Hypertrophy and Liver Function in ALPPS: Correlation with Morbidity and Mortality

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Keywords

ALPPS · Liver function · Posthepatectomy liver failure

Summary

Background: ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) was introduced with the promise to reduce posthepatectomy liver failure (PHLF) in extended hepatectomies but has higher morbidity and mortality rates compared to conventional methods of volume enhancement. There are few studies of the incidence of PHLF after ALPPS and little information on how to avoid PHLF by functional testing. It remains unclear what causes the compromise in liver function despite rapid volume gain and if any of the modifications proposed reduce the incidence of PHLF. This review summarizes published data on this topic. **Methods:** This is a systematic review that studies literature on the incidence of liver failure and assessment of liver function following ALPPS as well as modifications of the existing technique. Articles were searched in PubMed, evaluated, selected, and tabulated. **Results:** The literature search revealed 326 articles that met the selection criteria. PHLF criteria as defined by the International Study Group of Liver Surgery (ISGLS) were the most commonly used criteria, but PHLF was frequently not defined. PHLF occurred most frequently after stage 2 of ALPPS at around 30% in most larger studies. Hepatobiliary scintigraphy showed a discrepancy between volume and functional growth of the liver. Function increase was only 50% compared to volume increase. Mechanistic explanations using histologic analyses have been given to explain the immaturity of the liver after rapid hypertrophy. Modifications of ALPPS showed a comparable volumetric gain when compared to classic ALPPS, but data were lacking

to assess PHLF. **Conclusion:** ALPPS has relatively high rates of PHLF, morbidity, and mortality. This may be explained by data demonstrating functional growth when compared to volume growth. ALPPS should not be performed without functional assessment and with caution.

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Introduction

The amount of liver that can be removed by liver resection is limited by the metabolic and functional capacity of the future liver remnant (FLR) after resection. The prospective postoperative functional liver capacity has for the longest time been quantified by the volume of this FLR as determined by cross-sectional imaging. Therefore, surgeons have developed strategies to increase the volume of the remnant liver by either minimizing the amount of liver resected [1], downsizing the mass to be resected, or increasing the FLR prior to resection by occlusion of the contralateral portal vein [2]. Volume increase after portal vein occlusion is by no means as fast as volume increase after liver resection proper. Data from live donor hepatectomy and standard liver resections show that the liver volume almost doubles within 10 days after hemi-hepatectomy [3]. In contrast, both surgical portal vein ligation (PVL) and portal vein embolization (PVE) require 3–6 weeks of waiting time and a re-evaluation before the tumor-involved portion can be safely resected [4]. The congruity of volume and function was never really challenged, except by some who considered whether PVE may have a larger impact on liver function beyond its modest impact on liver volume over time [5]. These authors must have felt that PVE increased the function of the FLR even if the volume only changed a little bit.

In 2012, Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) was introduced and reduced the 3–6 weeks waiting time while increasing the extent of FLR growth [6]. The procedure hailed a simultaneous deportalization and in-situ parenchymal transection to induce the same rapid liver growth that can be observed after liver resection proper and allowed the resection of extensive tumor masses in 2 stages in 1–2 weeks. The inaugural ALPPS report describes a median volumetric increase of 74% over a median of 9 days [6], and the first multicenter report of an international registry reported 81% volume increase over a median of 7 days [6, 7].

Initially, ALPPS was praised as the most important surgical innovation in liver surgery for years [8], because presumably it eliminated the fear of posthepatectomy liver failure (PHLF), the most common and the most feared complication of extended resections. However, the first analyses showed that ALPPS has a perioperative mortality of 9% and a complication rate of Clavien-Dindo > 3a of 40% [9]. This appears high when compared to 2-stage hepatectomies with a mortality of 3% and a major morbidity rate of 40% in a recent meta-analysis [10]. Lack of experience and the difficulty of the procedure served as an explanation for these disappointing outcomes of ALPPS [11]. However, when complications and mortality were dissected in a more granular fashion, it became obvious that 75% of the reported 90-day mortalities had to be attributed to PHLF and that liver failure criteria were present in 14% of patients even after stage 1 when no liver tissue had been resected yet [9]. Although it remained difficult to determine how much major morbidity is simply procedure-related and not actually caused by PHLF, this analysis raised the suspicion that ALPPS may in fact generate rapid volumetric growth without the congruent growth in liver function that is required for adequate postoperative recovery. It also appeared that there had been an over-reliance on liver volume when deciding whether patients can undergo stage-2 resection, and that rapidly grown livers are not made of the ‘same material’ as liver grown slowly after PVE. This concern has led some surgeons to routinely evaluate the function of the growing FLR rather than relying on volume assessment alone.

