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Review Article

Chance and challenge of associating liver partition and portal vein ligation for staged hepatectomy

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ABSTRACT

Background: The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was first performed in 2007. The critical patient selection, timing to perform the second stage operation, and minimally invasive technique are three key factors for patient outcomes. The aim of this review is to summarize published data on these three aspects.
Data sources: Studies were identified by searching PubMed for articles published from January 2007 to October 2018, using the keywords "associating liver partition and portal vein ligation for staged hepatectomy" or "ALPPS" or "*in situ* split". Studies on colorectal liver metastasis (CRLM), perihilar cholangiocarcinoma (PHC), and hepatocellular carcinoma (HCC) indicated for ALPPS, cutoff values to determine the timing of stage 2, as well as modifications of ALPPS were included.
Results: The mortality of ALPPS for CRLM is declining, for PHC is high. In patients with HCC, essential hypertrophy makes the ALPPS safer. However, the degrees of fibrosis affect the hypertrophy. The future liver remnant volume is still the gold standard to start the second stage. Hepatobiliary scintigraphy plays an important role in quantitatively assessing liver function, whereas cutoff values need to be further calibrated. Less-invasive ALPPS modifications have increased and led to a decreased mortality.
Conclusions: ALLPS improved the CRLM outcomes; ALPPS is feasible in patients with PHC after failure of portal vein embolization; ALPPS may be an option for HCC patients with major vascular invasion and thrombosis. The simplified and less-invasive ALPPS is the trend.

Introduction

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has two steps, the first step is the intraoperative ligation of the right portal branch to the partition of the liver, the second step is an extended right hepatectomy. ALPPS was first performed by Schlitt et al. [1] in 2007. Schnitzbauer et al. first reported 25 cases in 2012 [2]. ALPPS revolutionized liver surgery for primarily unresectable hepatic tumors. Nevertheless, the early high mortality (9%−12%) and major morbidity (27%−44%) of the ALPPS procedure moderated surgeons' enthusiasm, and they adopted a more thoughtful approach [2,3]. With adjustment of indications and technical modification in ALPPS, the unacceptable high mortality and major morbidity rates continuously declined [4]. With more than 10 years of study, the ALPPS approach is now still at the early-stage, and further studies should concentrate on safety and prognosis. The critical patient selection, timing to perform the second stage, and minimally invasive technique are three key factors involved with short-term outcomes and long-term survival. Here, we review ALPPS with a focus on the indications, best cutoff values, and modified, less-invasive technique.

Search strategies and results

Studies were identified by searching PubMed for articles published from January 2007 to October 2018 using the keywords "associating liver partition and portal vein ligation for staged hepatectomy" or "ALPPS" or "*in situ* split". Studies on colorectal liver metastasis (CRLM), perihilar cholangiocarcinoma (PHC), and hepatocellular carcinoma (HCC) indicated for ALPPS in terms of future liver remnant (FLR) prior stage 1, FLR prior stage 2, FLR increase, days of interval, morbidity, and mortality were selected. In addition, all studies that reported cutoff values to determine the timing of stage 2, as well as mechanistic studies on the volume-function relationship, were evaluated. Modifications of ALPPS were reviewed only with first-proposed or representative studies. The

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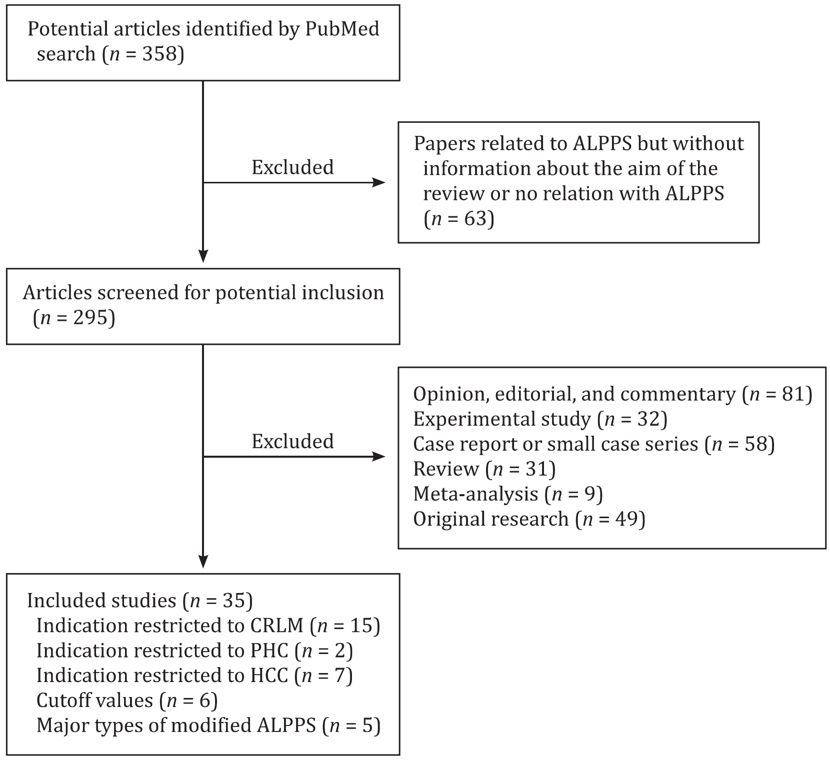

Fig. 1. Flow chart of databases searched, strategy used, and exclusions performed.

studies were chosen for recent report or more relevance to our aims of review if data were duplicated by one team. Language was restricted to English. Papers related to ALPPS but without information about the aims of this review or no relation to ALPPS were excluded.

