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Evolution of minimally invasive techniques and surgical outcomes of ALPPS in Italy: a comprehensive trend analysis over 10 years from a national prospective registry

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Abstract

Background Since 2012, Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) has encountered several modifications of its original technique. The primary endpoint of this study was to analyze the trend of ALPPS in Italy over a 10-year period. The secondary endpoint was to evaluate factors affecting the risk of morbidity/mortality/post-hepatectomy liver failure (PHLF).

Methods Data of patients submitted to ALPPS between 2012 and 2021 were identified from the ALPPS Italian Registry and evaluation of time trends was performed.

Results From 2012 to 2021, a total of 268 ALPPS were performed within 17 centers. The number of ALPPS divided by the total number of liver resections performed by each center slightly declined ($APC = -2.0\%$, $p = 0.111$). Minimally invasive (MI) approach significantly increased over the years ($APC = +49.5\%$, $p = 0.002$). According to multivariable analysis, MI completion of stage 1 was protective against 90-day mortality ($OR = 0.05$, $p = 0.040$) as well as enrollment within high-volume centers for liver surgery ($OR = 0.32$, $p = 0.009$). Use of interstage hepatobiliary scintigraphy (HBS) and biliary tumors were independent predictors of PHLF.

Conclusions This national study showed that use of ALPPS only slightly declined over the years with an increased use of MI techniques, leading to lower 90-day mortality. PHLF still remains an open issue.

Keywords Outcomes · ALPPS · Hepatectomy · Minimally invasive · Laparoscopy

The first description in 2007 at the University of Regensburg passing through the first large series published in 2011 [1] and the subsequent foundation of the International Registry [2], up to the publication of the results of the first Randomized Controlled Trial (LIGRO trial) [3] were the overall milestones in the fascinating and troubled history of ALPPS.

The members of the ALPPS Italian Registry are listed in the acknowledgments.

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Despite the pervasive enthusiasm for a new technique with the recognized potential to increase the resectability rate of liver cancer and to expand the pool of patients eligible for curative treatment, on the other hand, persistent concerns were raised about the safety profile of this procedure.

The reaction of the hepatobiliary community was to provide recommendations on the use of this approach, aiming to maintain acceptable morbidity and mortality rates, hence, the first International consensus was held in Hamburg in 2015 and the conclusions of this meeting were subsequently published in 2016 [4], thus becoming available on a large scale. In Italy the same desire to track and study the use, outcomes, and evolutions of this technique has led to the implementation of a dedicated Registry [5], which has traced the national ALPPS trends over the years and constituted the basis for specific studies [6]. Several hepatobiliary centers in

Italy were indeed contacted in January 2012 and offered the opportunity to participate in a national ALPPS Registry [5].

In these 10 years, ALPPS has resulted in the description of alternative non-surgical techniques with the rationale of being less invasive such as combining portal vein embolization (PVE) with partial parenchymal transection (PPT). On the other hand, the use of minimally invasive (MI) surgical approaches, laparoscopic and robotic, has also penetrated the ALPPS experience [6].

The primary aim of this study was to analyze the trends and the outcomes of ALPPS over 10 years on a national basis. The secondary endpoint was to evaluate factors, within a uni- and multivariable analysis, affecting the risk of morbidity/mortality/post-hepatectomy liver failure (PHLF). The allocation to MI approach within the whole series was also explored.

Methods

Study design

Data of patients enrolled in the ALPPS Italian Registry from its establishment (September 2012) to June 2021 were identified and constituted the study population. Detailed characteristics of the ALPPS Italian Registry are described elsewhere: briefly, it is a prospective intention-to-treat Registry open to inclusion of cases from any Italian center performing ALPPS, without any restriction criteria based on the numerosity of ALPPS performed [5]. The ALPPS Italian Registry was approved by the individual ethical committee of each center. Data entered into an anonymized database were monitored by the study coordinator in Maggiore Hospital (IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy) to check for data completeness and rule out an abnormal rate of missing variables.

To fulfill the *primary endpoint*, time-trend evaluation was conducted analyzing per year:

a) The number of centers performing ALPPS.
b) The number of ALPPS performed/divided by the total number of hepatic resections (HR) performed by each center.
c) The use of PVE, PPT, interstage hepatobiliary scintigraphy (HBS), and MI techniques.
d) The incidence of overall major morbidity, PHLF (after stage 2), and 90-day mortality.

