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REVIEW ARTICLE

Minimally Invasive Approach in the Setting of ALPPS Procedure: a Systematic Review of the Literature

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Abstract

Background Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) represents a new surgical technique for the resection of advanced hepatic malignancies with predicted insufficient future liver remnant. In some patients, ALPPS can be associated with an increased risk of poor outcomes. Minimally invasive surgery (MIS) has been proposed in combination with ALPPS with the intent to minimize this risk. We systematically evaluated the outcomes of MIS-ALPPS cases to compare the relative outcomes of open ALPPS versus MIS-ALPPS.

Methods A systematic review was done in accordance with the PRISMA guidelines. Search terms utilized included the following: ("ALPPS"[Title/Abstract] OR "associating liver partition and portal vein ligation for staged hepatectomy"[Title/Abstract] OR "in situ split"[Title/Abstract]) AND ("minimally invasive"[Title/Abstract] OR "laparoscopic"[Title/Abstract] OR "robotic"[Title/Abstract]).

Results Fifteen articles were identified, with a total of 27 patients reported. Colorectal metastatic disease was the most commonly observed indication for MIS-ALPPS (66.7%), followed by hepatocellular carcinoma (25.9%). Time passed from the first to the second stage ranged 7–30 days. MIS-ALPPS patients did not experience procedure failures between the first and second stages. Only four (15.4%) subjects had a grade IIIb complication. No perioperative mortality after the first or second stage was reported. Compared with open ALPPS, MIS-ALPPS demonstrated better results. Hospital stay duration ranged 8–33 days with a follow-up ranging 1–20 months.

Conclusions MIS-ALPPS appears to be safe, with potentially lower morbidities and mortalities relative to open patients. The present results should be considered with caution. A limited number of articles exist on this topic. Furthermore, selection biases exist when comparing open versus MIS-ALPPS data. Registry studies are needed to better define the outcomes of patients undergoing MIS-ALPPS.

Keywords Minimally invasive · Laparoscopic · Robotic · ALPPS

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Abbreviations

ALPPS	Associating liver partition and portal vein ligation for staged hepatectomy
CRLM	Colorectal liver metastases
HCC	Hepatocellular carcinoma
hCCA	Hilar cholangiocellular cancer
MIS	Minimally invasive surgery
NOS	Newcastle-Ottawa Quality Assessment Scale
PRISMA	Preferred Reporting Items for Systemic Reviews and Meta-Analyses
RALPP	Radiofrequency-assisted liver partitions with portal vein embolization for staged hepatectomy
sFLR	Standardized future liver remnant

Introduction

Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) represents a surgical innovation able to offer higher rates of resectability with respect to the conventional two-stage hepatectomy.[1] ALPPS can result in a more rapid increase in the functional standardized future liver remnant (sFLR).[2] Reports on ALPPS show high variability in indications, patient selection, and surgical strategies.[3,4] According to the first report of the international ALPPS registry, colorectal liver metastases (CRLM) are the most commonly observed indication, followed by hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA).[5]

After initial enthusiasm,[6] higher morbidity and mortality rates were reported in the first ALPPS case series.[7,8] Recently, new technical innovations have been proposed with the intent to minimize this risk.[9,10] As an example, the use of minimally invasive surgery (MIS) associated with ALPPS has shown promising results regarding operational safety and curative nature of the resection.[11] However, only a limited number of studies has been published explicitly investigating the combination of MIS and ALPPS.[12–26]

We aimed to systematically review the literature focused on the combined MIS-ALPPS approach, with the main end-point of analyzing the possible positive impact of MIS on clinical outcomes. The second end-point was to compare the outcomes of patients undergoing MIS-ALPPS versus subjects treated with open ALPPS.

Materials and Methods

Search Strategy

A systematic search identified studies focused on the role of MIS in the setting of ALPPS. The search strategy was done according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines, as well as PRISMA for abstracts.[27] A search of the electronic databases MEDLINE and PubMed was conducted using the following research terms: ("ALPPS"[Title/Abstract] OR "associating liver partition and portal vein ligation for staged hepatectomy"[Title/Abstract] OR "in situ split"[Title/Abstract]) AND ("minimally invasive"[Title/Abstract] OR "laparoscopic"[Title/Abstract] OR "robotic"[Title/Abstract]). Studies published before May 1, 2018, were taken into consideration.