A total of 358 publications were identified up to October 2018. After exclusion of duplicates, papers related to ALPPS but without required information or with no relation to ALPPS, 295 papers remained. Among these papers, 84 were opinion, editorial, or commentary series; 32 were experimental studies; 58 were case reports; 31 were review and 9 were meta-analysis; and single-center and multicenter original research accounted for 50 and 31 pieces, respectively. After selection, 35 papers were included in the final analysis. Articles were grouped under 5 topics: indication restricted to CRLM which accounted for 15 papers; indication restricted to PHC which accounted for 2 papers; indication restricted to HCC which accounted for 7 papers; 6 papers reported the cutoff values of ALPPS stage 2; 5 studies addressed on the modifications of ALPPS were reviewed. Fig. 1 displays the flowchart of paper selection.

Critical patient selection for ALPPS

Indication for CRLM

A total of 15 papers [5–19] are on patients with CRLM and reported the FLR prior to stage 1 and stage 2, FLR increase, morbidity, and mortality (Table 1). Some of the studies in Table 1 reported high mortality and morbidity. However, these reports included several tumor types. Some studies on CRLM only show that the mortality rate is only 5.0%−8.6% after stage 2 [3,11,20,21], which is in line with major conventional hepatectomy [22–24]. Moreover, several centers even had no 90-day mortality [5,6,8,10,15,16,19], which seems to confirm the safety of ALPPS in CRLM. However, it should be noticed that data from the ALPPS registry group consistently shows that the mortality is around 8% [3,11,18].

Although the reported surgical outcomes are promising and the resectability of ALPPS for CRLM is high, the long-term survivals are comparable to or even lower in some studies compared with conventional two-stage hepatectomy [7,8]. In general, 2-year overall survival (OS) ranged from 42% to 59% of in CRLM patients with ALPPS [8–11] (Table 1).

It is known that tumor status together with surgical technique determines prognosis. Tumor status such as the numbers, size, and response to chemotherapy that determine survival should be evaluated to screen the suitable candidates for hepatectomy. Cauchy et al. [22] reported that downstaging CRLM patients (whom they defined as slow responders), using 12 or more cycles of chemotherapy before major hepatectomy, demonstrated extremely high mortality (19%) and 50% major morbidity associated with poorer long-term outcomes compared to fast responders. This implies that downstaging CRLM patients may also not be suitable for the ALPPS approach due to high risk of mortality, much less achieving favorable oncologic outcomes. Olthof et al. [11] reported that patients with advanced CRLM (defined as 2 of the following 3 criteria were met: ≥6 metastases, ≥2 FLR metastases, or ≥6 involved segments, excluding segment 1) with an ALPPS approach had similar OS compared to matched patients with palliative systemic therapy. In addition, patients with advanced CRLM had a poorer OS and disease-free survival than those meeting <2 criteria in the ALPPS registry.

When deciding whether CRLM is suitable for ALPPS, the short-term and long-term outcomes should be considered. Although short-term outcomes of ALPPS for CRLM are currently satisfactory, the long-term outcomes remain the primary concern, and that OS of ALPPS patients significantly overwhelming palliative systemic therapy can be accepted. In general, patients who have a poor survival scenario for conventional major hepatectomy should not be candidates for ALPPS. Patients with advanced CRLM as

Table 1
Summary of data of patients diagnosed with CRLM indicated for ALPPS.