To achieve the *secondary endpoint*, all perioperative factors potentially affecting the risk of morbidity/mortality/PHLF and all the preoperative factors potentially affecting the enrollment to MI techniques were screened and entered the uni- and multivariable analysis. A time threshold based on the year of publication of the recommendations from Oldhafer et al. [4] was used to divide the study population into 2 eras (2012–2016; 2017–2021) and to adjust the results of the multivariable analysis.

Variables

Complications were classified according to the Clavien classification [7] of surgical complications: those graded ≥ IIIA were considered a "major" complication. PHLF was classified according to the International Study Group of Liver Surgery definition [8] but only clinically significant PHLF (grade B/C) was considered. Mortality was defined as any death occurring during the interval of both stages or within 90 days after stage 2.

Liver remnant volumes were assessed using cross-sectional imaging by computed tomography (CT) and standardized future liver remnant (sFLR) was assessed in each patient using the Vauthey formula: $-794.41 + 1267.28 \times$ body surface area (m2) [9]. FLR/BW was calculated as the ratio (%) between FLR volume and patient's body weight (BW), assuming a mean physical liver density of 1.00 g/mL [10]. Interstage HBS was performed according to single institution protocols, together with liver volumetry, to assess liver function before proceeding to stage 2 [11].

Highly experienced MI liver surgery (MILS) centers were defined as those centers performing on average over the 10-year period at least 30% of their cases by MI approach (laparoscopic and/or robotic) [12]. Total number of HR per year was also provided by each center in order to calculate the ratio ALPPS/HR. High-volume centers were defined as those performing on average over the 10-year period > 100 HRs per year [13].

Surgical technique

Participation to the ALPPS Italian Registry did not superimpose a specific surgical technique, which was defined according to single institutions preference and protocols. The nomenclature defined in the first report from the International ALPPS Registry was used to describe ALPPS resection types [14]. Partial ALPPS was performed in the same setting as complete ALPPS with PPT as the only difference (i.e., transection down to the level of hepatic veins without compromising hepatic inflow or outflow [4]).

Statistical analysis

Differences in baseline characteristics of patients were assessed using the Mann–Whitney test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate. A time-trend analysis was performed using the annual percent change (APC) as the summary measure for the rate of change over the period 2012–2020. In our analysis, the APC was estimated by fitting a log-linear regression model, assuming the heteroscedasticity and uncorrelation of the random errors based on the Poisson distribution. Time-trend analysis was conducted with Joinpoint Regression Program V.4.8.0.1 (April 2020; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). Univariable logistic regression analysis was used instead for the independent effects of considered variables on inclusion to MILS, major morbidity, 90-day mortality, and PHLF. All variables associated at univariable analysis with a p value < 0.20 were included in the multivariable analysis. The variables were entered into a backwards stepwise logistic regression for the final model. Predictors were discarded at a p value > 0.20. To allow for the convergence to finite estimates in conditions of separation because of the rarity of some of the potential outcomes, a penalized Firth logistic regression was used. All data were analyzed using Stata version 15 (StataCorp. 2017. *Stata Statistical Software: Release 15.* College Station, TX: StataCorp LP). All tests were two sided and the significance level was set at 5%.

Results

During the 10-year period, a total of 268 ALPPS were enrolled within 17 centers active in the ALPPS Italian Registry providing their data on an intention-to-treat basis. The median number of cases entered into the Registry by each center was 10 ranging from 3 to 54 (Supplementary Fig. 1). Overall, 247 out of 268 (92.2%) ALPPS were successfully completed. Within the centers participating to the Registry, 10 out of 17 (58.8%) were highly experienced MILS centers, whereas 7 out of 17 (41.2%) were high-volume centers for liver surgery. The median age of the patients was 63 (range 24–84) and there were 169 males (63.1%). The baseline characteristics of the 268 study patients are shown in Supplementary Table 1.

