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ALPPS Versus Portal Vein Embolization for Hepatitis-related Hepatocellular Carcinoma

A Changing Paradigm in Modulation of Future Liver Remnant Before Major Hepatectomy

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Objective: The aim of this study was to evaluate the short- and long-term outcome of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for hepatitis-related hepatocellular carcinoma (HCC).

Summary Background Data: ALPPS has been advocated for future liver remnant (FLR) augmentation in liver metastasis or noncirrhotic liver tumors in recent years. Data on the effect of ALPPS in chronic hepatitis or cirrhosis-related HCC remained scarce.

Methods: Data for clinicopathological details, portal hemodynamics, and oncological outcome were reviewed for ALPPS and compared with portal vein embolization (PVE). Tumor immunohistochemistry for PD-1, VEGF, and AFP was evaluated in ALPPS and compared with PVE and upfront hepatectomy (UH).

Results: From 2002 to 2018, 148 patients with HCC (hepatitis B: n = 136, 92.0%) underwent FLR modulation (ALPPS, n = 46; PVE: n = 102). One patient with ALPPS and 33 patients with PVE failed to proceed to resection (resection rate: 97.8% vs 67.7%, $P < 0.001$). Among those who had resections, 65 patients (56.5%) had cirrhosis. ALPPS induced absolute FLR volume increment by 48.8%, or FLR estimated total liver volume ratio by 12.8% over 6 days. No difference in morbidity (20.7% vs 30.4%, $P = 0.159$) and mortality (6.5% vs 5.8%, $P = 1.000$) with PVE was observed. Chronic hepatitis and intraoperative indocyanine green clearance rate ≤39.5% favored adequate FLR hypertrophy in ALPPS. Five-year overall survival for ALPPS and PVE was 46.8% and 64.1% ($P = 0.234$). Tumor immunohistochemical staining showed no difference in expression of PD-1, V-EGF, and AFP between ALPPS, PVE, and UH.

Conclusions: ALPPS conferred a higher resection rate in hepatitis-related HCC with comparable short- and long-term oncological outcome with PVE.

Keywords: ALPPS, hepatectomy, hepatocellular carcinoma, liver remnant, portal vein

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Insufficient future liver remnant is an important factor that precludes patient from upfront major liver resection as it predisposes to developing posthepatectomy liver failure and mortality.[1,2] Augmentation of future liver remnant (FLR) by portal vein embolization (PVE) was the conventional approach to improve the safety of major hepatectomy. Recently, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)[3,4] has been popularized as an alternative approach for FLR augmentation. Through the establishment of the international ALPPS registry[5] and procedural familiarization, there has been an improvement in the short-term outcome resulting in an inter-stage morbidity and 90-day mortality rate from 10% to 3%, and from 17% to 4%, respectively.[6] Nonetheless, most of the evidence focus on ALPPS procedure for bilobar colorectal liver metastases,[7–9] or other nonhepatitis-related liver tumors.[4,10] Results on the short-term and oncological outcome of ALPPS solely for hepatocellular carcinoma (HCC) due to viral hepatitis remained relatively scarce. Besides, evidence on the effect of ALPPS on portal flow modulation and its effect on FLR liver function in chronic hepatitis/cirrhosis remained uncertain. Hence, the objective of this study was to evaluate the role of ALPPS for hepatitis-related HCC.

MATERIALS AND METHODS

Prior institutional review board approval for research protocol on ALPPS was obtained. All HCC patients with insufficient FLR volume that required modulation before major hepatectomy in the Department of Surgery, The University of Hong Kong from December 2013 to December 2018 were recruited into our clinical trial for ALPPS. Before the inception of ALPPS program in our center, PVE was the standard method for FLR augmentation since April 2002 and they formed the control cohorts. Prospectively collected ALPPS-related data, including clinicopathological features, perioperative outcome, and survival data, were reviewed and compared with those who underwent hepatectomy after PVE (ie, PVE group). Subgroup analysis was performed to study the impact of ALPPS on portal flow hemodynamics and FLR function. Both postoperative and long-term oncological outcome were the primary endpoints of the study. Tumor immunohistochemistry (IHC) and mRNA analysis were also performed to study ALPPS effect on tumor microenvironment in comparison with PVE and upfront hepatectomy (UH) after matching for tumor size and number in a 1:1 ratio.

Selection Criteria

The selection criteria for ALPPS were detailed previously.[11] In short, our indications for ALPPS in HCC remained identical to PVE, that s, future liver remnant volume <35% in unilobar HCC, or <40% in bilobar HCC, indocyanine green clearance (ICG) rate <20% at 15 minutes, child A liver function, serum platelet count $\geq 100 \times 10^9$/L, and patent right portal vein. Exclusion criteria were complete right portal vein thrombosis, serum platelet count $<100 \times 10^9$/L, clinical signs of portal hypertension such as ascites, and/or intra-abdominal varices, and the presence of distant metastasis.

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Portal Hemodynamic Measurement

Based on the notion that portal vein embolization induced FLR hypertrophy via flow augmentation,[12] portal hemodynamics was evaluated by direct measurement of FLR portal flow using intraoperative Doppler ultrasonography at 4 different time points: baseline flow, flow after right portal vein ligation, after parenchymal split, and flow at stage II ALPPS. Portal pressure was measured after direct cannulation of the main portal vein before and after right portal vein ligation.

FLR Functional Assessment

FLR functional assessment was undertaken by ICG measurement (0.5 mg/kg) at different time points preoperatively and intraoperatively using the LiMON device (Pulsion Medical Systems, Munich, Germany). Preoperative ICG was measured within 2 weeks before stage I operation. To mimic a right hepatectomized situation and assess the FLR function, ICG was measured after the right portal vein and hepatic artery were temporarily clamped during stage I operation, and repeated at stage II operation after removal of the tumor-bearing liver to assess the hypertrophied FLR function after ALPPS.