Studies	Source	Year	*n*	FLR prior to stage 1	Days between stage 1 and 2	FLR prior to stage 2	FLR increase	Major morbidity	90-day mortality	Survival
Hernandez-Alejandro et al. [5]	Single-center	2015	14	sFLR 19%	8	sFLR 37%	sFLR 93% ± 28%	≥IIIB 14%	0	9-month OS 100%
Oldhafer et al. [6]	Single-center	2014	7	FLR 424 mL (222–605)	13	FLR 532 mL (409–873)	FLR increase 65% (16%–97%)	≥III 14.29%	0	NR
Ratti et al. [7]	Multicenter	2015	12	FLR 22%	11 (7–12)	FLR 36%	FLR increase 47%	≥IIIA 41.7%	8.3%	1-year OS 92%; 1-year DFS 67%
Adam et al. [8]	Single-center	2016	17	sFLR 24%	12 (9–39)	sFLR 36%	NR	≥IIIA 41%	0	2-year OS 42%
Bjornsson et al. [9]	Multicenter	2016	23	sFLR 20.2% (16.1%–39.2%)	5 (5–8)	sFLR 35.5% (25.9%–59.5%)	sFLR 64.3% (−17% to 238%)	≥IIIB 13.6%	4%	2-year OS 59%
Zattar-Ramos et al. [10]	Single-center	2016	9	FLR 453 mL (213–790)	21 (7–35)	FLR 634 mL (410–957)	FLR increase 48%	≥IIIB 0%	0	2-year OS 59% from surgery
Olthof et al. [11]	ALPPS registry	2017	295	FLR 338 mL (260–441) (*n* = 275)	11 (8–15)	FLR 615 mL (481–732) (*n* = 271)	FLR increase 74% (46%–100%)	Stage 1 ≥ IIIA 11.1% stage 2 ≥ IIIA 28.5%	8%	2-year OS 42%; 2-year DFS 18%
Kikuchi et al. [12]	Single center	2017	12	FLR 33.6% ± 9.1%	7	FLR 45.6% ± 6.3%	Around FLR 43% (calculated by reported data)	Stage 1 ≥ IIIA 33%; stage 2≥ IIIA 27.3%	9.1%	NR
Linecker et al. [13]	Bi-institutional	2017	45	sFLR 424 mL (208–657) in p-ALPPS; 383 mL (168–791) in ALPPS	15 in p-ALPPS; 17 in ALPPS	sFLR 39% in p-ALPPS; 37% in ALPPS	sFLR 64% in p-ALPPS; 60% in ALPPS	≥IIIB 13% in p-ALPPS; 36% in ALPPS	0 in p-ALPPS; 27.27% in ALPPS	NR
Sandstrom et al. [14]	Multicenter	2018	48	sFLR 22.4% ± 4.3%	11	sFLR 37.1% ± 7.5%	68% ± 38%	≥IIIA 43%	8.3%	NR
Serenari et al. [15]	Single-center	2018	26	sFLR 25% (18%–27%)	10 (7–17)	sFLR 44% (37%–49%)	FLR 99% (55%–146%)	≥IIA 38.5%	0	1-year OS 83.4%; 3-year OS 48.9%
Sparrelid et al. [16]	Single-center	2017	11	sFLR 18.7% (16.1%–23.8%)	6	sFLR 31.2% (27.5%–36.0%)	FLR 61.8% (19.3%–120%)	≥IIIA 36.36%	0	NR
Vondran et al. [17]	Single-center	2018	6	FLR 20.9% (13.2%–27.1%)	11 (9–14)	NR	FLR 67.9% (32.5%–94.1%)	≥IIIA 33%	16.6%	Mean DFS was 5.7 mon
Schnitzbauer et al. [18]	ALPPS Registry	2018	403	Right tri-ALPPS 359 ± 147 mL; Right-hepa-ALPPS 422±149 mL	Right tri-ALPPS 16.9 ± 29.5 d; Right-hepa-ALPPS 22.5 ± 50.5 d	Right tri-ALPPS 1227 ± 609 mL; Right-hepa-ALPPS 1422 ± 583 mL	FLR right tri-ALPPS 81%; Right-hepa-ALPPS 77%	Right tri-ALPPS vs. right-hepa-ALPPS stage 1≥ IIIA 7.7% vs. 13.66%, stage 2 ≥ IIIA 30% vs. 33.3%	Right tri-ALPPS 8.6%; Right-hepa-ALPPS 6.5%	Median survival rT was 30.1 ± 12.3 mon; rH 31.7 ± 11.8 mon
Wanis et al. [19]	Bi-institutional	2018	47	FLR 22% ± 5.3%	8 (7–11)	FLR 42% ± 9.6%	NR	≥IIIB 21%	0	3-year OS 50%; 3-year DFS 13%

CRLM: colorectal liver metastasis; ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; FLR: future liver remnant; sFLR: standardized FLR; OS: overall survival; DFS: disease-free survival; rT: right trisectionectomy associating liver partition and portal vein ligation for staged hepatectomy; rH: right hepatectomy associating liver partition and portal vein ligation for staged hepatectomy; NR: not reported.

previously defined have a poor survival. Patients without response to chemotherapy or require prolonged chemotherapy have high mortality and morbidity after major resection. Despite the beneficial suggestions from the abovementioned papers, prospective randomized controlled trials are still rare. So far, failed standard two-stage hepatectomy due to insufficient hypertrophy may be the most suitable candidates for ALPPS.

Indication for PHC

Two papers elaborating the FLR prior to stage 1 and stage 2. One paper was reported by the ALPPS registry group [25], and the other was a case series that introduced a modified ALPPS technique in three patients with PHC [26] (Table 2).

PHC patients treated with ALPPS often have high mortality rates (27%–48%) [3,25]. The main reason is extensive resection and that the FLR is not insufficient. The second reason is preoperative cholangitis [27]. The third reason is that the bile canalicular-ductule networks in the FLR are immature in ALPPS which may result in prolonged cholestasis following final hepatectomy in ALPPS [28]. Studies based on the ALPPS registry demonstrated that high serum bilirubin before stage 2 is an independent predictor of 90-day mortality [3,20]. These results illustrated that an aggressive surgical strategy associated with inherent unfavorable factors made the ALPPS procedure more dangerous for PHC patients than for those with other types of tumors.

Currently, portal vein embolization (PVE) is still primarily recommended by most surgeons when extended hepatectomy is needed for PHC, considering the high mortality from classic ALPPS.