Trends

The number of centers performing ALPPS did not significantly change over the years ($APC = +0.6\%$, 95% CI − 0.47% to + 6.2%, $p = 0.797$) (Fig. 1a). The number of ALPPS cases increased from 22 in 2012 to 28 in 2020 ($APC = +3\%$, 95% CI − 1.3% to + 7.5%, $p = 0.146$) (Fig. 1b). However, dividing the number of ALPPS by the total number of liver resections performed by the same centers, ALPPS/HR slightly declined over the study period from 2.5% in 2012 to 2.4% in 2020 ($APC = -2.0\%$, 95% CI − 4.6% to + 0.6%, $p = 0.111$) (Fig. 1c).

Trends in the proportion of each indication were then evaluated to assess general shifts in utilization of ALPPS for most common liver tumors. ALPPS for PHCC decreased from 19% in 2012 to 17.9% in 2020 ($APC = -6.1\%$, 95% CI − 22.7% to + 13.9%, $p = 0.462$). A less pronounced decrease was observed for CLRM from

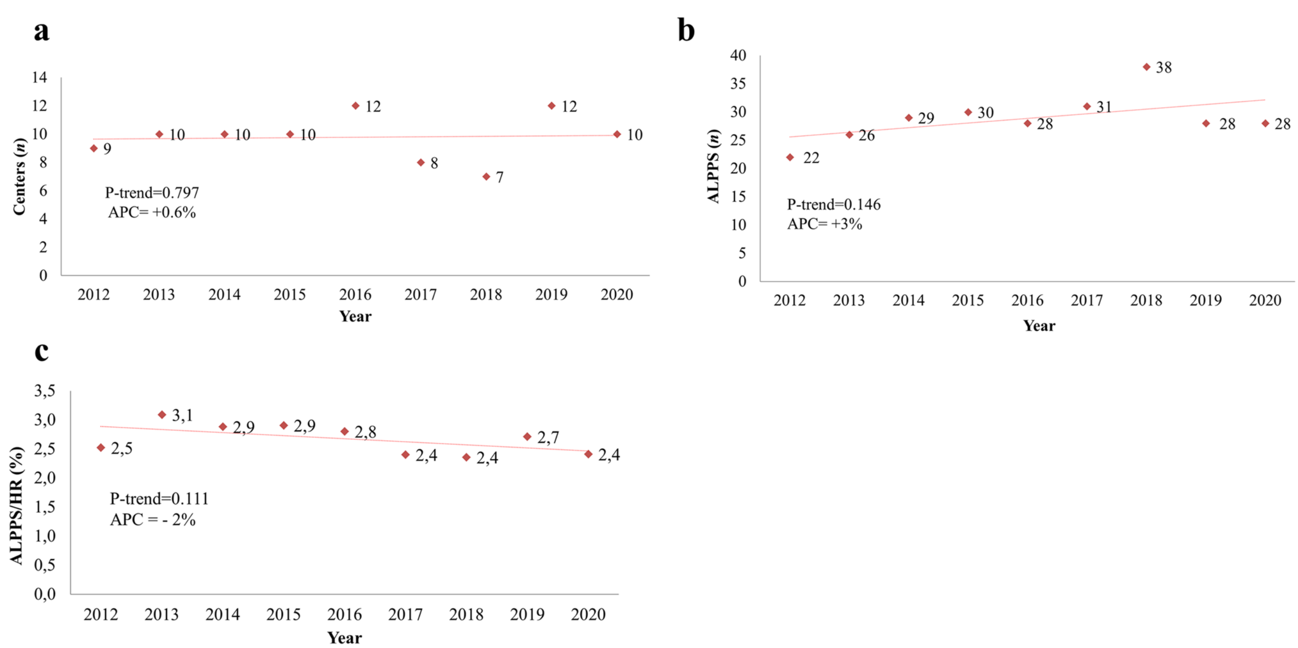

Fig. 1 Yearly trend of number of centers (**a**), number of Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) (**b**), and ALPPS on overall number of hepatic resection (HR) (**c**) performed from 2012 to 2020. APC, annual percent change