Since January 2017, hepatic scintigraphy using Technetium-99 (Tc99) mebrofenin radioisotope was deployed for FLR functional assessment.[13] The scan was performed within 1 week before the ALPPS procedure, and was repeated 1 to 2 days before stage II operation. The function was assessed by the proportion of mebrofenin cleared from the blood stream by the FLR and expressed as the percent per minute per square meter of body surface area (%/min/m^2) to adjust for the difference in metabolism between individuals.

Operative Technique for Stage I Operation

Details of our technical approach to ALPPS were previously described.[14,15] For a right hepatectomy or trisectionectomy, hilar dissection was performed for isolation of the right hepatic artery and portal vein. The right portal vein was then divided and the right hepatic artery was encircled by nonabsorbable suture. Parenchymal split was performed by Cavitron ultrasonic dissector (Excel, Integra) using anterior approach. Partial split was adopted during the initial development of ALPPS in our center but with cumulative experience, complete split was adopted from case no. 12 onward. Partial split was reserved for right trisectionectomy, or tumors located between right posterior section and the caudate lobe. Contrast-enhanced computed tomography (CT) with volumetry was performed on postoperative days 6 to 7. Total liver volume was measured by estimated standard liver volume (ESLV) by Urata.[16] Stage II operation for completion hepatectomy was arranged the next day if FLR/ESLV $\geq$35%, or another CT volumetry will be repeated on days 10 to 11 to reassess the FLR volume if inadequate FLR hypertrophy was observed.

Procedural Technique for PVE

PVE was performed via percutaneous transhepatic approach with direct puncture of the right portal vein ipsilateral to the tumor by interventional radiologist. Selective cannulation of right portal vein branches was performed followed by embolization using 10 mL mixture of 20% *n*-Butyl-cyanoacrylate. S4 branches were not embolized. A completion portovenogram was performed to confirm complete occlusion of the ipsilateral portal vein and patency of the contralateral portal vein as well as the main portal vein.

Tumor Immunohistochemistry and Quantitative PCR

Tumor specimens were collected for immunohistochemical stainings and quantitative PCR in the last 21 patients in the ALPPS groups. All paraffin sectioned tumor tissue blocks sampled from the resected specimens were cut at 5 μm and dewaxed. After rehydration, antigen retrieval was performed using 1X Citrate Buffer (PH = 6.0). Slides were then blocked with 5% BSA buffer and incubated with antibodies (AFP, PD-L1, and VEGF) for direct antibody binding (DAB) detection. Stained slides were scanned and digitalized by Nano Zoomer S210 (Hamamatsu Photonics, Japan) and quantified by "Analysis algorithm Positive Pixel Count Version 9." Total RNA was extracted from liver tumor using Trizol reagent (Life Technologies, USA). Real-time PCR was performed to measure the mRNA expression with an Applied Biosystems ViiA7 PCR machine (Life Technologies). Tumor immunohistochemical stainings and tumor-related mRNA expressions in ALPPS were then compared with that of PVE and UH (ie, control group) after matching for tumor size and number in a 1:1 ratio.

Statistical Analysis

Continuous variables were expressed by median and compared by Mann–Whitney *U* test. Categorical variables were compared with Fisher exact test. Postoperative morbidities and mortalities were graded according to the Clavien classification. Survival analysis was performed by Kaplan–Meier methods and compared with groups using log-rank test. Subgroup analysis was performed after stratification according to AJCC TNM tumor stage (7th edition). P value <0.05 was considered to be statistically significant. Logistic regression was employed to identify clinical factors that favored FLR hypertrophy after stage I operation toward the median rate of hypertrophy. Statistical analysis was performed by SPSS computer software (version 23.0, IBM).

RESULTS

From January 2002 to December 2018, a total of 148 patients with HCC underwent FLR modulation (ALPPS, n = 46; PVE: n = 102) in the Department of Surgery, The University of Hong Kong due to inadequate FLR. Among them, 33 patients (32.3%) with PVE failed to proceed to hepatectomy due to inadequate FLR hypertrophy (n = 13), tumor progression (n = 10), poor liver function (n = 6), patient withdrawal (n = 2) and procedure-related mortality (n = 1). The remaining patients were included for analysis (Table 1). For the ALPPS group, 89.1% patients had hepatitis B-related HCC. 45.7% of them had histologically proven cirrhosis. The tumor size was 8.5 cm in diameter. Preoperative transarterial oily chemoembolization was given in the ALPPS group as primary treatment by another institution (n = 4) and for downstaging (n = 1), and as bridging treatment (n = 25) and under another clinical trial protocol (n = 8) in the PVE group. The time to CT scan (6 vs 31 d, $P < 0.001$) and hepatectomy (7 vs 48 d, $P < 0.001$) was shorter in the ALPPS group. More importantly, ALPPS attained a higher resection rate than PVE (97.8% vs 67.7%, $P < 0.001$). There was no significant difference in the type of liver resections between the 2 groups, though 4 planned major liver resections in the PVE group were changed to large segmentectomies due to small cirrhotic remnants with 2 of them had right portal vein recanalization on intraoperative assessment.

Effect on FLR Growth Kinetics, Portal Hemodynamics and FLR Function

ALPPS induced a much greater FLR volume gain and FLR hypertrophy rate than PVE (Table 2). After excluding patients with failed ALPPS or PVE (Table 2), ALPPS still induced a much greater FLR hypertrophy rate (FLR volume gain by 48.8%, or an increment of FLR/ESLV from 24.6% to 37.6%, ie, an additional 12.8% over 6 d) than PVE. The percentage of FLR volume gain was more pronounced in chronic hepatitis than cirrhosis (52.7% vs 32.5%, $P = 0.025$), but the speed of liver regeneration as expressed by the daily rate of hypertrophy (24.6 vs 20.7 mL/d, $P = 0.205$), or daily FLR/ESLV ratio increment (2.1% vs 1.6%, $P = 0.07$) showed no significant difference. On logistic regression analysis (Supplementary Table 1,