Table 2
Summary of data of patients diagnosed with PHC indicated for ALPPS.

Studies	Source	Year	*n*	FLR prior to stage 1	Days between stage 1 and 2	FLR prior to stage 2	FLR increase	Major morbidity III	90-day mortality
Olthof et al. [25]	ALPPS registry	2017	29	20% of TLV	8 (7–14)	31% of TLV	68%	≥IIIA 83%	48%
Sakamoto et al. [26]	Single-center	2018	3	26.2% of TLV	21 (17–31)	39.8% of TLV on day of 14	42.9%	One developed pleural effusion	0

PHC: cholangiocarcinoma; ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; TLV: total liver volume.

Table 3
Summary of data of patients diagnosed with HCC indicated for ALPPS.

Studies	Source	Year	*n*	Numbers of patients with fibrosis or cirrhosis	FLR prior to stage 1	Days between stage 1 and 2	FLR prior to stage 2	FLR increase	Major morbidity III	90-day mortality
Serenari et al. [32]	Multicente	2016	8	6 patients with cirrhosis	sFLR 23.5% (15%–35%)	8.5 (6–15)	sFLR 39.5% (31%–52%)	sFLR 56.5% (14%–178%)	Stage 1 ≥ IIIA 25%; Stage 2 ≥ IIIA 37.5%	12.5%
D'Haese et al. [33]	ALPPS Registry	2016	35	10 patients with fibrosis and 4 with cirrhosis	Median of 420 mL	11 (8–14)	Median of 639 mL	FLR 47%	≥IIIB 26.9%	31%
Chan et al. [34]	Single-center	2016	17	8 patients with chronic hepatitis and 9 with cirrhosis	sFLR 24.2% (16.7%–45.4%)	6 (5–22)	sFLR 38.5% (27.9%–56.9%)	sFLR 48.7%	≥IIIA 11.8%	5.9%
Cai et al. [35]	Single-center	2017	12	11 patients with Child-Pugh A cirrhosis and 1 with Child-Pugh B cirrhosis	FLR 29.2% (14.7%–39.7%)	10.5 (7–44)	FLR 38.5% (10.1% –74.6%)	FLR 28.1% (−31.2% to 94.8%)	Stage 1 ≥ IIIB 25%; Stage 2 ≥ IIIB 40%	50%
Wang et al. [36]	Single-center	2017	10	1 patients with fibrosis and 9 with cirrhosis	FLR 31% (19%–37%)	28 (13–31)	FLR 47% (40%–58%)	FLR 53% (35%–133%)	≥IIIB 20%	10%
Wang et al. [37]	Single-center	2018	45	26 patients with fibrosis and 13 with cirrhosis	sFLR 26.9% (17.9%–39.2%)	12 (6–28)	sFLR 41.3% (33.1%–60.5%)	sFLR 56.8% (8.3%–103.5%)	≥IIIB 11.1%	11.1%
Chia et al. [38]	Single-center	2018	9	6 patients with fibrosis	FLR 16.1% (12.7%–28.8%)	7 (7–10)	NR	FLR 40.2% (22.1%–65.3%)	Stage 1 ≥ IIIB 11.1%; Stage 2 ≥ IIIB 14.2%	11.1%

HCC: hepatocellular carcinoma; ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; FLR: future liver remnant; sFLR: standardized FLR; NR: not reported.

The major weakness of PVE is the high failure rate to advance to resection compared to ALPPS (20% vs. 1%, $P = 0.001$) [29]. Nagino et al. [30] reported that the incidence of unresectability after PVE was 32.2% in gallbladder cancer and 12% in cholangiocarcinoma. This suggests that rescue-ALPPS is still a possibility for patients with PHC after failure of PVE. Nowadays, classic ALPPS does not seem suitable for PHC, but the less-invasive, modified ALPPS, especially combined with PVE and partial split, and partial transileocecal PVE ALPPS [26] and mini-ALPPS [31] have been proposed to reduce the mortality of classic ALPPS for PHC. The key refinement is PVE associated with partially partitioning the liver to reduce the invasive procedure in stage 1 surgery. In addition, using a no-touch technique is in accord with oncological principle for the treatment of PHC. However, both reported modifications of ALPPS had a low number of cases. In summary, patients with PHC without cholangitis and high serum bilirubin are still the candidates of less-invasive, modified ALPPS, especially after failure of PVE.

Indication for HCC

Table 3 lists 7 studies on ALPPS for HCC patients [32–38]. Median time between stages 1 and 2 was from 6 to 28 days. Major morbidity and 90-day mortality varied greatly.

ALPPS is commonly accepted for CRLM and strongly skeptic for PHC. However, ALPPS for HCC needs caution. ALPPS registry shows around 10% of HCC patients need ALPPS [3,20]. D'Haese et al. [33] compared perioperative outcomes and survival rates of patients with HCC and those with CRLM in the ALPPS registry, and found that 90-day mortality was significantly higher for HCC than for CRLM (31% vs. 7%; $P = 0.001$). In addition, the relative hypertrophy rate in HCC patients was significantly lower than that in CRLM patients (47% vs. 76%; $P < 0.002$) and tended to vary inversely with the degree of fibrosis. Despite these poor results, many centers are still using ALPPS to treat HCC patients. Chan et al. [34] and Wang et al. [37] reported favorable results, in which major morbidity was about 11%, and the hospital mortality rate was 5.9%–11.1% in HCC patients with chronic viral hepatitis or cirrhosis.