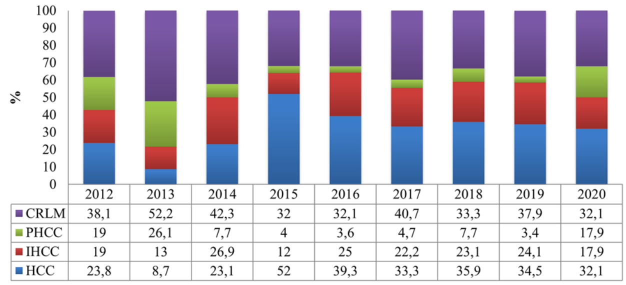

Fig. 2 Column chart showing the trend of indications (%) for Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) from 2012 to 2020. CRLM, colorectal liver metastases; PHCC, perihilar cholangiocarcinoma; IHCC, intra-hepatic cholangiocarcinoma; HCC, hepatocellular carcinoma

38.1% in 2012 to 32.1% in 2020 ($APC = -$ 1.8%, 95% CI − 6.3% to + 3%, $p = 0.398$), whereas ALPPS for IHCC ($APC = +$ 3.7%, 95% CI − 5.6% to + 13.8%, $p = 0.392$) and HCC ($APC = +$ 5.8%, 95% − 5.8% to + 18.7%, $p = 0.289$) increased over the years, the latter increasing from 23.8% in 2012 to 32.1% in 2020 (Fig. 2).

With regard to the portal vein occlusion technique chosen for liver hypertrophy, PVE was increasingly and significantly performed over the years from 4.5% in 2012 to 46.4% in 2020 ($APC = +$ 30.4%, 95% CI + 12.5–51.2%, $p = 0.004$). Partial parenchymal transection was also progressively adopted from 4.5% in 2012 to 53.6% in 2020 ($APC = +$ 14.3%, 95% CI + 3.3% to + 26.5%, $p = 0.017$). (Supplementary Fig. 2a, b) Interstage HBS has become to be included as part of the functional assessment since 2015. Thereafter, it has increased over the years until 2020 when it was performed in 35.7% of all cases ($APC = +$ 32.2%, 95% CI − 2.5% to + 79.2%, $p = 0.067$). Of note, only 3 centers routinely performed HBS (Supplementary Fig. 2c).

Minimally invasive approach of stage 1 has been more and more frequently adopted (10 centers) over the years and has significantly increased since 2015, in particular from 3.3% in 2012 to 46.4% in 2020 ($APC = +$ 49.5, 95% CI + 22.2% to + 83%, $p = 0.002$). MI approach of stage 2 was less widespread (4 centers) but has raised since 2017 from 3.4% to 30.4% in 2020 ($APC = +$ 55.4%, 95% CI + 30.7% to + 84.7%, $p = 0.001$) (Fig. 3a, b).

Post-hepatectomy liver failure (following stage 2) decreased from 45.5% in 2012 to 26.1% in 2020 ($APC = -$ 7.2%, 95% CI − 12.5% to + 0.6%. $p = 0.067$) (Fig. 4a) as well as major morbidity from 52.4% in 2012 to 28.5% in 2020 ($APC = -$ 6.6%, 95% CI − 12.9–0.2%, $p = 0.056$) (Fig. 4b). Ninety-day mortality slightly declined over the study period from 18.2% in 2012 to 17.9% in 2020 ($APC = -$ 3.1%, 95% CI − 12.4% to + 7%, $p = 0.474$) (Fig. 4c).

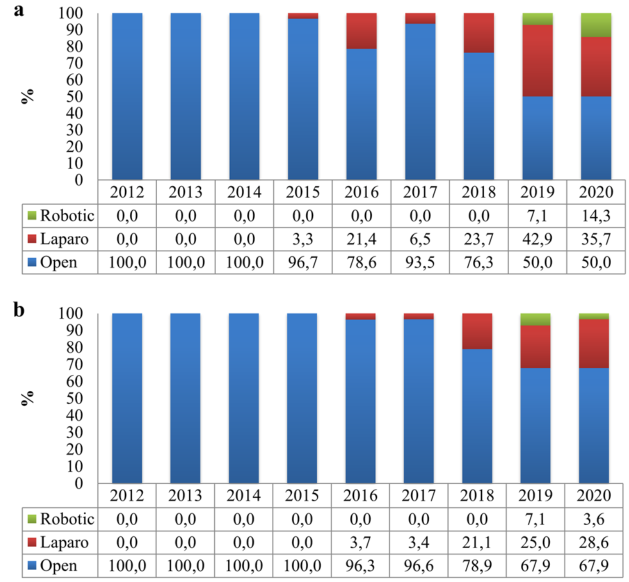

Fig. 3 Column chart showing the percentage of cases (first stage, **a**—second stage **b**) per year approached either laparoscopically or robotically from 2012 to 2020