The purpose of this review is to summarize what we know about liver-related mortality and morbidity after ALPPS and to enumerate the studies that have attempted to shed light on the conundrum of volume and function in ALPPS. The review also investigates which mechanistic explanations have been presented to understand the functional deficiency of the rapidly volume-expanded liver in ALPPS. Finally, we ask if any of the proposed ‘better’ modifications of the ALPPS operation do not have the problem of functional deficiency of ‘classic’ ALPPS.

Methods

PubMed was searched using the following algorithm: (((‘ALPPS’(Title/Abstract) OR ‘associating liver partition and portal vein ligation for staged hepatectomy’(Title/Abstract)) OR ‘in situ split’(Title/Abstract))). A list of all references was made, and ti-

tles were screened. Studies that provided information on outcomes of ALPPS in terms of complication and mortality in relation to liver function following ALPPS were selected for abstract review. Additionally, all studies examining liver function tests to guide resection in ALPPS as well as mechanistic studies to better understand the volume-function relationship were evaluated in abstract format. Modifications of ALPPS and their outcomes were reviewed. Language was restricted to English. Opinion, editorials, letters, and commentary were excluded. Single case reports and technical letters that were deemed highly relevant to our review were included, given the emerging nature of the topic. There was no restriction on study types. Several studies were excluded based on the full text review.

After selection, articles were grouped under 4 topics:

- Liver-related morbidity and mortality after ALPPS.
- Interstage liver function in ALPPS.
- Mechanisms proposed to explain the lack of congruence of volume and function.
- Impact of modifications of ALPPS on the volume/function dilemma.

Results

Literature Review Results

Figure 1 shows the review and selection process. 326 references were initially identified and 58 abstracts reviewed. A total of 29 full text articles were selected for the review.

Incidence of Liver Failure and Higher Complications after ALPPS

A total of 18 studies reported major complications and mortality after ALPPS and related those findings to postoperative liver function and PHLF (table 1). The most common criteria used in defining PHLF were the liver failure criteria of the International Study Group of Liver Surgery (ISGLS) [12], followed by the 50-50 criteria [13]. The peak bilirubin criterion [14] was used in only 2 studies. 7 of the listed studies employed more than one criterion to evaluate PHLF. 3 studies did not specify the criteria used. The incidence of PHLF after ALPPS using any combination of the three criteria ranged from 8 to 36% with the majority of larger studies demonstrating a rate of around 30%. Perioperative complications were reported using the Clavien-Dindo grading system [15] in all but 2 studies. Clinically significant morbidity after ALPPS was 13–44% and 14–36% for grades 3a or higher and 3b or higher, respectively. 1 study demonstrated no mortality and a very low morbidity but reported a 29% rate of ISGLS-defined liver failure. Only 1 study examined how many mortalities after ALPPS were likely due to PHLF by analyzing the causes of 28 mortalities in 320 patients. The study showed that up to 75% of all mortalities after ALPPS were likely a consequence of PHLF. It was also shown that PHLF by ISGLS criteria after stage 1 and a MELD (Model for End-stage Liver Disease) score > 10 prior to stage 2 were significant risk factors for 90-day mortality after ALPPS, while standardized FLR volume prior to stage 2 or experience of the center performing ALPPS

Fig. 1. Flowchart of databases searched, the strategy used, and exclusions performed.

were not [9]. A correlation between FLR volume and complications did not exist. Next to MELD score or ISGLS criteria after stage 1, kinetic growth rate of the FLR [16] and a dedicated ALPPS futility score [17] have been proposed to assess the risk of stage-2 resection.