TABLE 1. Clinicopathological Data of ALPPS and PVE Patients

	ALPPS (n = 46)	PVE (n = 69)	*P*
M:F	42:4	64:5	1.000
Age	58.5 (26–80)	60 (27–85)	0.623
BMI	24.4 (18.8–28.6)	23.2 (18.0–33.1)	0.502
Diabetes mellitus	8 (17.4%)	15 (21.7%)	0.568
Hypertension	14 (30.4%)	29 (42.0%)	0.208
HBsAg positivity	41 (89.1%)	62 (89.9%)	0.704
Anti-HCV positivity	1 (2.2%)	2 (2.9%)	
Steatohepatitis	4 (8.7%)	4 (5.8%)	
Indocyanine green clearance rate	10.1 (3.8–30.2)	10.6 (4.7–79.9)	0.396
Liver status			
Cirrhosis	21 (45.7%)	44 (63.8%)	0.055
Chronic hepatitis	25 (54.4%)	25 (36.2%)	
Tumor size	8.5 (2–16.0)	7 (1.5–17.0)	0.636
Tumor number	1 (1–3)	1 (1–3)	0.117
AFP, ng/mL	81 (2–187,420)	39 (1–90,400)	0.757
Microvascular invasion	26 (56.5%)	32 (46.4%)	0.234
Tumor differentiation			0.260
Well	6 (10.9%)	12 (17.4%)	
Moderate	31 (69.6%)	46 (66.7%)	
Poor	7 (15.2%)	10 (14.5%)	
Unclassified	2	1	
Preoperative TACE	5 (10.9%)	33 (47.8%)	<0.001
Time to CT scan after ALPPS stage I or PVE, d	6 (4–22)	31 (14–264)	<0.001
Time to hepatectomy, d	7 (6–70)	48 (22–280)	<0.001
Right hepatectomy	23 (50.0%)	44 (63.8%)	0.069
Extended right hepatectomy	12 (26.1%)	16 (23.2%)	
Right trisectionectomy	10 (21.7%)	5 (7.2%)	
Segmentectomy	0	4 (5.8%)	
Right portal vein ligation + in situ split only	1	—	
Blood loss, mL			
ALPPS stage 1/resection	515 (0–2,000)	700 (200–6,400)	0.015
ALPPS stage 2/resection	420 (20–8,000)	700 (200–6,400)	0.002
Total blood loss	955 (60–9,200)	700 (200–6,400)	0.030
Overall complication rate	20.7%	30.4%	0.159
Complication after ALPPS 1	21.7%	—	—
Complication after ALPPS 2	19.6%	—	—
Hospital mortality rate	3 (6.5%)	4 (5.8%)	1.000
Hospital stay, d	18 (12–44)	8 (3–50)	<0.001
Tumor recurrence rate	21 (45.7%)	33 (47.8%)	0.819
Pattern of recurrence			
Intrahepatic	13 (28.3%)	13 (18.8%)	0.587
Extrahepatic	3 (6.5%)	7 (10.1%)	
Concurrent intra/extrahepatic recurrences	5 (10.8%)	13 (18.8%)	

http://links.lww.com/SLA/B679), chronic hepatitis, intraoperative ICG ≤39.5%, absence of postoperative complications especially after stage II operation were identified to predict FLR hypertrophy >1.0% (FLR/ESLV)/d after ALPPS. The median time to stage II operation was 7.5 days (7–19 d) when all these favorable factors were present and increased to 14 days (11–17 d) when none of these factors were present. No significant independent risk factors for mortality after ALPPS was found on multivariable analysis.

Right portal vein ligation in stage I operation substantially increased FLR flow from 70.2 (35.6–272.0) to 197.0 (65.3–1179.6) mL/min/100 g ($P < 0.001$) and remained elevated at 183.2 (46.7–464.0) mL/min/100 g after parenchymal split ($P < 0.001$). The flow then decreased to 87.4 (36.0–195.7) mL/min/100 g after stage I operation during the waiting period to stage II operation ($P < 0.001$) (Fig. 1A). Portal pressure increased from 9.0 (2.0–25.0) mm Hg to 14.5 (2.0–36.0) mm Hg ($P < 0.001$) after stage I operation. When stratified according to liver status, it was apparent that the FLR flow started to undergo autoregulation soon after right portal vein ligation in chronic hepatitis, whereas in cirrhosis this autoregulation seemed to be later and started only after stage I operation. All patients proceeded to staged II operation except 1 patient (no. 48) who had a substantial portal flow increment from 272 to 1179.6 mL/min/100 g after right portal vein ligation. For this patient, the portal pressure also increased from 16 to 21 mm Hg with occurrence of ascites after stage I operation, but the FLR volume only marginally increased (FLR/ESLV increased from 19.0% to 20.5%). As a result, stage II operation was not performed due to insufficient FLR with evidence of portal hypertension. He was subsequently discharged home and later received radiotherapy for tumor control.

The median preoperative ICG value was 10.1% (3.8%–30.2%), and increased to 39.5% (15.4%–54.4%) during stage I operation ($P < 0.001$) and 33.7% (9.7%–66.4%) after hepatectomy in stage II operation ($P = 0.001$) (Fig. 1B). Among them, 9 patients completed hepatic scintigraphy during ALPPS (Supplementary Table 2, http://links.lww.com/SLA/B679). Using the cutoff limit of 2.77%/min/m^2 to define adequate FLR function,[13] ALPPS induced an increased Tc99 uptake by the FLR in 5 patients (55.6%) and no significant change in Tc99 uptake in the remaining 4 (44.4%) patients. Although all patients (100%) with increased Tc99 uptake were chronic hepatitis, 75% (n = 3) of the patients with minimal change in Tc99 uptake had cirrhosis ($P = 0.048$). Moreover, changes in Tc99 uptake were negatively correlated with intraoperative ICG values (Fig. 1C). In other words, an improved FLR function from stage I to II operation as indicated by increased Tc99 uptake was associated with a reciprocal change in intraoperative ICG value.