Screening Process

The present qualitative systematic review included a priori search criteria of journal articles among adult (age ≥ 18 years) human patients. Studies were limited to the English language.

Exclusion criteria were as follows: (a) studies reporting non-MIS-ALPPS procedures, (b) papers lacking sufficient details, (c) review articles, (d) nonclinical studies, (e) expert opinions, (f) letters, and (g) conference summaries. Case reports were considered for the analysis.

Study Selection

Two reviewers (FM and FG) independently screened the identified studies and the extracted data. In case of disagreement, the paper was discussed by all the authors.

Quality Assessment

Selected studies were reviewed based on representativeness of the study population, comparability of cohorts, adequate assessment of outcomes, sufficient duration of follow-up, adequacy of follow-up, and source of study funding. The quality of the studies was assessed using the Newcastle-Ottawa Quality Assessment Scale: studies with scores > 6 were defined as high-quality ones.[28]

The characteristics of each study were collected (Table 1). The following features were collected: first author's name, reference of the study, year of the study, number of cases, patient age, patient gender, liver segments involved by tumor, tumor type, number of full MIS cases, number of cases treated with laparoscopic first stage and open second stage, blood loss during the two stages, operative time during the two stages, sFLR values reported before the first and the second stages, time between the two stages, Clavien-Dindo >IIIA complication,[29] duration of hospital stay, and months of follow-up.

Results

The selection process of the articles is shown in Fig. 1. A total of 32 articles for screening was initially identified. After checking the references of these articles, four additional studies were identified and included in the screening. Sixteen and five articles were removed after the evaluation of title/abstract and full text, respectively. Lastly, 15 articles were identified ($N = 27$) (Table 1).[12–26]

All the selected articles were case reports or case series. Consequently, a Newcastle-Ottawa Quality Assessment Scale value was impossible to estimate as the study quality was generally poor on this topic.

In the 27 patients, age ranged 33–76 years. Sixteen (59.3%) patients were males and ten (37.0%) females; in one (3.7%) case, no gender was specified.

CRLM were reported in 18 (66.7%) subjects, HCC in seven (25.9%), and CCA poly-adenomatosis in one (3.7%). In 26 (96.3%) patients, both first and second ALPPS stages were

Table 1 Main characteristics of the patients undergoing MILS-ALPPS

Author (reference)	Year	Number	Age (ranges)	Sex (M/F)	Liver segments involved	Tumor type	Full MILS = Y	Blood loss in stage 1/ stage 2 (mL), median (range)		Operative time in stage 1/stage 2 (min), median (range)		sFLR prior to stage 1/ stage 2 (%)		Time between stages (days)	Cumulative CD > IIIA	LOS (days, range)	FU (months)
Brustia R[12]	2013	1	45	F	4	Poly-adenomatosis	Y	NA	NA	300	300	22	39	7	N	15	NA
Cai X[13]	2014	1	64	M	4	HCC	Y	100	300	315	215	36	38	14	N	NA	NA
Xiao L[14]	2015	1	NA	NA	4	HCC	Y	NA	NA	255	210	27	41	13	N	12	4
Gringeri E[15]	2015	1	66	M	5	HCC	Y (RALPP)	0	0	120	215	16	30	10	N	18	NA
Gall T[16]	2015	4	62 (48–71)	3/1	5	CRLM	Y	NA	NA	140	NA	NA	NA	NA	N	NA	3
Cillo U[17]	2015	1	53	M	7	CRLM	Y	0	700	170	630	NA	NA	15	N	10	2
Vicente E[18]	2016	1	58	M	6	CRLM	Y	NA	NA	NA	NA	28	40	13	NA	NA	NA
Boggi U[19]	2016	1	64	F	1	hCCA III-A	N (stage 1 = MIS) (RALPP)	0	150	NA	NA	25	42	15	N	25	20
Jiao L[20]	2016	1	76	M	6	CRLM	Y (RALPP)	0	600	110	350	26	39	14	N	33	NA
Surjan R[21]	2016	1	65	M	7	CRLM	Y	150	100	250	200	26	37	21	N	26	11
Machado MA[22]	2017	1	42	F	7	CRLM	Y (reversal)	0	0	300	180	NA	NA	21	N	10	18
Machado MA[23]	2017	10	58 (36–69)	6/4	7 (6–8)	9 CRLM, 1 HCC	Y	200 (110–300)	320 (150–800)	300 (208–340)	180 (140–300)	19 (13–30)	39 (29–51)	21 (9–30)	N	11 (8–20)	NA
Rong Z[24]	2017	1	33	F	3	HCC	Y (RALPP)	0	100	60	240	21	32	22	N	32	1
Ha HT[25]	2017	1	44	F	4	HCC	Y	NA	NA	260	130	22	30	9	N	16	15
Pekolj J[26]	2018	1	61	M	4	HCC	Y (MIS-AL-PPS)	0	NA	150	300	23	37	10	N	8	NA