Assessment of Interstage Liver Function

Table 2 lists the 5 studies investigating interstage liver function assessment. So far, hepatobiliary scintigraphy (HBS) has been the test of choice due to its ability to selectively evaluate regions of the liver for function. Early reports evaluated only the proportion of HIDA (hepatobiliary iminodiacetic acid scan) signal coming from the FLR as a percentage of the total HIDA signal prior to stage 2 [18]. Since this approach yielded no information about total function of the liver, it was generally abandoned by most. Later studies used an uptake index derived from an analysis of HIDA uptake from the blood pool in the first 5 min, as established by the Amsterdam group [19]. There are only 2 studies in ALPPS so far using this methodology [20, 21]. These studies, including 10 and 28 patients, respectively, showed that functional increase was less (28 and 29% over 6 and 7 days, respectively) than volume increase (57 and 78% over 6 and 8 days, respectively). ICG-R15 (indocyanine green retention rate at 15 min) is a global liver function test based on the pro-

portion of remaining ICG after intravenous (i.v.) injection after 15 min and was used in 2 studies. One study showed ICG-R15 decreased from 9.9 to 7% between stages but increased to 33% after stage 2 [21]. Another study showed an increase from 3.6 to 5.4% postoperatively [16]. LiMAx (maximum liver function capacity) is another global liver function test based on hepatic enzyme metabolism, which is quantified using a breath test after i.v. methacetin has been administered. It has so far only been published in 1 single case report which demonstrated a dramatic decrease in global liver function between stage-1 and stage-2 ALPPS [42].

Investigations into the Mechanism of Function and Volume

A total of 5 studies addressed the potential mechanism of the function/volume question after ALPPS (table 3). A first effort was directed at making sure that the volume increase measured with volumetry in ALPPS is not just edema or regenerative steatosis by using functional magnetic resonance imaging (MRI) data. It was concluded that volume increase after ALPPS is indeed cellular proliferation and not edema or steatosis according to MRI [23]. A second study came to the same conclusion [24].

Matsuo et al. [25] focused their investigation on histology specimens from patients undergoing ALPPS. Histology, electron microscopy, and immunohistochemistry staining showed findings consistent with immature hepatocytes. In a second study, immunohistochemistry and electron-microscopy of bile duct canaliculi showed weaker MDR1 staining, immature microvilli, and leaky tight junctions, despite an adequate quantity of bile duct canaliculi overall [26].

Modifications of ALPPS

A total of 7 studies on 6 different modification techniques were reviewed (table 4). Volume increase in ALPPS modification studies ranged from 53 to 76%. PHLF was reported at 13.6% in only 1 study [27]. The remaining studies reported no liver failure. However, in the majority of the studies, the criteria used to define PHLF were not specified. There was no information on liver function based on HBS, ICG, or LiMAx.

Discussion

This review gives a first synopsis of data published on the volume/function problem to explain the high morbidity and mortality after the novel ALPPS procedure. It points to the available evidence that liver failure and major complications after ALPPS are higher than would be expected with the extensive increase in liver volume. It supports the claim that the high liver failure rate despite increase in volume is likely due to an intrinsic functional defect following rapid hypertrophy in classic ALPPS. This results in uncertainty as to when to progress to resection after ALPPS stage 1 has been performed. The mechanistic understanding of why rapid hypertrophy fails to provide some patients with adequate liver function despite increases in volume is still preliminary, and so far there is no data to conclude that the new ALPPS modifications proposed are helpful to overcome the volume-function problem of rapid hypertrophy.

