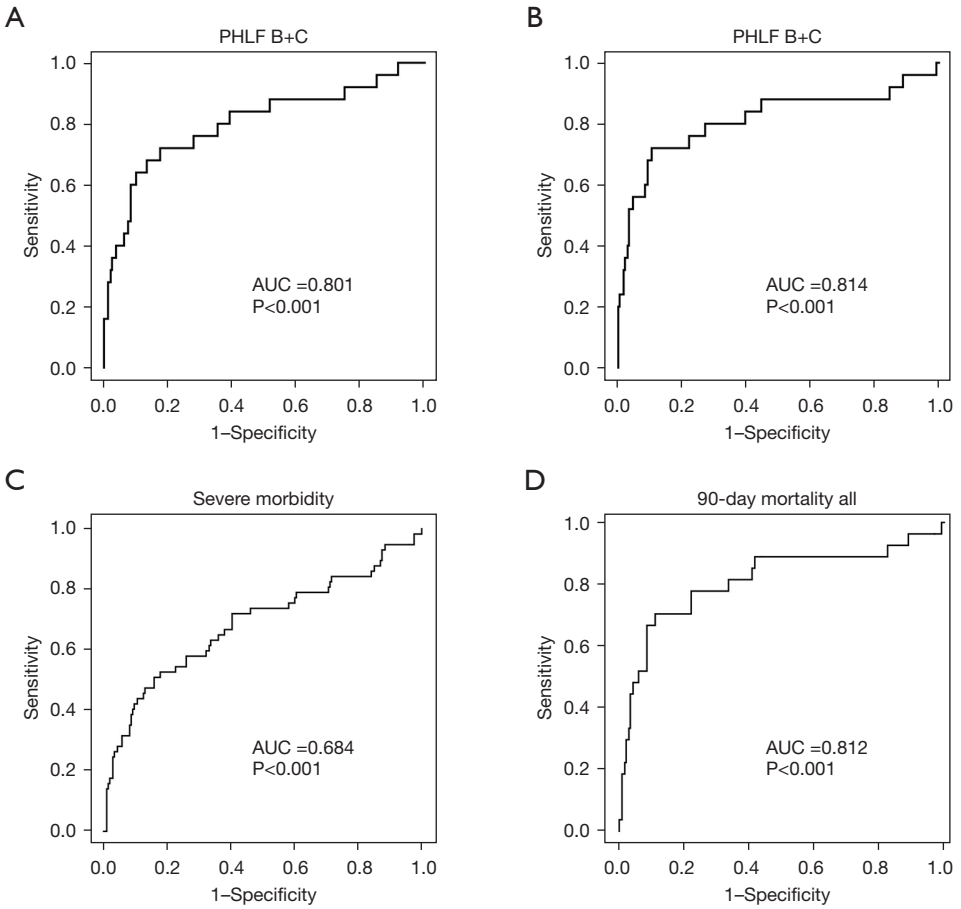


Figure 4 AUCs for preoperative outcome prediction. (A) PHLF B + C risk based on the ALLPS risk score for our study's cohort. (B) PHLF B + C risk combined on the APRI + ALBI score with the ALPPS risk score (part II). (C) Severe morbidity prediction. (D) 90-day mortality based on the combined score. ALBI, albumin-to-bilirubin index; APRI, AST-to-platelets ratio; AST, aspartate transferase; AUC, area under the curve; PHLF, post-hepatectomy liver failure.

cohort with an APRI/ALBI score exceeding −0.37 before stage II, showing a PHLF prevalence of up to 28%. The low-risk group showed a PHLF B + C incidence of 3.13%. As the APRI/ALBI score continuously improves after the first stage of ALPPS, it allows for the dynamic assessment of liver function recovery during the interstage phase. It might, therefore, allow for optimized timing to proceed with stage II of ALPPS.

Our results have significant clinical implications and show that volumetry alone as a predictive parameter is inaccurate to predict clinically relevant PHLF. In contrast, the APRI/ALBI score shows that if the score does not decrease below the low-risk threshold of −0.95, postponing stage II until this low-risk level is reached appears advisable. Consequently, continuous monitoring of APRI/ALBI during the interstage phase is advocated, and reaching optimal thresholds can help identify the most suitable timing to progress to stage II with minimal risk for PHLF, major morbidity and 90-day mortality. In this context, we did observe a trend towards higher incidence of PHLF B + C in shorter interstage intervals, suggesting that some patients' liver function was not sufficiently recovered after the first stage and might have benefited from a delay in the 2nd stage of ALPPS.

To our knowledge, this is the first study to propose a specific timing for ALPPS stage II based on the risk of developing post-stage II PHLF, which could lead to major complications and death since there is no curative therapy for PHLF. Specifically, we introduce a clinical model with defined cut-offs and risk categories for PHLF. Current

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literature addressing the best timing for stage II to avoid the serious complications of PHLF is scarce.