Perioperative Outcomes

ALPPS was associated with more total perioperative blood loss than PVE group. Postoperative complication rate after stage I was 21.7% and after stage II was 19.6%. All post-ALPPS stage I-related complications were either grade 1 or 2 (Table 3). No difference in overall postoperative complication rates (20.7% vs 30.4%, $P = 0.614$) and hospital mortality rate (6.5% vs 5.8%, $P = 1.000$) between ALPPS and PVE was observed. The length of hospital stay for ALPPS group and PVE group was 18 and 8 days, respectively ($P < 0.001$).

For the operative mortalities with ALPPS (patient nos. 10, 16, and 34; Table 3), the median age was 69 (67–74) years old. Ascites were present after stage I operation in patient nos. 10 and 34. Although no risk factors for mortality were identified on multivariable analysis, occurrence of refractory ascites after stage I was regarded in our center as a warning sign against stage II operation as 2 out of 3 early mortalities developed this complication before stage II operation. As we adopted this precautionary measure, one patient (no. 48) did not proceed to stage II operation and no further mortality was reported.

Oncological Outcome: ALPPS Versus PVE

The 1-, 3- and 5-year disease-free survival (DFS) rate (Fig. 2A–C) for ALPPS were 63.2%, 34.9%, and 25.0%, and the corresponding rates for PVE were 61.4%, 41.8%, and 40.7%, respectively ($P = 0.267$). When stratified according to tumor stage, the 1, 3, and 5-year DFS rates for stage I/II for ALPPS were 81.4%, 54.3%, and 40.7%, and the corresponding rates for PVE were 74.3%, 53.8%, and 53.8% ($P = 0.664$). For stage III/IV HCC, the 1-, 3-, and 4-year DFS rates for ALPPS were 51.1%, 20.5%, and 13.6%, and for PVE were 38.3%, 20.4%, and 15.3% ($P = 0.987$).

The 1-, 3-, and 5-year overall survival (OS) rates (Fig. 2D, F) for ALPPS were 84.7%, 60.2%, and 46.8%, and the corresponding

TABLE 2. Volumetry and Growth Kinetics Between ALPPS and PVE: Intention-to-treat Analysis; for Patients Who Completed Stage II or Post-PVE Hepatectomy

	ALPPS (n = 46)	PVE (n = 102)	*P*
Intention-to-treat analysis			
ESLV, mL	1237.0 (1054.1–1440.3)	1236.6 (924.4–1491.1)	0.843
Pre-ALPPS or PVE FLR, mL	302.1 (181.9–524.0)	301.1 (142.0–554.0)	0.756
Post-ALPPS or PVE FLR, mL	468.7 (243.0–795.7)	426.7 (163.2–817.8)	0.094
Pre-ALPPS or PVE FLR/ESLV, %	24.5 (15.7–37.1)	24.9 (11.8–44.5)	0.855
Post-ALPPS or PVE FLR/ESLV, %	37.4 (20.5–56.9)	35.5 (15.7–67.5)	0.117
Increment in FLR/ESLV, %	12.3 (1.5–32.3)	9.2 (−3.17 to 41.4)	0.022
Absolute increment in FLR volume, mL	154.8 (18–405.0)	115.7 (−31.5 to 514.9)	0.024
Absolute increment in FLR volume, %	48.0 (8.0–133.2)	37.88 (−15.2 to 170.0)	0.030
Increment in FLR volume per day, %	7.3 (0.5–26.6)	1.6 (−0.47 to 6.3)	<0.001
Rate of hypertrophy, cc/d	22.7 (1.2–81.0)	4.8 (−1.1 to 19.1)	<0.001
Increment in FLR/ESLV per day, %	1.9 (0.1–6.5)	0.4 (−0.1 to 1.5)	<0.001
	ALPPS (n = 45)	**PVE (n = 69)**	***P***
For patients who completed stage II or post-PVE hepatectomy			
ESLV, ml	1237.7 (1054.01–1440.3)	1255.8 (1025.6–1489.4)	0.545
Pre-ALPPS or PVE FLR, mL	302.6 (181.9–524.0)	299.5 (142.0–480.0)	0.760
Post-ALPPS or PVE FLR, mL	474.0 (316.0–795.7)	455.1 (200.0–817.8)	0.495
Pre-ALPPS or PVE FLR/ESLV, %	24.6 (15.7–37.1)	24.8 (11.8–34.8)	0.788
Post-ALPPS or PVE FLR/ESLV, %	37.6 (26.7–56.9)	36.2 (15.7–67.5)	0.479
Increment in FLR/ESLV, %	12.8 (2.7–32.3)	10.5 (−2.5 to 41.4)	0.340
Absolute increment in FLR volume, mL	155.2 (31.0–405.0)	128.3 (−31.5 to 514.9)	0.366
Absolute increment in FLR volume, %	48.8 (8.5–133.2)	46.8 (−13.6 to 170.0)	0.536
Increment in FLR volume per day, %	7.4 (1.41–26.6)	1.6 (−0.5 to 6.3)	<0.001
Rate of hypertrophy, cc/d	23.1 (5.1–81.0)	4.8 (−1.1 to 19.1)	<0.001
Increment in FLR/ESLV per day, %	1.9 (0.4–6.5)	0.4 (−0.1 to 1.5)	<0.001

rates for PVE were 88.2%, 73.5%, and 64.1% ($P = 0.234$). When stratified according to tumor stages, the 1-, 3-, and 5-year OS rates for stage I/II for ALPPS were 81.4%, 69.8%, and 58.2%, and the corresponding rates for PVE were 93%, 85.5%, and 74.5%, respectively ($P = 0.183$). For stage III/IV tumors, the 1-, 3-, and 4-year OS rates for ALPPS were 89.4%, 50.1%, and 33.4%, and for PVE were 79.5%, 51.8%, and 51.8% ($P = 0.755$).