Tab. 1. Incidence of liver failure and complications after ALPPS

Author [ref.]	Year	n	Criteria for liver failure	PHLF after stage 1, n (%)	PHLF after stage 2, n (%)	Clavien grade 3a or higher, n (%)	Clavien grade 3b or higher, n (%)	Liver-related mortality ^a , n (%)
Linecker [17]	2016	47 vs. 481 ^b	ISGLS	10 (23) vs. 36 (9)	NR	NR	15 (33) vs. 30 (7)	17/45 (36)
Schadde [9]	2015	320	ISGLS 50-50 Bili > 7 ^c	44 (14) 4 (1) 5 (2)	93 (30) 27 (9) 21 (7)	NR	NR	21/28 (75)
Schadde [28]	2014	202	50-50	16 (9)		80 (40)	56 (28)	8/19 (42)
Truant [36]	2015	62	50-50	3 (5)	15 (25)	25 (40)	NR	3/8 (38)
Olthof [20]	2016	60	ISGLS ^d	1 (2)	5 (8)	24 (40)	NR	2/4 (50)
Schadde [7]	2014	48	50-50	0	6 (13)	NR	13 (27)	NR
Kambakamba [16]	2016	36	ISGLS 50-50	NR NR	13 (36) 8 (22)	NR	13 (36)	NR
Alvarez [18]	2015	30	ISGL + 50-50	0	4 (13)	13 (43)	9 (31)	0
Wanis [37]	2017	30	ISGLS 50-50	2 (7) 0	8 (31) 1 (4)	NR	8 (26)	0
Serenari [30]	2017	20	Bili > 7 all 3 ^d	1 (5) 0	1 (5) 3 (15)	5 (25) ^d	NR	1/1 (100)
Alvarez [38]	2013	15	ISGLS	3 (20)		5 (33)	4 (27)	0
Hernandez-Alejandro [39]	2015	14	ISGLS + 50-50	4 (29)		NR	2 (14)	0
Tanaka [34]	2015	11	ISGLS	2 (18)	4 (36)	4 (36)	2 (18)	0
Sala [40]	2012	10	ISGLS	2 (20)		2 (20)	0	0
Li [41]	2013	9	ISGLS	0	2 (22)	2 (22)	3 (33)	0
Vivarelli [42]	2015	9	50-50	0	1 (11.1)	4 (44.4)	NR	1/1 (100)
Ratti [43]	2014	8	ISGLS + 50-50	1 (13)	0	3 (38)	1 (13)	0
Matsuo [25]	2016	8	ISGLS	2 (25)		1 (13)	NR	0
Matsuo [26]	2017	8	ISGLS 50-50	3 (37.5) 0		3 (37.5)	NR	0

^aLiver-related mortality is the percent of 90-day mortality.

^bNumbers reported as futile vs. non-futile operations in the study.

^cPeak bilirubin criterion was modified in this study to reflect bilirubin > 7 mg/dl on postoperative day 5 due to data availability.

^dISGLS grade A was excluded in these studies.

PHLF = Posthepatectomy liver failure; ISGLS = International Study Group of Liver Surgery definition of liver failure according to Rahbari et al. [29]; 50-50: fifty/fifty criterion for liver failure according to Balzan et al. [13]; Bili > 7 = bilirubin > 7 mg/dl according to Mullen et al. [14]; NR = not reported.

Very few reports on ALPPS analyzed the morbidity and mortality under the aspect of whether they are actually caused by PHLF, the very reason why regenerative maneuvers like PVE, PVL, or ALPPS are performed in extended liver resection to start with. Curiously, studies on ALPPS do not report PHLF using any of the common metrics in their analyses. The 2 studies that dissected out morbidity and mortality after ALPPS in larger cohorts beyond established severity gradings and typing of complications came to the conclusion that the vast majority of complications is due to PHLF despite adequate liver volumes prior to stage 2 [9, 28]. The first registry analysis showed that of the 19/202 patients with 90-day mortality, 8 patients were judged to have liver failure by their clinicians and the incidence of liver failure by 50-50 criteria in all patients was 9% [28]. The second registry analysis focused entirely on mortality and showed that 21/28 (75%) mortalities were caused by liver failure and that 32% of all patients had liver failure using any of three criteria (ISGLS, 50-50, and peak bilirubin > 7 mg/dl). 20% of patients with liver failure died within 90 days after ALPPS [9].