One of the main concerns with ALPPS in HCC is whether patients with concomitant hepatic fibrosis or cirrhosis can develop adequate hypertrophy. D'Haese et al. [33] and Wang et al. [37] found that hypertrophy showed a linear negative correlation with the degrees of fibrosis. However, despite this trend, kinetic growth rates (KGRs) were extremely different between the two reports. The KGRs with different degrees of fibrosis reported by D'Haese et al. [33] were much lower than those in Wang's study [37], which may explain the high morbidity and mortality. However, when compared with non-HCC patients, hypertrophy was relatively lower in HCC patients with fibrosis or cirrhosis. Nevertheless, hypertrophy could meet the minimal volume requirement (>30% for patients with normal liver, and >40% for patients with chronic hepatitis or cirrhosis) prior to stage 2 operation. To improve the surgical outcomes, Shindoh et al. [39] suggested that in patients with marginal hepatic functional reserve with indocyanine green retention rate at 15 min (ICG-R15) of 10%–20%, FLR > 50%

is recommended, and the degree of hypertrophy >10% is needed for impaired liver function to prevent postoperative hepatic insufficiency.

In general, indication for ALPPS in patients with HCC is mainly at the intermediate stage and is commonly associated with major vascular invasion, portal vein tumor thrombus, and large tumor size. ALPPS has the potential advantage in situations of portal branch invasion or hepatic vein invasion when the classic two-stage approach cannot feasibly be performed because of the risk of rapid thrombotic progression. The hypertrophy with different degrees of fibrosis should be further studied.

Timing for stage 2 of ALPPS

One of most key questions is when to undergo the second stage of ALPPS. The 7 days interval as an important time point has been used widely whereas this dogmatic method has caused severely high complication rates and mortality. On the other hand, a delayed second stage usually leads to adhesions that increase the difficulty of stage 2 and the risk of tumor progression. Therefore, a credible method to determine the suitable timing of stage 2 is crucial. Several cutoff values based on volumetric methods, hepatobiliary scintigraphy (HBS) or biochemical liver function test have been proposed to help to determine the safe timing of stage 2.

Cutoff values based on volumetric methods

Truant et al. in 2007 first proposed that the remnant liver volume/body weight cutoff value for second stage liver resection is 0.5% [40], which was translated from the living-donor liver transplantation model with a sensitivity of 100% and a specificity of 78% for prediction of postoperative mortality. Schnitzbauer et al. [2] also suggested that the left lateral liver lobe volume to body weight ratio (LLL-BWR) above 0.5% is the cutoff for the second stage of ALPPS. Majority of the patients in these two studies had CRLM with no or a low degree cirrhosis, and all underwent right hepatic trisectionectomy. The other widely used cutoff for ALPPS was standardized FLR (sFLR) > 30% of the original liver volume for patients with normal liver, and >40% for patients with cirrhosis [41]. However, although many patients reached the volumetric criteria prior to stage 2, some of them still developed post-hepatectomy liver failure (PHLF) after ALPPS. Schadde et al. [20] demonstrated that liver failure developed in 31% of patients with sFLR of 30% to 40% and in 16% of patients with sFLR > 40% prior to stage 2 in the ALPPS registry. This suggested that liver volume does not always accurately estimate liver function. Liver function is more essential than liver volume. Previous studies reported that total liver function declined sharply, by as much as almost 40%, after stage 1 [42,43], and then recovered within a median of 7 days with liver function of the deportalized part of the liver's progressive attenuation in favor of the FLR [44]. The hypertrophic FLR is supposed to be immature, particularly in stage 1, and the deportalized part of the liver takes the main responsibility for liver function before resection [44]. In most cases of hepatectomy, the increase of liver volume corresponds concomitantly with functional increase but is not completely synchronized. The functional increase is partially independent of volume increase. In ALPPS, the increase in liver function was roughly half of the volumetric increase [42,45]. Therefore, stage 2 should be postponed, particularly when major complications or any other situations occur after stage 1. Shindoh and colleagues in 2013 proposed a new concept named kinetic growth rate (KGR), which can reflect the regenerative capacity of the liver [46]. Kambakamba et al. [47] found that a KGR > 6%/day significantly reduced the risk of PHLF after ALPPS stage 2, whereas sFLR > 30% did not significantly predict the risk of PHLF. Nevertheless, no patients developed PHLF, and perioperative outcomes were improved when KGR > 6%/day was combined with sFLR > 30%. KGR should be a useful auxiliary tool with other volumetric parameters to decide the appropriate timing for ALPPS stage 2.