M male, *F* female, *MIS* minimally invasive surgery, *Y* yes, *N* no, *sFLR* standardized future liver remnant, *CD* Clavien-Dindo, *LOS* length of stay, *FU* follow-up, *NA* not available, *HCC* hepatocellular carcinoma, *RALPP* radiofrequency-assisted liver partition with portal vein embolization for staged hepatectomy, *CRLM* colorectal liver metastasis, *hCCA* hilar cholangiocarcinoma, *ALPPS* associating liver partition with portal vein ligation for staged hepatectomy

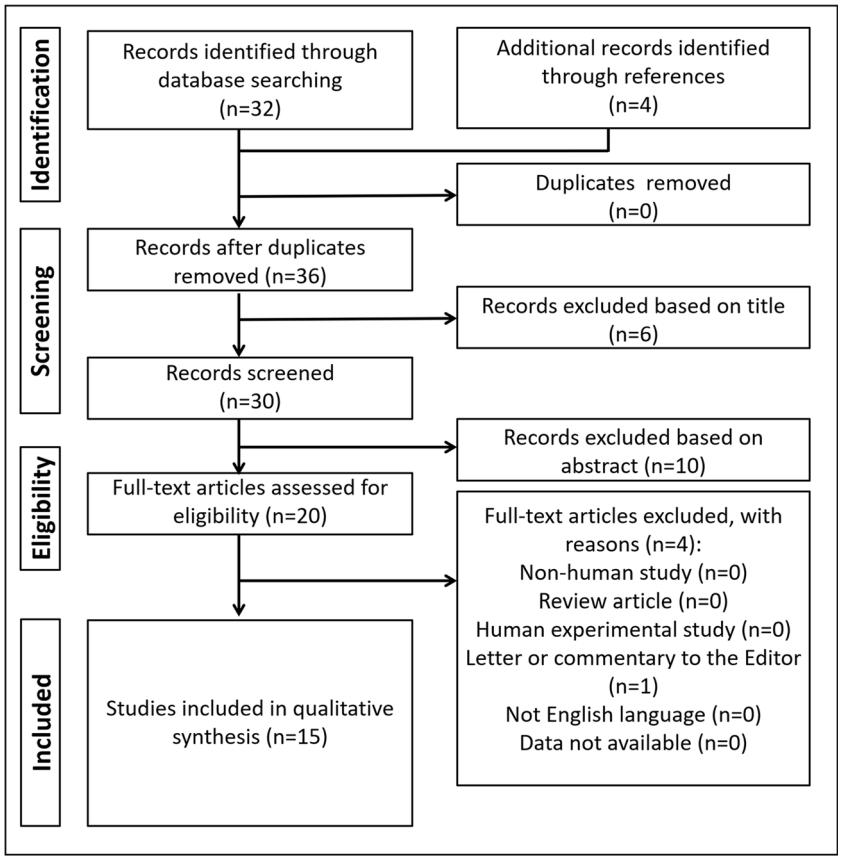

Fig. 1 PRISMA flow chart showing the selection process of the analyzed articles

completed in a minimally invasive way. In particular, 18 (66.7%) procedures were laparoscopic ALPPS, three (11.1%) laparoscopic radiofrequency-assisted liver partitions with portal vein embolization for staged hepatectomy (RALPP), one (3.7%) laparoscopic reversal ALPPS, one (3.7%) laparoscopic mini-ALPPS with portal embolization, and one (3.7%) laparoscopic ALPPS with a round-the-liver ligation. In one case (3.7%), the first stage was completed with a minimally invasive procedure (laparoscopic RALPP) and the second with an open approach.

Data on blood loss during the two ALPPS stages were reported in 19 patients. No blood losses were reported in 7 on 19 (36.8%) subjects during the first stage. A maximum value of 300 cm^3 was observed in the remaining 12 subjects. During the second stage, two (10.5%) patients had no hematic loss. A maximum value of 800 cm^3 was reported in the remaining 17 subjects. In the entire population, a blood transfusion was required in three (11.1%) patients. Operative times ranged 60–340 min and 140–630 min in the first and second stages, respectively.