Because PHLF presents in so many different ways, it remains difficult to attribute complications incurred to liver failure without formally assessing at least some to the accepted liver failure criteria based on postoperative laboratory values of INR (international normalized ratio) and total bilirubin at postoperative day 5 and beyond [13, 14, 29]. Meticulous reports on liver failure criteria should therefore be encouraged for any future reports on ALPPS outcomes. It is interesting to note that liver failure by ISGLS criteria in published series is only 8.3% [20] or 15% [30] in the 2 series in which HBS was performed to guide clinical management, and 36% in a series [16] in which no HBS was used. It suggests that clinical management with HBS may be able to avoid liver failure after ALPPS.

Interestingly, outcomes after ALPPS in the registry studies are very similar to outcomes reported for a contemporary series of 285 extended hepatectomies in an experienced liver resection center. Only 23% of these extended hepatectomies had preoperative PVE to increase the size of the FLR [31]. There was an incidence of PHLF of 28% and a mortality rate of 9%, and 84% of these mortalities

Tab. 2. Assessment of interstage liver function in relation to volume

Author [ref.]	Year	n	Baseline function assessment	Interstage functional assessment				LiMAx	MELD	functional KGR, %/day	volume KGR, %/day	Functional increase ^a , %	Volume increase, %	Days between stages, n
				ISGLS after stage 1	ICG	HBS	AI, %/min/m ²							
Linecker [17]	2016	47 vs. 481 ^b	7 vs. 6 MELD)	yes	NR	NR	NR	NR	NR	NR	NR	NR	77 vs. 70	5
Schadde [9]	2015	320	NR	yes	NR	NR	NR	NR	>10 ^c	NR	NR	NR	NR	14
Olthof [20]	2017	60	3.7 (AI) ^d	yes	NR	40.4	5.5 ^d	NR	NR	NR	NR	29	78	7–8
Kambakamba [16]	2016	36	3.6 (ICG-R15)	yes	5.4 (R15)	NR	NR	NR	NR	NR	6.9	NR	53.7	6
			22.3 (ICG-PDR)		20.2 (PDR)									
Alvarez [18]	2015	30	NR	yes	NR	41	NR	NR	NR	NR	13.8	NR	90	6
Serenari ^e [30]	2017	20	NR	yes	NR	30 vs. 41	0.94 vs. 2.07	13 vs. 23	NR	NR	NR	NR	NR	6
Tanaka [34]	2015	10	NR	yes	NR	47.6	NR	NR	NR	NR	NR	52	54	7
Sparrelid [21]	2017	9	9.9 (ICG-R15)	NR	7 (R15)	33.9	2.6	NR	NR	4.7	9.4	28	57	6
			1.8 (AI)											
			25.3 (% of counts)											
Oldhafer [22]	2016	1	282 (LiMAx)	NR	NR	NR	NR	NR	245 then 371	NR	NR	-13 (LiMAx) then +31	60 then 82	7 then 11

^aBased on hepatobiliary scintigraphy, with the exception of the study using LiMAx.

^bNumbers reported as futile vs. non-futile operations in the study.

^cMELD > 10 indicates increased risk of 90-day mortality.

^dAmsterdam index was modified in this study to be expressed as %/min. Body surface area was not used in the calculation.

^eResults were provided as patients with liver failure vs. no liver failure. Combined results could not be calculated with the given data.

ISGLS = Post-resection liver failure criteria of the International Study Group for Liver Surgery; ICG = indocyanine green; ICG-R15 = indocyanine green clearance measured as plasma retention at 15 min (%); ICG-PDR = indocyanine green plasma disappearance rate (%/min); HBS = hepatobiliary scintigraphy; uptake in % = future liver remnant (FLR) function calculated by radioactivity count of FLR divided by total liver radioactivity count (%); AI = Amsterdam Index calculated using uptake kinetics between 150 and 350 s in %/min/m² as described by Dinant et al. [35]; HIBA = Hospital Italiano de Buenos Aires index calculated by multiplying total liver uptake between 150 and 350 s by uptake in % according to Serenari et al. [30]; LiMAx = liver maximum function capacity test based on hepatocyte metabolism (μg/h/kg); MELD = Model for End-Stage Liver Disease; KGR = kinetic growth rate (%/day); NR = not reported.