Subgroup survival analysis for hepatitis B-related HCC alone (Fig. 2G, H) showed that the 1-, 3-, and 5-year DFS rates for ALPPS were 63.8%, 43.5%, and 29%, and for PVE were 59.3%, 39.6%, and 37.5% ($P = 0.559$). The 1-, 3-, and 5-year OS rates for ALPPS were 85.1%, 68.8%, and 53.5%, and for PVE were 87.0%, 70.8%, and 62.6% ($P = 0.628$).

Concerning the effect on tumor microenvironment, no significant difference in the level of tumor expression of PD-1 (Fig. 3A), VEGF (Fig. 3B), and AFP (Fig. 3C) between ALPPS, PVE, and UH was observed (Supplementary Table 3, http://links.lww.com/SLA/B679). The levels of mRNA expression of PD-L1 (Fig. 4A) were lower in ALPPS than either PVE or UH, but no difference in VEGF mRNA (Fig. 3B) expression among the 3 groups was observed. The oncological outcome was also comparable among all 3 groups (Fig. 4A, B).

DISCUSSION

Our study showed that ALPPS improved resection rate in hepatitis-related HCC with comparable safety profile with PVE. However, the inception of ALPPS was criticized for the high incidence of bile leakage and septicemia.[5,17] This would be particularly hazardous for our cohort burdened by cirrhosis as bile leakage with sepsis in this situation is notorious for its association with liver failure.[18,19] Hence, every effort was made to minimize the chance of bile leakage when ALPPS was first started in our center. The use of cavitron ultrasonic dissector for parenchymal transection was particularly useful for ALPPS as it allowed clear identification and ligation of individual bile ducts, whereas the leakage test after parenchymal spilt permitted identification of occult leakage and its repair. As such, bile leakage was uncommon in our series. Moreover, the use of anterior approach avoided extensive dissection at subhepatic and paracaval region that could avoid severe adhesion formation in that area as well as avoiding iatrogenic tumor rupture during stage I operation,[15] both of which attributed to maximal preservation of untouched surgical fields that would facilitate stage II operation.

To date, studies reporting the outcome of ALPPS mainly focused on colorectal liver metastasis.[6–8] However, the short-term outcome of ALPPS solely for hepatitis-related HCC was seldom reported and should be regarded as a separate entity due to the fact that liver hypertrophy in chronic liver disease was less substantial than normal livers [20] with paucity of data on the underlying changes in portal flow hemodynamics during the ALPPS procedure. It remained uncertain if there was any adverse effect on the FLR due to increased sinusoidal shear stress when FLR portal flow substantially increased after contralateral portal vein ligation and parenchymal split.[21–23] This was our initial concern based on the clinical experience derived from small-for-size syndrome in living donor liver transplantation.[24] Our findings, which shed some light into this issue, showed that although portal pressure was increased soon after right portal vein ligation, FLR portal flow increased by almost 3-folds, but the addition of parenchymal split was not associated with substantial flow increment. This finding further consolidated the understanding that the effect of parenchymal split was predominantly on the induction of liver growth factor release[25] rather than a flow dynamic issue solely, wehreas the flow increment after portal vein ligation substantially enhanced the efficiency of

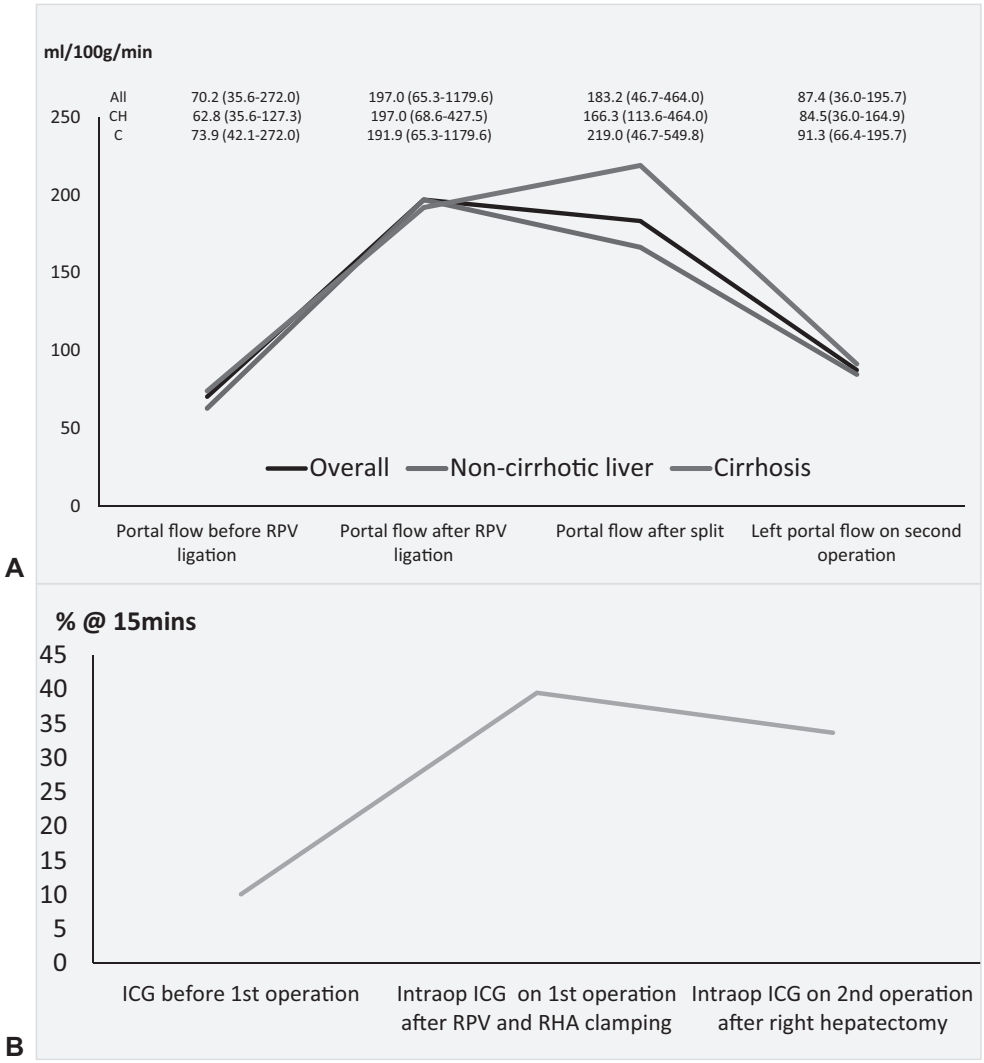

FIGURE 1. (A) Changes in portal hemodynamics during ALPPS procedure; (B) changes in ICG value during ALPPS procedure; and (C) correlation between Tc99 uptake by FLR and intraoperative ICG assessment of FLR in livers affected by chronic hepatitis. CH indicates chronic hepatitis; C cirrhosis. $R_2 = -0.886$, $P = 0.003$.