Cutoff values based on hepatobiliary scintigraphy (HBS)

HBS is a useful tool to predict postoperative liver failure. De Graaf et al. [48] proposed a critical cutoff value for FLR function (FLR-F) of 2.69%/min/m^2. The sensitivity and specificity of ^{99m}Tc-mebrofenin-HBS to predict postoperative liver failure after major liver resection are 89% and 87%, respectively. This cutoff value is now the most widely used in clinical practice. Chapelle et al. [49] developed a new cutoff value for estimation of FLR-F (eFLR-F) at 2.3%/min/m^2, they combined the ratio of the future liver remnant volume (FLRV%) measured by MRI and the total liver function measured by ^{99m}Tc-mebrofenin HBS, and the combination yield a positive predictive value (PPV) and negative predictive value (NPV) for PHLF of 92% and 99%, respectively. However, we noticed that half or more patients with PHC developed PHLF in both studies [48,49]. Therefore, the application of cutoff value in patients with PHC is less accurate than in those with other types of tumor. The reason of this conflict is that patients with PHC may comorbid with cholangitis and hyperbilirubinemia. Olthof et al. [50] stratified FLR by various cutoff values for predicting the incidence of PHLF in patients with PHC who underwent major liver resection. If a FLRV cutoff is 45%, the NPV is >90% for PHLF in PHC patients without cholangitis, whereas it declined to <70% if PHC patients have cholangitis. It is reported that both ^{99m}Tc-mebrofenin and unconjugated bilirubin are transported into human hepatocytes by OATP1B1 and OATP1B3 [51,52], suggesting that the two behave in a competitive manner, and that liver function might be underestimated when levels of bilirubin are high. Therefore, Olthof et al. [53] established a cutoff for FLR-F of 8.5%/min in PHC patients with a bilirubin below 50 μmol/L, which resulted in an NPV for PHLF of 94% and a PPV of 41%. The authors did not recommend HBS to be performed on patients with bilirubin level above 50 μmol/L. Serenari et al. [54] compared three HBS parameters, including counts within the FLR (FLR-C), FLR-F, and the newly developed Hospital Italiano de Buenos Aires index (HIBA-i), to predict PHLF during ALPPS; the receiver operating characteristic (ROC) analysis demonstrated that a cutoff value for HIBA-i of 15% was the best to identify PHLF with a sensitivity of 100% and a specificity of 94%. Although only 4 patients with PHLF were included in the analysis, HIBA-i seems a promising modality for PHLF prediction.

Currently, estimations of FLR-F and remnant liver volume are two main methods to predict PHLF. Both methods have their pros and cons. For volumetric methods, FLR-BWR and sFLR have been verified and widely used. In other words, due to the value of quantitative functional assessment of the liver remnant, functional methods have great prospects in surgical decision before major liver resection.

However, both methods have their disadvantages. Despite the gold standards to determine the timing of stage 2 operation, volumetric methods do not ensure absolute safety after a radical resection. A recent study conducted by Schnitzbauer et al. [18] aiming to evaluate the necessity of two-stage hepatectomies by comparing outcomes of the right hepatectomy ALPPS and right trisectionectomy ALPPS in patients with CRLM found that about one third of patients who met the standards of one stage of hepatectomy were over-indicated for ALPPS. The authors tried to explore the reasons that prompted surgeons to perform two-stage hepatectomy by supposing that surgeons tried to preserve more FLR-F for tumor resection preparation when FLR or total liver volume was small or liver function was compromised due to preoperative chemotherapy. However, data analysis vetoed all hypotheses. It seemed that surgeons followed their subjective perception rather than objective criteria of resectability to determine a two-stage hepatectomy, so we may assume that volumetric methods do not always give surgeons full confidence to perform a radical liver resection. Actually, when the ability to predict PHLF was compared between functional and volumetric criteria, the functional criteria usually overwhelmed the volumetric criteria. de Graaf et al. [48] used FLR-F, FLRV%, and sFLR to predict PHLF, and the outcomes indicated that FLR-F had better comprehensive predictive abilities than others in sensitivity, specificity, PPV, and NPV. Furthermore, both team of de Graaf's studies [48,55] reported that liver volume was usually overestimated when FLR-BWR and sFLR criteria were used.

Is it time to replace the volumetric methods with functional methods when we make a decision to start the stage 2 procedure? The answer is obviously no. Despite better ability to predict PHLF, a robust and widely verified cutoff value based on HBS has not been established. For instance, the cutoff value for FLR-F of 2.69%/min/m^2 reported by de Graaf et al. [48], which indicates for liver resection, had great heterogeneity. Besides, this has not been validated by other studies. Moreover, various cutoff values based on HBS have been reported. The FLR-F cutoff of 1.69%/min/m^2 reported by Serenari et al. [54] and a preliminary FLR-F cutoff of 5.6%/min without correction for body surface area by Olthof et al. [42] indicate that differences of imaging device and calculation methods may lead to great bias among centers. Thus, currently, it is irrational to use FLR-F to determine the timing of stage 2 directly. Compared to cutoff values of volumetric methods, functional methods need a standardization and therefore have a long way to go.