Minimally invasive ALPPS

Overall, 47 out of 268 cases (17.5%) were approached using a MI technique of which 41 laparoscopically and 6 robotically. Among them, 2 (4.3%) were converted to open due to bleeding ($n = 1$) and adhesions ($n = 1$). Twenty-eight out of the 45 patients (62.2%) who completed stage 1 by MI technique were approached at the second stage laparoscopically ($n = 25$) or robotically ($n = 3$). Only one patient received laparoscopic resection at the second stage after an initial open first stage. Eight out of 29 patients (27.6%) were converted. Reasons for conversion were adhesions ($n = 4$), bleeding ($n = 3$), and oncological concerns ($n = 1$).

When analyzing the perioperative outcomes of stage 1 of ALPPS (Table 1) and comparing MI cases with open cases, PPT of the liver (75.6% vs. 26%) and PVE (53.3% vs. 11.7%) were significantly ($p < 0.001$) more performed within MI cases. With regard to postoperative outcomes, overall morbidity was significantly lower after MI approach (11.1% vs. 14.8%, $p < 0.001$). Also, discharge after stage 1 was significantly more implemented after MI surgery (82.2% vs. 15.7%, $p < 0.001$). Stage-2 MI completed cases were performed in median 15 days later compared to open cases (11 vs. 26 days, $p < 0.001$) (Table 2). Among analyzed outcomes, in-hospital mortality was nil after MI surgery vs. 10.6% after open surgery ($p = 0.116$), whereas PHLF was significantly reduced in MI cases (0% vs. 26.5%, $p = 0.007$). Hospital stays were significantly shorter after MI cases (13 vs. 22 days, $p = 0.001$).

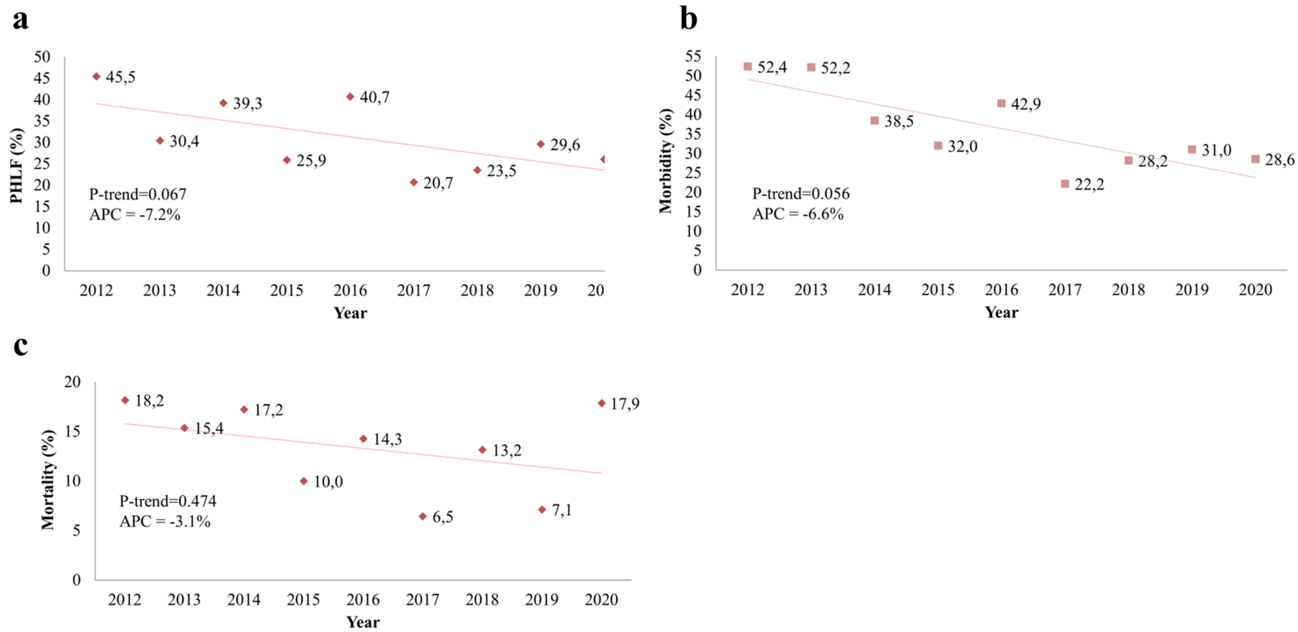

Fig. 4 Yearly trend of incidence of post-hepatectomy liver failure (PHLF) (**a**), major morbidity (**b**), and 90-day mortality (**c**) from 2012 to 2020