TABLE 3. ALPPS-related Complications

	Stage I	Stage II
Grade I	• Pleural effusion (n = 5)	
Grade II	• Mild ascites, relieved by diuretics (n = 3) • Gross ascites, not relieved by diuretics (n = 2)	Mild ascites, relieved by diuretics (n = 5)
Grade III		Intestinal obstruction requiring enterolysis (n = 1)
Grade IV		
Grade V		Hemorrhage and liver failure (n = 1) Liver failure (n = 1) Sepsis with multiorgan failure (n = 1)

delivery of these growth factors, hence resulting in rapid liver regeneration. However, endothelial injury resulting from the sinusoidal shear stress induced by enhanced portal flow was mitigated by autoregulation of the portal system. Our data showed the FLR portal flow decreased toward baseline levels while waiting to stage II operation. The overall liver function was therefore not affected as the deportalized liver still provided some function (as indicated by the stable overall liver uptake of Tc99 before and after ALPPS; supplementary data, Table 5, http://links.lww.com/SLA/B679), whereas the FLR underwent modulation during the waiting period. On the contrary, failure to autoregulate FLR portal flow in the presence of elevated portal pressure would be harmful and should be viewed as a caution to completion hepatectomy. In this situation, an additional portal flow modulatory procedure such as splenic artery ligation, or embolization should be considered,[23,26] or to defer stage II operation until further FLR hypertrophy was accomplished.

Despite rapid FLR hypertrophy, there was skeptism if ALPPS would also improve the FLR function. Recently, Serenari et al reported the efficacy of hepatic scintigraphy in the assessment of FLR function after ALPPS in noncirrhotic livers,[27] but data applicable to chronic liver disease were lacking. Our study showed that although ALPPS improved the FLR function as well as increasing the FLR volume in chronic hepatitis, there seemed to be no apparent effect on FLR function in cirrhosis. This was in concordance with emerging evidence that the recovery of cellular function of these immature regenerative hepatocytes in the hypertrophied FLR lagged behind the rapid volumetric increment[28–30] and this functional recovery would certainly be delayed in