The kinetic growth rate (KGR) based on repetitive CT or MRI scans has been utilized to determine the timing of stage II. Still, significant variability in the identified cutoff values has been shown thus far (21,22). Importantly, volumetric growth during ALPPS has been shown not directly to correlate with functional liver recovery (23). Accordingly, several functional tests have been proposed: serial HIDA scans were used to find the best timing for stage II. However, in this initial study no cut-off or timing for the 2nd stage of ALPPS was specified (23). A sequent study on HIDA and pre-stage II prediction of PHLF revealed that patients with a HIDA result of <15% were associated with an 80% incidence of PHLF B + C (24). While the HIDA scan appears to be an attractive tool in this setting, it remains costly, time-consuming and not universally available. A direct comparison or combination of the HIDA assessment and APRI/ALBI would be an interesting assessment for future research. The LiMAx test was also examined in the ALPPS setting. A small retrospective cohort of 17 patients evaluated LiMAx dynamics, revealing function impairment after stage I, followed by subsequent improvement. However, this study only described perioperative LiMAx dynamics but did not explore whether LiMAx is relevant to predicting PHLF for optimizing stage II timing (25). In the setting of standard partial hepatectomy, we were recently able to document that the APRI/ALBI score outperformed LiMAx and ICG for predicting PHLF B + C, further demonstrating the close association of this score with liver function recovery (26). In addition to liver function tests, monitoring serum phosphate between stages shows promise for the timing of liver resection. A 40% drop in phosphate levels after ALPPS stage I significantly correlated with better outcomes (morbidity and mortality) after stage II (27). While certainly a helpful clinical parameter, this model does not allow for optimized timing for the 2nd stage of ALPPS.

Previous research has addressed the issue of predicting futile outcomes before the 2nd stage of ALPPS (19). Within our analyses, we could document that the addition of APRI/ALBI led to an improvement in predictive potential of this model for PHLF B + C. This indicates that the addition of functional liver assessment improves the predictive power of the established score for futile outcomes but also documents that other patient-related factors should also be considered to define the optimal timing of stage II. We believe that the unique benefit of adding the APRI/ALBI score in this scenario is its ability to be monitored and, therefore, allows for continuous assessment of the patient's liver function to recover sufficiently to undergo the 2nd stage of ALPPS.

Historically, the APRI/ALBI score evolved from two independently developed scores, each of which was used in different scenarios. The APRI score was introduced to assess the degree of fibrosis in hepatitis C patients and, more recently, correlated with liver alterations after chemotherapy (28,29). The ALBI score was introduced to assess liver function in HCC patients, giving an estimate of HCC prognosis and likely clinical deterioration (12). The score correlated with both fibrosis and cirrhosis in HCC patients. Thus, these two scores combine liver functionality with pathological parenchyma damage. Hence, the three risk groups this study identifies using the APRI/ALBI score appear to be a holistic reflection of liver function and parenchyma damage. In our study, the high-risk group exhibited a 28% PHLF B + C incidence after stage II with an AUC of 0.775. In an international cohort of over 12,000 patients undergoing single-stage major hepatectomies, identical accuracy predicted PHLF B + C prediction with an AUC of 0.77 (20). This indicates that the combination of APRI and ALBI appears to be a reliable model for determining liver function and liver parenchyma damage.

Currently, there is no literature in the ALPPS context that thoroughly examines PHLF risk based on a score or test method like our proposed model. Instead, the focus has been on enhancing ALPPS surgical and perioperative techniques to reduce PHLF risk and improve safety. Some authors suggest extending the interstage phase to achieve adequate hypertrophy and function gain of the FLR. A small 2019 study reported positive postoperative outcomes after waiting 21 to 36 days in a group of 8 patients (30). Similarly, our study showed three PHLF risk groups with different cumulative PHLF B + C incidences according to the interstage phase length. It was observed that the FLR initiates liver regeneration within hours after partial hepatectomy, peaking at about 1 week (31). Considering many ALPPS patients have extensive pretreatment with multiple chemotherapy cycles causing parenchyma damage, this could explain the need for a minimum interstage phase before performing stage II (32). Our results would indicate that a standard interstage interval is presumably suboptimal. An individual patient-based approach with the APRI/ALBI score, closely monitoring volumetric grain as well as functional recovery of the liver, will be more suitable to further improve outcomes of the ALPPS procedure. If the APRI/ALBI score before stage II indicates a high risk

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of relevant PHLF, we propose to postpone the surgery until the score reaches safer levels. Our data suggest that the APRI/ALBI score represents an attractive tool in this scenario.

It must be stressed that the APRI/ALBI score exclusively depends on routine laboratory parameters usually available in patients undergoing liver surgery. This method is far more cost-effective than traditional tools like LiMAx, ICG, or HIDA.

In interpreting our results, the following limitations need to be pointed out: one limitation of this study is its retrospective nature, potentially introducing bias from evolving patient selection for ALPPS. To mitigate bias, we only included patients from centers with over 10 completed ALPPS cases in the registry. Further, our analyses are prone to statistical overfitting, and future validation of our results is necessary. However, we believe that extensive published evidence of the ability of the APRI/ALBI score to reflect liver function recovery provides a strong rationale for its use in ALPPS patients. However, this score needs to be explored in an independent validation cohort.

Conclusions

The APRI/ALBI score before stage II of the ALPPS procedure showed a high accuracy in predicting PHLF B + C, severe morbidity, and 90-day mortality. This score tends to undergo normalization in the interstage phase and should be diligently monitored until it attains optimal ranges. Our data proposes three clinically useful PHLF B + C risk groups based on the pre-stage II APRI/ALBI score. Also, this score can determine the likely 90-day mortality after stage II. We propose a graphical model to assist healthcare professionals in strategically timing the second phase of ALPPS surgery to mitigate postoperative complications.

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None.

Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed in accordance with the Declaration of Helsinki and its subsequent amendments. Patients were entered after signing their respective written informed consent forms. This study was approved by the Cantonal Ethics Committee of Zurich (KEK 2013-0326; ClincialTrials.gov NCT01924741).

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