Tab. 3. Investigations into the mechanism of function and volume in ALPPS

Author [ref.]	Year	n	Subject	Method	Findings
Eshmuminov [23]	2017	16	hepatocyte proliferation	human histology MRI	no increased steatosis or cellular edema
Olthof [44]	2016	12	functional vs. volume growth in rabbits after ALPPS	HBS	volume but no functional increase when compared to PVE in rabbits
Sheng [24]	2017	10	hepatocyte proliferation	DKI IHC	true liver hypertrophy in ALPPS
Matsuo [25]	2016	8	hepatocyte maturity	human histology IHC electron microscopy	immaturity of hepatocytes
Matsuo [26]	2017	8	bile duct canaliculi network maturity	human histology IHC electron microscopy	structurally and functionally immature bile canalicular network

MRI = Magnetic resonance imaging; HBS = hepatobiliary scintigraphy; PVE = portal vein embolization; DKI = diffusion kurtosis imaging; IHC = immunohistochemistry.

ties fulfilled ISGLS criteria for liver failure. In contrast, a recent meta-analysis on outcomes after 459 2-stage hepatectomies for colorectal liver metastases reported a mortality rate of only 3% and a major complication rate of 40% without further information on liver failure criteria [10]. The 2-stage hepatectomy approach with the regenerative liver surgery maneuvers of PVE and PVL should improve the morbidity and mortality of extended resections. Given these data, it is fair to conclude that ALPPS has the same risk of liver failure, mortality, and complications incurred by extended resection and does not seem to reduce this risk.

The most important practical question in clinical ALPPS management is how to assess function and volume prior to proceeding to stage-2 resection. The overarching problem in the field of measuring liver function in ALPPS remains that HBS so far appears to be the only available tool to measure regional liver function in the western world [32] but there is no standardized methodology of HBS that is easily reproducible. Despite this, all 5 studies using HBS in ALPPS, including 1 case report [33], converge on the fact that while there is some increase in liver function in the FLR after ALPPS, the functional increase is always less than the volume increase between stage 1 and stage 2 (table 2). Most worrisome are the 2 studies that use HBS uptake kinetics to quantify regional liver function (also called the ‘Amsterdam index’). Both studies come to the conclusion that the functional increase of the FLR after ALPPS is only 37% [20] or 49% [31] of the volume increase, respectively. Such findings indicate that volume, currently the principal determinant for progression to the second stage, overestimates the function of the FLR by up to 50%, which may easily explain the high incidence of liver failure despite adequate volume. In the study of 27 patients with paired measurements, only 7 patients achieved an increase in liver function in their FLR beyond 50%, and 4 of these patients took more than 7 days to get beyond 50% function [20].

In the first reports, HBS was quantified by giving the proportion of scintigraphic signal that can be captured during the uptake phase or during the entire scan from the FLR and the portal vein-

deprived side [18]. The downside of this ‘% of counts’ technique is that it does not indicate a drop in liver function in case the overall liver function decreases. It simply provides clinicians with a proportion of total function without quantifying total function. The study that reported a volume increase of 52% with a functional increase of 54% used this methodology and appears to indicate a congruence of volume and function increase [34].

In contrast, the Amsterdam group has long ago developed a method to derive liver function from uptake kinetics between 150 and 350 s after injection using the HBS scan, and established their index for liver function expressed as uptake per min per m² [32]. Based on a series of liver resections, it has been shown that 2.7%/min/m² likely represents adequate liver function to master metabolic demands after resection [35]. An initial case report of this methodology in ALPPS [33] and a subsequent study using this methodology showed an astonishing functional deficit of the rapidly volume-increased liver [20].

The 2 studies with paired measurements prior to stage 1 and prior to stage 2 had too few outcome events to allow a solid C-statistic to determine a cut-off for preoperative liver function for the FLR [20, 31]. Studies with no paired measurements before and after stage 1 are not able to provide information on the effect of rapid hypertrophy on function changes [30], but they may provide information on when to proceed with stage 2 based on functional data. The Buenos Aires group attempted to develop a cut-off, but unfortunately they invented a new HBS metrics model, the ‘Hospital Italiano of Buenos Aires (HIBA)’ score, which makes their results difficult to compare to other uptake kinetics data published so far and difficult to reproduce for other centers [30]. Although there appears to be an emerging consensus among many groups that ALPPS should not be performed without HBS regional liver function tests prior to stage 2, the newly developed HIBA score cut-off of 15% has to first be validated by other centers.