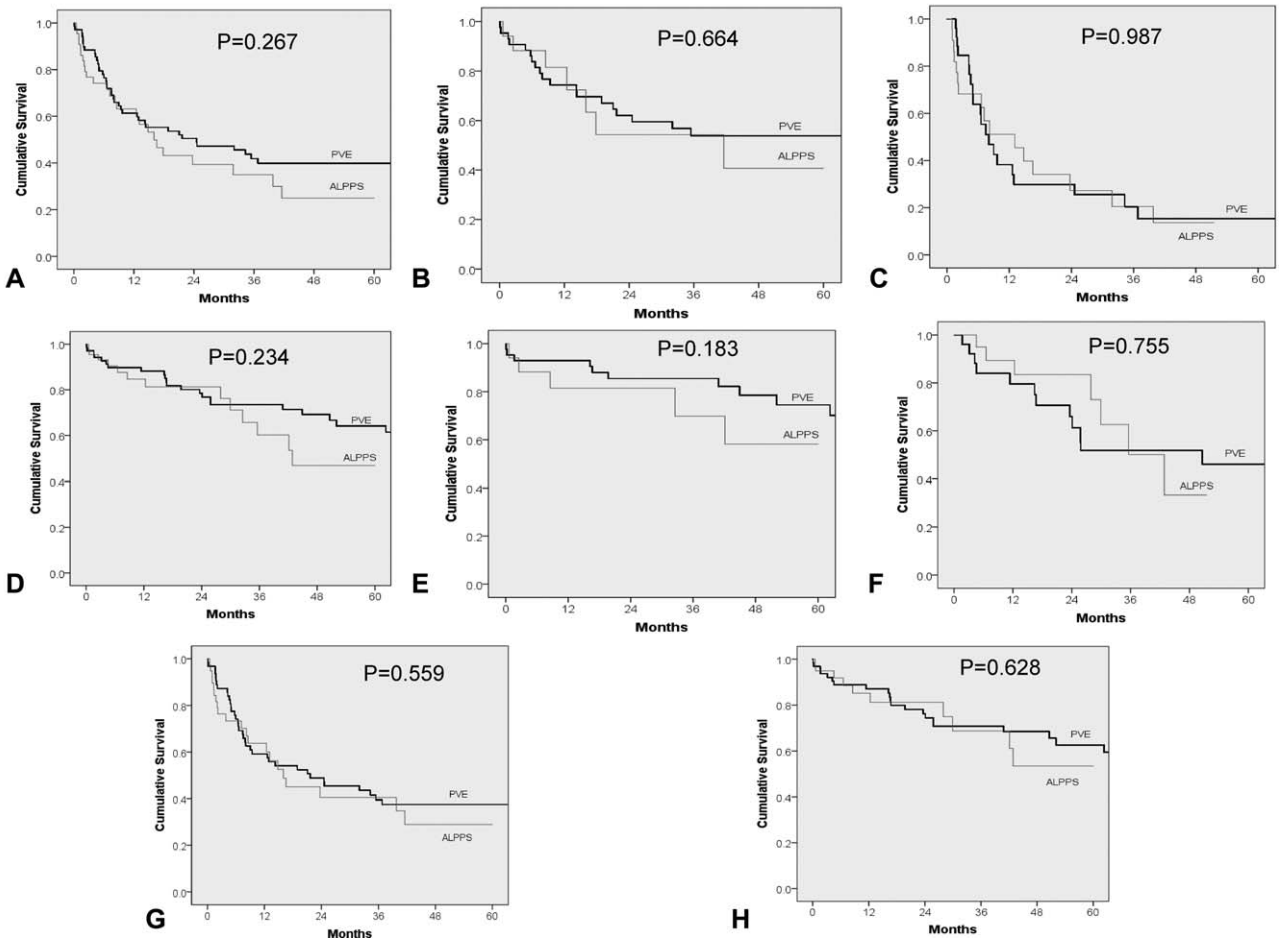

FIGURE 2. Survival outcome for ALPPS and PVE: (A) DFS for both groups; (B) DFS for stage I/II, (C) DFS for stage III/iv; (D) OS for all groups; (E) OS for stage I/II; (F) OS for stage III/iv; (G) DFS for hepatitis-B related HCC; (H) OS for hepatitis-B related HCC.

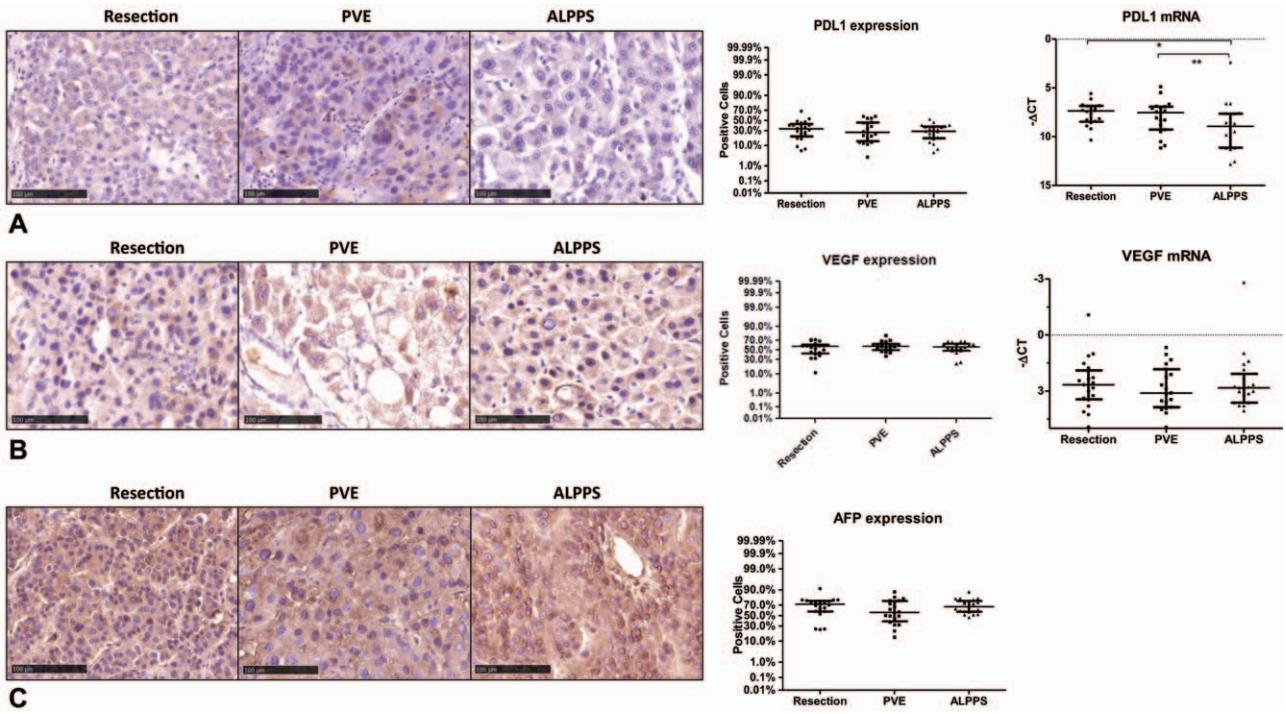

FIGURE 3. Tumor IHC and mRNA expression in ALPPS, PVE and UH: (A) PD-L1 (brown stain) (ALPPS vs PVE: IHC—$P = 0.62$; mRNA—$P = 0.03$; ALPPS vs UH: IHC—$P = 0.24$; mRNA: $P < 0.01$); (B) VEGF (brown stain) (ALPPS vs PVE: IHC—$P = 0.67$, mRNA—$P = 0.81$; ALPPS vs UH: IHC—$P = 0.95$; mRNA—$P = 0.57$), and (C) AFP (brown stain) (ALPPS vs PVE IHC: $P = 0.11$; ALPPS vs UH: $P = 0.92$).

cirrhosis. The clinical implication would be that a much longer waiting period to stage II operation would be necessary for cirrhotic livers to allow more time for the hepatocytes to undergo full functional recovery.

From a clinical perspective, it was practically important for surgeons to identify perioperative factors that could predict adequate FLR hypertrophy to estimate the timing of the second-stage operation more precisely. Chronic hepatitis, intraoperative ICG value