Table 1 Perioperative outcomes of stage 1 of overall study population and by comparing open vs. minimally invasive (MI) completion of stage 1

Variable	Total ALPPS ($n=268$)	Open ($n=223$)	MI ($n=45$)	*p* value
Parenchymal transection, *n* (%)				< 0.001
Complete	176 (65.7)	165 (74)	11 (24.4)	
Partial	92 (34.3)	58 (26)	34 (75.6)	
Portal vein occlusion, *n* (%)				< 0.001
PVL	218 (81.3)	197 (88.3)	21 (46.7)	
PVE	50 (18.7)	26 (11.7)	24 (53.3)	
Pringle Maneuver, *n* (%)	93 (34.7)	63 (28.3)	30 (66.7)	< 0.001
Operative time, min, median (IQR)	275 (210–360)	275 (210–360)	260 (200–385)	0.955
Simultaneous CR resection, *n* (%)	22 (8.2)	17 (7.8)	5 (11.1)	0.465
FLR cleaning, *n* (%)	61 (22.8)	47 (21.6)	14 (31.1)	0.167
Postoperative morbidity,	109 (40.5)	98 (43.9)	11 (24.4)	0.015
Major morbidity, *n* (%)	28 (10.4)	33 (14.8)	5 (11.1)	0.518
Perioperative mortality, n (%)	5 (1.9)	5 (2.2)	0	0.311
PHLF grade B/C, *n* (%)	15 (5.6)	13 (5.8)	2 (4.4)	0.712
Discharge before stage 2, *n* (%)	72 (26.9)	35 (15.7)	37 (82.2)	< 0.001
FLR/sTLV, %, median (IQR)	34.3 (28.7–43.2)	35 (28.7–43.4)	32 (28.7–40.3)	0.355
FLR/BW, %, median (IQR)	0.72 (0.61–0.91)	0.75 (0.62–0.91)	0.69 (0.61–0.85)	0.484
Time stage 1-CT, days, median (IQR)	9 (7–17)	8 (6–13)	21 (11–35)	< 0.001
Volume increase, %, median (IQR)	50 (30.3–78.1)	49.2 (30–77.7)	61.1 (35.9–85.7)	0.250
Completion of stage 2, *n* (%)	247 (92.2)	206 (92.4)	41 (91.1)	0.773

ALPPS associating liver partition and portal vein Ligation, *BW* body weight, *CCI* comprehensive complication index, *CR* colorectal, *CT* computed tomography, *IQR* interquartile range, *FLR* future liver remnant, *HBS* hepatobiliary scintigraphy, *MI* minimally invasive, *PHLF* post-hepatectomy liver failure, *PVE* portal vein embolization, *PVL* portal vein ligation, *sTLV* standardized total liver volume

Table 2 Perioperative outcomes of stage 2 of completed ALPPS and by comparing open vs. minimally invasive (MI) completion of stage 2

Variable	Completed ALPPS ($n = 247$)	Open ($n = 226$)	MI ($n = 21$)	p value
Time stage 1–2, days, median (IQR)	12 (8–20)	11 (8–17)	26 (20–36)	< 0.001
Type of hepatectomy, n (%)				0.924
Right	114 (46.2)	104 (46)	10 (47.6)	
Right extended	128 (51.8)	117 (51.8)	11 (52.4)	
Left	4 (1.6)	4 (1.8)	0	
Left extended	1 (0.4)	1 (0.4)	0	
Pringle maneuver, n (%)	73 (29.5)	49 (22.5)	24 (82.8)	< 0.001
Operative time, min, median (IQR)	239 (170–310)	210 (160–275)	340 (297–400)	< 0.001
Major morbidity, n (%)	75 (30.4)	76 (33.6)	4 (19)	0.172
PHLF grade B/C, n (%)	60 (24.3)	60 (26.5)	0	0.007
Hospital stay, days, median (IQR)	22 (17–31)	22 (17–31)	13 (11–19)	< 0.001
In-hospital mortality, n (%)	24 (9.7)	24 (10.6)	0	0.116
90-day mortality, n (%)	34 (12.7)	26 (11.5)	1 (4.8)	0.344
R0, n (%)	213 (86.2)	192 (84.9)	21 (100)	0.160