Cutoff values based on biochemical liver function test

Biochemical liver function test results are the main basis on which to estimate liver condition before and after hepatectomy. The synthetic, excretory, and detoxifying functions are the three main aspects of function the liver maintains and can be reflected by prothrombin time (PT), international normalized ratio (INR), and serum bilirubin concentration. The level of PT-INR reflects the ability of the liver to synthesize coagulating factors, whereas the level of total bilirubin (TBil) reflects the capacity of bilirubin metabolism. The 50–50 criterion is the representative biochemical parameter to predict liver failure-related mortality after hepatectomy [56]. In major hepatectomy, Yokoyama et al. [57] reported that a combination of PT-INR $\geq$ 1.68 and TBil $\geq$ 4.0 mg/dL on postoperative day (POD) 5 can strongly predict postoperative mortality for patients who underwent major hepatectomy. In ALPPS, Schadde et al. [20] demonstrated that bilirubin and creatinine before stage 2 strongly predicted mortality after stage 2. In addition, a model for end-stage liver disease (MELD) score $\geq$10 calculated with bilirubin, INR, and creatinine can predict liver-related 90-day mortality with a sensitivity of 82% and a specificity of 67%. The 50–50 criterion proposed by Balzan et al. [56] included the extent of resection in major and minor hepatectomy. To preserve the homogeneity of the study, a majority of patients included in a study by Mullen et al. [58] were metastatic and noncirrhotic with normal baseline liver function, and all underwent a major hepatectomy. A powerful cutoff value for peak bilirubin >7 mg/dL was found to result in an NPV for liver failure-related death of 99.8% and a PPV of 32.6%. Furthermore, the cutoff value was confirmed and modified into day 5 bilirubin >7 mg/dL by the Schadde group [20]; it had the highest accuracy, with a PPV of 33% and an NPV of 94% for 90-day mortality after ALPPS stage 2 in that study.

Monitoring PT-INR and bilirubin as well as other biochemical parameters, used as indirect indicators of liver function, enables accurate assessment of liver function and predicts risks of liver failure before and after hepatectomy. When a decrease of liver capacity in synthesis and excretory function is found, either synthesis or metabolic aspects should be supported immediately. However, these parameters reflect global liver function but not the FLR that is changed in preparation for ALPPS stage 2 and is susceptible to blood transfusions. Therefore, biochemical parameters should be used in combination with volumetric and other parameters.

The different cutoff values and their diagnostic accuracy in predicting 90-day mortality or PHLF are summaried in Table 4.

Table 4
Different cutoff values and their diagnostic accuracy in predicting 90-day mortality or PHLF.

Studies	Cutoff values	Diagnostic accuracy
Schnitzbauer et al. [2] and Truant et al. [40]	LLR/BWR > 0.5%	Median interval of 9 days without liver-related mortality, overall 90-day mortality was 12% [2]. Predict postoperative mortality with a sensitivity of 100% and a specificity of 78% [40].
Sandstrom et al. [14] and Clavien et al. [41]	sFLR > 30% in normal liver, sFLR > 40% in cirrhosis	Median interval of 11 days, ≥III A morbidity was 43%, and total mortality was 9.1% [14].
Schadde et al. [20]	MELD score ≥ 10	Predict liver-related 90-day mortality with sensitivity of 82% and specificity of 67%.
	Day 5 bilirubin > 7 mg/dL	90-day mortality was 28%, predict 90-day mortality with a sensitivity of 54% and specificity of 84%, and with a PPV of 33% and an NPV of 94%.
Kambakamba et al. [47]	KGR > 6%/day, sFLR > 30%	Major morbidity 10% and predict mortality with an NPV 100% and a PPV of 75%.
de Graaf et al. [48]	FLR-F of 2.69%/min/m^2	Predict postoperative liver failure with a sensitivity of 89% and a specificity of 87% in a one-stage major liver resection. Only 2 case reports implement the criteria in ALPPS.
Olthof et al. [53]	FLR-F of 8.5%/min	Only applicable for PHC patients with a bilirubin below 50 μmol/L, with an NPV of 94% and a PPV of 41%.
Serenari et al. [54]	HIBA-i of 15%	Predict postoperative liver failure with a sensitivity of 100%, specificity of 94%, with a PPV of 80% and an NPV of 100%.

PHLF: post-hepatectomy liver failure; FLR: future liver remnant; BWR: body weight ratio; sFLR: standardized FLR; KGR: kinetic growth rate; FLR-F: FLR function; NPV: negative predictive value; PPV: positive predictive value; ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; HIBA-i: Hospital Italiano de Buenos Aires index; MELD: model for end-stage liver disease.

Modified ALPPS techniques

A variety of modifications of ALPPS have been undertaken to reduce invasiveness and improve safety. In general, the modifications may be divided into three main categories: PVE-ALPPS, partial partition of the liver during the first stage (p-ALPPS), and salvage ALPPS. PVE-ALPPS replaces the portal vein ligation procedure with PVE to avoid dissecting the hilum, which is quite important in PHC, due to tumor infiltration of the hepatoduodenal ligament. The representative technique is hybrid ALPPS: *in-situ* split liver parenchyma combined with postoperative right PVE to avoid touching the right hilum to achieve oncological efficacy [59].