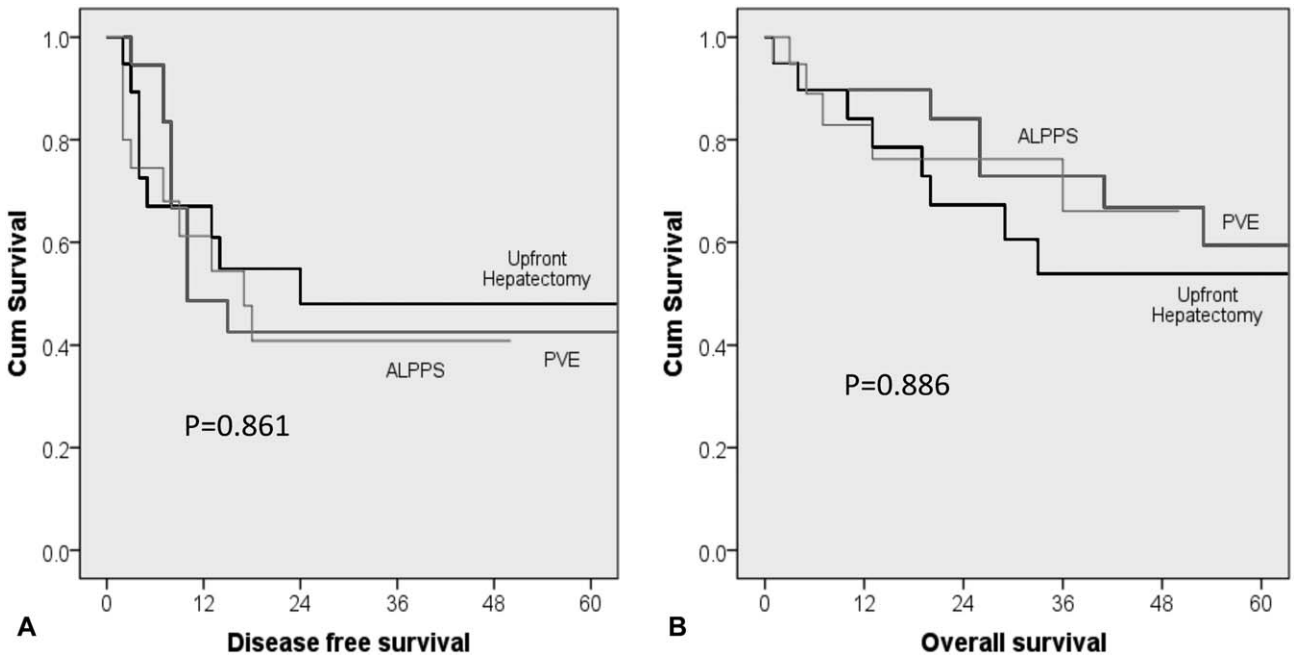

FIGURE 4. Survival outcome for ALPPS, PVE and UH. (A) Disease-free survival: $P = 0.861$; (B) overall survival: $P = 0.886$.

≤39.5% at stage I operation, and absence of postoperative complications all had a positive effect on FLR hypertrophy. In particular, presence of stage II-related complications was shown to affect FLR hypertrophy. In other words, a suboptimal FLR hypertrophy predisposed the patient to postoperative risk of stage II procedure and the decision to withhold stage II operation should be considered until an adequate liver hypertrophy was attained. On the contrary, all stage II operations were completed after approximately 1 week when all favorable factors were present. Of all these factors, intraoperative ICG measurement was a useful clinical tool that could help clinicians plan the time of stage II operation. It was simple and easy to perform. It provided an instant feedback on FLR function and, more importantly, on the chance of adequate FLR hypertrophy. Hence, for chronic hepatitis with an intraoperative ICG value <39.5%, stage II operation could be planned at around 1 week after stage I operation. For cirrhotics or intraoperative ICG >39.5%, a longer waiting time (≥2 wk) to stage II operation was deemed necessary. Besides, changes in FLR function detected on hepatic scintigraphy correlated well with the changes in intraoperative ICG value between stage I and II operation implying that intraoperative ICG measurement could be used as a surrogate marker for hepatic scintigraphy to assess FLR function which is a more financially affordable and accessible option than scintigraphy for many centers globally.

As the tumor blood supply in HCC was predominately derived from the hepatic artery,[31] one major concern about the oncological feasibility for ALPPS was whether the sudden disruption of portal flow in stage I operation and the reciprocal enhanced hepatic arterial flow due to the buffer response would induce any changes in tumor microenvironment during the waiting period.[32] Recent studies showed that tumor overexpression of PD-L1 and AFP was associated with early recurrence and poor survival[33,34] and VEGF correlated with tumor invasiveness and prognosis in HCC.[35,36] All of which, however, were not overexpressed in ALPPS when compared with the controls implying that it had no excessive stimulatory effect on tumor growth. More importantly, the long-term survival in ALPPS was comparable with that of PVE regardless of tumor stage, and without discernable difference in the pattern of tumor recurrence. Hence, ALPPS should be regarded as a safe and effective oncological procedure and be included into the management algorithm for FLR modulation in HCC. ALPPS optimized the chance for hypertrophy by surgical means and avoided the PVE-specific complications.[37,38] We proposed ALPPS to be reserved for FLR/ESLV <30% and PVE for FLR/ESLV 30% to 40% based on the findings in our study that FLR volume gain and growth rate was more substantial in ALPPS than PVE. In other words, the FLR was more likely to reach an adequate volume at a much faster rate in ALPPS but at the expense of more blood loss than PVE. Hence, judicious use of ALPPS would be indicated for those patients who certainly need substantial FLR volume gain to optimize their chance for liver resection. For those with borderline insufficient FLR volume in the range of 30% to 40%, PVE would be suffice for FLR modulation with less surgical trauma, albeit at a slower pace. The exception would be tumors with macrovascular invasion that conferred significant risk of tumor progression during the longer waiting time with PVE[39] and in this situation, ALPPS should be considered.

Our study was not a randomized controlled trial and hence it would be subject to selection bias. However, such bias effect could be reduced by the standardized selection criteria under a single-team approach throughout the study period. Besides our cohort predominantly consisted of patients with hepatitis B-related large and solitary HCC with inadequate FLR. Whether the oncological efficacy of ALPPS could be applied to hepatitis C-related multifocal HCC is yet unknown.

CONCLUSIONS

ALPPS conferred higher chance of resectability than PVE in hepatitis-related HCC in a timely manner with comparable postoperative and oncological outcome. An intraoperative ICG <40% at stage I operation predicted adequate FLR hypertrophy and offered guidance to the timing of stage II operation.

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