In 21 cases, the estimated sFLR value before the first stage was < 30% in all but one patient (mean = 22%). The absolute sFLR value after the first stage always increased (> 30%, mean = 38%). The relative sFLR calculated comparing the values before and after the first stage always increased (mean = 78%). Seventeen of 21 (81.0%) patients reported a relative liver growth of > 50%.

The time passed between the first and second stages ranged 7–30 days, with no failures reported between the stages. According to the Clavien-Dindo classification, four (15.4%) patients had a complication grade ≥IIIa after the first or second stage. No perioperative mortality was reported. Patient duration of hospital stay ranged 8–33 days, with a follow-up ranging 1–20 months.

Comparing the 27 MIS-ALPPS patients with six different open ALPPS studies,[1,23,30–33] laparoscopic patients had better results (Table 2, Fig. 2a–d). No failures were reported between the two stages in MIS-ALPPS patients, while the open series reported rates ranging 0–25% (Fig. 2a). Complication rates were lower in MIS-ALPPS patients, with 15.4% versus 31.5–73.3% of complication rates reaching at least a grade of IIIa after the first or second stage in MIS-ALPPS and open ALPPS, respectively (Fig. 2b). Similarly, 15.4% versus 19.1–46.7% of complications classified at least a grade of IIIb after the first or second stage were observed in MIS-ALPPS and open ALPPS, respectively (Fig. 2c). No in-hospital deaths were observed in the MIS-ALPPS series, while reported mortality ranged 0–26.7% in the open series (Fig. 2d).

Table 2 Comparison of the MIS-ALPPS cases with monocenter or registry studied based on exclusively open ALPPS cases

Variables	MIS-ALPPS ($n = 27$)[12–26] *N* (%)	Machado ($n = 20$)[23]	Ratti ($n = 8$)[30]	Schnitzbauer ($n = 403$)[31]	Alvarez ($n = 15$)[32]	Schnitzbauer ($n = 25$)[1]	Nadalin ($n = 15$)[33]
Male gender	16 (61.5)*	12 (60.0)	6 (75.0)	259 (64.3)	9 (60.0)	14 (56.0)	7 (46.7)
Tumor type							
CRLM	18 (66.7)	17 (85.0)	5 (62.5)	403 (100.0)	10 (66.7)	14 (56.0)	5 (33.3)
Other	9 (33.3)	3 (15.0)	3 (37.5)	0 (–)	5 (33.3)	11 (44.0)	10 (66.7)
Failure to reach 2nd stage	0 (–)	2 (10.0)	2 (25.0)	0 (–)	0 (–)	0 (–)	0 (–)
Highest complication ≥IIIa in both stages	4 (15.4)*	10 (50.0)	4 (50.0)	127 (31.5)**	6 (40.0)	10 (40.0)	11 (73.3)**
Highest complication ≥IIIb in both stages	4 (15.4)*	7 (35.0)	2 (25.0)	77 (19.1)**	4 (26.7)	9 (36.0)	7 (46.7)**
In-hospital mortality	0 (–)	1 (5.0)	1 (12.5)	29 (7.2)**	0 (–)	3 (12.0)	4 (26.7)

MIS minimally invasive surgery, *ALPPS* associating liver partition with portal vein ligation for staged hepatectomy, *CRLM* colorectal liver metastasis