Of course the lack of congruence of volume and function after ALPPS has to be explained mechanistically. The first concern

Tab. 4. Modifications of ALPPS and available data on liver failure and function

Author [ref.]	Year	n	Modification	Volume increase, %	PHLF, n (%)	PHLF criteria used	Clavien-Dindo grade 3a or higher, n (%)	Clavien-Dindo grade 3b or higher, n (%)
Robles [27]	2016	22	ALTPS	61	3 (14)	NR	NR	NR
Wang [45]	2017	10	RALPPS	53	0	NR	NR	2 (20)
Petrowsky [46]	2015	6	p-ALPPS	60	0	NR	NR	2 (33)
Gall [47]	2014	5	RALPPS	62	0	NR	0	0
De Santibanes [48]	2016	4	Mini ALPPS	63	0	50-50	NR	NR
Peng ^a [49]	2016	4	TBPVE	66	NR	NR	NR	NR
Li [50]	2014	2	Hybrid ALPPS	76	0	NR	1 (50)	NR

^aFull text paper was not available in English; abstract was published in English and was used for data.

PHLF = Posthepatectomy liver failure; ALTPS = Associating Liver Tourniquet with Portal vein ligation for Staged hepatectomy; modification of ALPPS where a tourniquet is used to obliterate the flow between the portal vein-supplied and the portal vein-deprived part of the liver; RALPPS = radiofrequency-assisted ALPPS where transection is replaced by radiofrequency ablation; p-ALPPS = partial ALPPS where only partial transection is performed instead of complete transection; TBPVE = terminal branches portal vein embolization, a variation of PVE pioneered in China; NR = not reported.

raised was that the rapid and extensive volume increase in ALPPS is not true cellular proliferation of functioning hepatocytes, but interstitial edema or intracellular fat accumulation/regenerative steatosis. 2 MRI studies, 1 in patients and 1 in rats, have now debunked this concern [23, 34]. Both studies show convincingly that ALPPS induces true cellular proliferation.

Interestingly, both hepatocytes and bile duct canaliculi, however, displayed characteristics of immaturity in histology [25, 26]. Whether these deficiencies are a transient or permanent defect of rapid hypertrophy has yet to be determined. The studies suggest that progressing to stage 2 within a week may be premature despite the impressive volumetric increase.

It may well be that the problem with liver function is an intrinsic problem only for classic ALPPS, and that the modified ALPPS approaches overcome the problem of volume/function. Unfortunately, the reports on ALPPS modifications report on very small series of patients and are generally limited to demonstrating a volume increase as large as that seen in classic ALPPS. The main focus of these reports seems to be to develop less invasive procedures based on the assumption that the complications of ALPPS stem largely from surgical severity and lack of experience of the surgeons. Functional studies of the FLR have not been added to these reports on modifications, and the awareness of the volume/function problem is limited. At this stage, reports on modifications should carefully address PHLF or, even better, evaluate liver function before and after ALPPS using metrics like HBS, LiMAx, or ICG.

The limitations of this review are primarily the small number of published studies in an emerging field as well as the small sample size in each study. It also appears that clinicians reporting on their experience with ALPPS have only limited access to liver function tests such as HBS, LiMAx, or ICG. There also remains the concern of a reporting bias across all the small uncontrolled series, especially the reports from the voluntary international ALPPS registry which has not been subject to independent monitoring or audit.

Conclusion

In summary, ALPPS has a high incidence of liver failure caused by a discrepancy between volumetric growth and functional increase of the FLR, which is alarming and needs to be better understood. Direct measurement of regional liver function may protect from liver failure after stage 2, but there is no consensus on reliable metrics. So far, there is no proof that efforts to improve ALPPS by modifications are effective to address this problem. Until these questions are addressed, ALPPS should be considered to be an experimental procedure and only be used in a highly controlled research environment.

Disclosure Statement

The authors do not have a conflict of interest for this article.

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