The p-ALPPS was developed by Petrowsky et al. [60] and switches a complete split with a partial split (>50% plane) of the liver parenchyma. To perform p-ALPPS, the depth of liver transection should not exceed 3–5 cm in mini-ALPPS [31]. A tourniquet is positioned according to the section site. The tourniquet was tightened to occlude all vessels that connected the pertinent lobes for staged hepatectomy [61].

Other modifications, including radiofrequency-assisted liver partition with portal vein ligation [62], laparoscopic microwave ablation, and portal vein ligation for staged hepatectomy [63], create an avascular groove with energy devices that preserve the inflow and outflow structures, similar to p-ALPPS.

Salvage ALPPS could include the types of ALPPS that are performed following an insufficient hypertrophy after PVE or portal vein ligation; it also could be a suitable alternative for less aggressive tumors and for patients with high risks of mortality from short-term continuous surgery.

To sum up the modifications of ALPPS procedures in recent years, Linecker et al. [4] demonstrated that the proportion of less-invasive ALPPS variants has increased and led to a decreased 90-day mortality rate. Because complex stage 1 surgery and interstage major complications are associated with high risks of mortality in ALPPS registry studies [4,24], it is suggested that the simplified and less-invasive ALPPS procedures, such as p-ALPPS and mini-ALPPS, could be the future trend. However, despite comparable hypertrophy found between classic ALPPS and the modified ALPPS in a few small studies [31,60], problems about unexpected liver failure are still not resolved [34].

Discussion

After more than 10 years of exploration, the indications for ALPPS are clearer. Roughly, 85% of patients with CRLM, 10% with HCC and 5% with PHC are indicated for ALPPS. Despite low morbidity and 90-day mortality reported by several centers for patients with CRLM, it must be pointed out that some patients, who should have undergone one-stage major hepatectomy, were over-indicated for ALPPS, which led to the improved surgical outcomes. ALPPS may well have been abused. The real short-term outcomes may not be so optimistic. As to long-term outcomes, the tumor characteristics and response to preoperative chemotherapy as well as other tumor biology should be evaluated before ALPPS is performed to obtain satisfactory oncology outcomes.

There are insufficient studies and inconclusive surgical outcomes to evaluate the safety of patients with HCC for whom ALPPS is indicated. The limited high-quality papers from the ALPPS registry group and Chinese centers reported extreme discrepancy of morbidity and 90-day mortality. It seems that Asia's outcomes and attitudes toward ALPPS were more positive than those in Western countries, although an overwhelming majority of patients are associated with chronic viral hepatitis or cirrhosis. Another important finding is that the KGR with different degrees of fibrosis differs greatly between Eastern and Western countries. Despite the lower growth compared to non-HCC patients, gratifying results of nearly 90%−100% of patients could proceed to subsequent stage 2 operation after sufficient volume is obtained. Severe fibrosis and slight cirrhosis are not contradictions for ALPPS. HCC-associated portal vein tumor thrombus or hepatic vein tumor thrombosis is a potential indication for ALPPS due to rapid hypertrophy that promises a complete hepatectomy.

Few reports with large case series concentrate on the clinical research on PHC for ALPPS. We cannot draw any conclusions about the implementation prospects without credible evidence. The high incidence of unresectability after PVE leaves room for ALPPS. Modified ALPPS such as p-ALPPS and mini-ALPPS may reduce invasiveness and improve safety. Indicating ALPPS for PHC should be more cautious to avoid cholangitis, hyperbilirubinemia, and other risk factors, based on existing evidence.

So far, we do not have a universally accepted cutoff value to determine the timing of the second-stage procedure. All methods have their shortcomings. Although it is well known that an increase in liver volume is not equal to a corresponding increase in function, it is difficult to find a better method to replace volumetric evaluation. Surgeons have to wait until the increased FLR volume meets or exceeds the classic volumetric criteria, so conservative surgeons usually make a delayed ALPPS. FLR-F evaluation by HBS has more potential advantages than volumetric methods. However, no currently reported robust cutoff values based on HBS are produced from the small numbers of patients or heterogeneous diagnoses that can be widely applied. Standardizing imaging and calculation methods are the urgent tasks for HBS. Before a sophisticated cutoff value based on HBS is made, volumetric methods are still the gold standard for ALPPS, and biochemical liver function tests also have a certain value for predicting PHLF.

The use of classic ALPPS has been gradually declining. Varieties of modifications have been proposed and introduced by case report or small case series. PVE-ALPPS and p-ALPPS are two types of modifications that essentially changed the principle of the classic ALPPS. Most of other modifications are about using different surgical instruments to partition the liver. To improve the acceptability of one type of modified ALPPS, three directions should be considered. One of the most important points is to reduce the surgical invasiveness of stage one to reduce the interstage complications that proved to be independent risk factors for 90-day mortality. Another is to simplify the surgical procedure to make it easy to accomplish. Third, all modifications are supposed to have an oncological value. After all, the main advantage of ALPPS is to have a complete resection at the intermediate stage of the tumor and improve survival.

Contributors

HZM proposed the study. XF performed the research and wrote the first draft. Both authors contributed to the design and interpretation of the study and to further drafts. XF is the guarantor.

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