ALPPS associating liver partition and portal vein Ligation, *IQR* interquartile range, *MI* minimally invasive, *PHLF* post-hepatectomy liver failure

Multivariable analysis

Multiple logistic analyses demonstrated which variables were independent risk factors for major morbidity, 90-day mortality, and PHLF (Table 3). In particular, biliary tumors were predictors of both higher complications ($OR = 3.28$, 95% CI 1.82–5.88, $p < 0.001$), and mortality ($OR = 4.67$, 95% CI 1.88–11.58, $p < 0.001$). MI completion of stage 1 was protective against 90-day mortality ($OR = 0.05$, 95% CI 0.003–0.95, $p = 0.040$) as well as enrollment within high-volume centers for liver surgery ($OR = 0.32$, 95% CI 0.14–0.74, $p = 0.009$). The use of interstage HBS ($OR = 0.11$, 95% CI 0.02–0.49, $p = 0.026$) and biliary tumors ($OR = 2.26$, 95% CI 1.17–4.35, $p = 0.015$) were the only predictors of PHLF. Inclusion to MILS was significantly predicted by 2017–2021 era ($OR = 8.22$, 95% CI 3.46–19.55, $p < 0.001$) and by enrollment within highly experienced MILS centers ($OR = 5.74$, 95% CI 1.29–25.57, $p = 0.022$).

Discussion

The current study showed that use of ALPPS in Italy only slightly decreased over the last 10 years since its introduction. Conversely, a significant and increasing trend was observed with regard to the MI approach of ALPPS which

Table 3 Multivariable Logistic Regression Analysis

	Variable	OR	CI 95%	p value
Major morbidity	Biliary tumors	3.28	1.82–5.88	< 0.001
	ASA score (3–4)	2.26	1.28–3.98	0.005
	PVE	0.26	0.11–0.63	0.003
90-day mortality*	Biliary tumors	4.67	1.88–11.58	0.001
	Age	1.06	1.01.1.11	0.012
	High-volume centers	0.32	0.14–0.75	0.009
	MI stage1	0.05	0.003–0.95	0.040
PHLF[a]	HBS	0.11	0.02–0.49	0.026
	Biliary tumors	2.26	1.17–4.35	0.015
Inclusion to MILS	Era (2017–2021)	8.22	3.46–19.55	< 0.001
	Experienced MILS centers	5.74	1.29–25.57	0.022

ASA american society of anesthesiologists, *HBS* hepatobiliary scintigraphy, *MILS* minimally invasive liver surgery, *PHLF* post-hepatectomy liver failure, *PVE* portal vein embolization

*Firth logistic regression

[a]Analysis conducted on completed ALPPS

was associated with lower 90-day mortality. Interstage functional assessment by means of HBS was found to be a strong independent and protective factor against PHLF.

After the first report in 2012 [1], ALPPS seemed to be one of the most promising surgical techniques in the field of liver surgery. However, despite the early enthusiasm around ALPPS which led also to the creation of an International Registry [2], the first published series showed a very high rate of morbidity and mortality [14]. These series were able to demonstrate that complications were mostly related to unfavorable baseline patient characteristics. In particular, biliary tumors, older age, and decrease of liver function in the interstage were recognized as the most relevant predictors of ALPPS mortality [5, 15]. Some modifications of the original technique, such as the mini-ALPPS (PVE combined with PPT) [16] or use of interstage HBS [17], have been proposed aiming to improve these outcomes.

The ALPPS Italian Registry was born together with the initial implementation of the original technique, in an era still far from the recognition of the transversal importance of registries on a national and international scale. The creation of a national Registry specifically dedicated to ALPPS constituted a significant event as it represented the historical basis to follow the trends and evolutions of this technique in Italy, a country where hepatic surgery is performed by centers with heterogeneous features in terms of volume of activity, penetration of the MI approach, characteristics of patients, and disease treated [18]. It was created maintaining the criteria of inclusiveness (using broad inclusion criteria and few exclusion criteria) and representativeness (to provide a reliable representation of the national picture), which currently constitute—10 years after its foundation—the prerequisite for being able to pursue the primary and secondary objectives of this study.

Although recent studies showed a non-inferiority of ALPPS compared to the classical two-stage approach [3], the role of ALPPS has seemed to be cast aside in the recent years. However, in our study, the number of ALPPS when divided by the number of HR, only slightly decreased over the years, showing that the room dedicated to the ALPPS remained unchanged (about 2% of all liver resections), at least in Italy. What significantly changed, as showed in our trend analyses, were the modifications of the original technique, including the use of PPT, PVE, and the MI approach. In particular, MI approach of stage 1 has been increased over the years [19, 20]. This might be explained by the widespread of MI techniques in liver surgery as well as by the higher feasibility of the first stage using laparoscopic (and more recently robotic) techniques, at least compared to a second stage major hepatectomy. Our multivariable analysis showed that especially centers with higher experience in MILS resulted more prone to favor this approach in the most recent years. On the contrary, MI approach of the second stage, given its higher technical complexity related with reiterative surgery together with baseline difficulties described in right-sided hepatectomies [21–23], was less widespread. Of note, in our study, MI approach of stage 2 was attempted in almost two-thirds of MI first stages, confirming, however, the growing interest in completing laparoscopically or robotically the ALPPS procedure [24]. Although the risk of conversion in ALPPS still remains significant and higher compared with average conversion rates in MILS, conversion did not significantly affect the risk of morbidity and/or mortality, justifying such an approach [25].

The use of less-invasive techniques to perform the first stage of ALPPS has been showed to decrease the overall impact of surgery irrespectively from the approach chosen for stage 2 [6]. Similarly, in our study, MI completion of stage 1 was found to be significantly associated with decreased 90-day mortality, together with other well-known risk factors such as biliary tumors and older age. This could be explained by the fact that MI stage 1 was associated with a significant lower incidence of interstage complications, thus decreasing major complications after stage 2. In addition, high-volume centers for liver surgery were also found to be protective against 90-day mortality, suggesting that ALPPS should be performed not only by expert surgeons but also in the context of hospitals which can provide the best care for these complex patients especially when they develop postoperative complications, namely failure to rescue [26, 27]. For this reason, as it was recently suggested for pancreatic surgery, maybe it might be worth developing centralization policies also for complex liver surgery and/or disease as ALPPS is [28].

Last but not least, multivariable analysis showed that independent predictors of PHLF were interstage HBS and biliary tumors. Quite a few reports have been published to date regarding HBS in ALPPS [17, 29] showing a clear discrepancy between function (lower) and volume (higher), even though precise cutoffs for a safe second stage have not yet been established [30]. The use of interstage HBS as a confirmatory test before proceeding to stage 2 may have significantly decreased the incidence of PHLF (the latter demonstrating the steepest learning curve among all the outcomes analyzed in our study) thus making HBS one of the most useful tools in this setting. Regarding biliary tumors, the associated cholestasis commonly seen in PHCC may have significantly increased the risk of liver failure in these patients [5] given also that liver function cannot be predicted accurately by HBS since elevated plasma bilirubin affects the hepatic uptake of mebrofenin.

Due to the specific focus of the Registry on ALPPS since its foundation, the main limitation of the present report is the impossibility to evaluate the time trends and outcomes in relationship with the use of conventional techniques for liver hypertrophy and with new emerging technique. This limit may constitute the basis for the implementation of more comprehensive registries on liver hypertrophy techniques. Another limitation is that the small number of centers and adoption of Firth logistic regression prevented us from taking into account the clustering of patients within hospitals in the analysis, leading to potentially underestimated standard errors. The analysis of larger datasets with an adequate number of second-level units would allow overcoming this issue.

In conclusion, this study showed that use of ALPPS remained stable over the years with the introduction of several modifications of the original technique. Among them, an increased use of less-invasive techniques was evident leading to improved 90-day mortality. PHLF still remains an open issue in ALPPS and the use of interstage HBS is always highly recommended as well as performing ALPPS in experienced centers.

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Declarations

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