*Calculated on 26 cases

**Complications after stage 2 and deaths after 90 days from stage 2

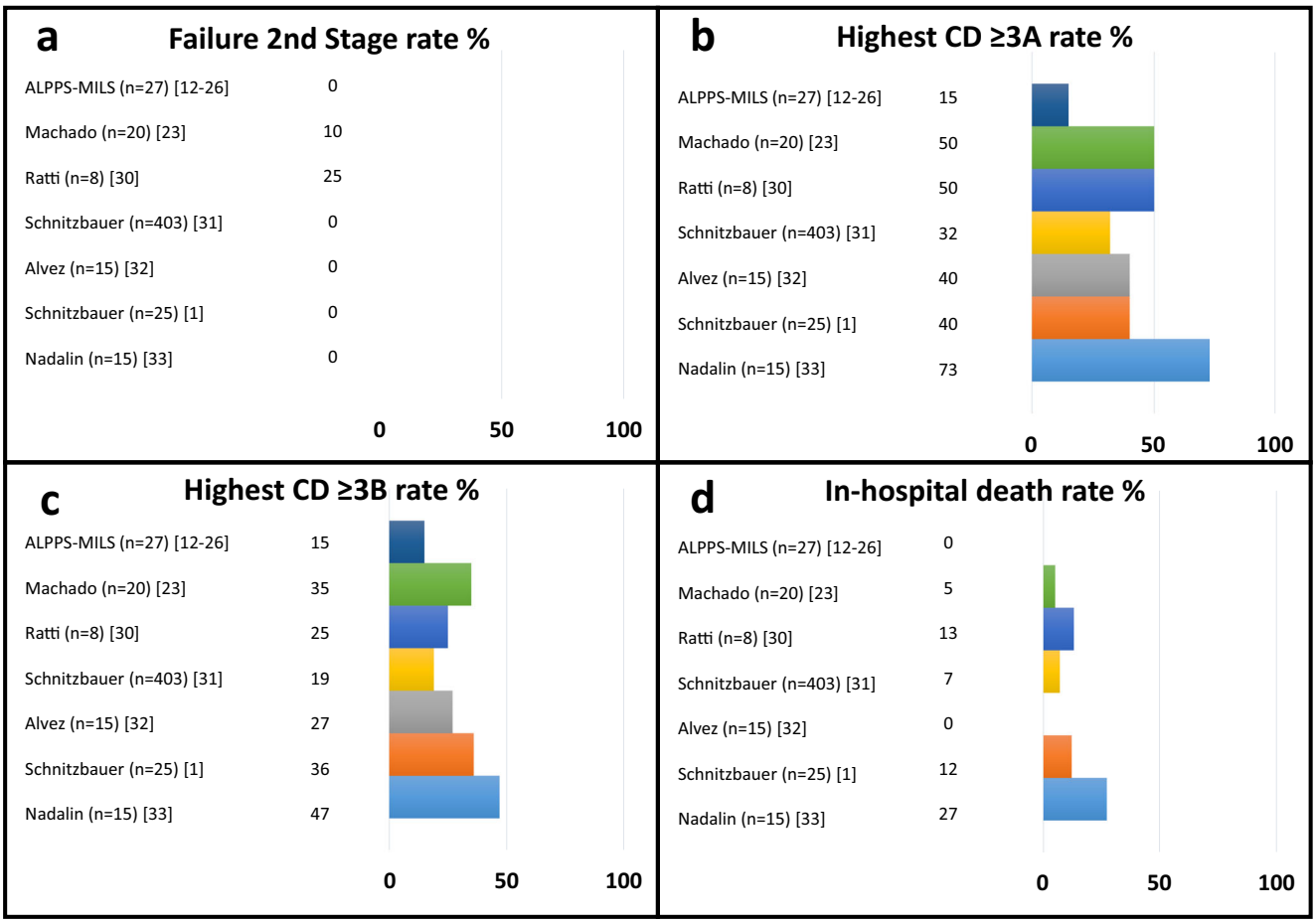

Fig. 2 **a** Percentages of failures of second ALPPS stage in the MIS and open series. **b** Percentages of Clavien-Dindo complications ≥IIIa in the MIS and open series. **c** Percentages of Clavien-Dindo complications ≥IIIb in the MIS and open series. **d** Percentages of in-hospital deaths in the MIS and open series

Discussion

Open ALPPS has failed to demonstrate a survival superiority relative to conventional two-stage hepatectomy due to higher complication rates.[1,30–33] In contrast, the main advantage of ALPPS with respect to the conventional two-stage hepatectomy is the lower rate of failures between the first and second stages.[1–4] MIS-ALPPS may represent a compromise, minimizing the complication rates while maintaining a high rate of fast liver remnant growth.

Laparoscopy was introduced into surgical practice approximately 30 years ago.[34] After some initial difficulties, MIS has been also implemented in the management of liver tumors.[35,36] MIS is connected with lower rates of postoperative complications,[37] blood loss,[38] and overall death.[39] In case of cirrhosis, the possibility to treat HCC patients with MIS minimizes the risk of postsurgical liver failure,[40] severe ascites,[41] and death.[42] Consequently, the combination of MIS with ALPPS appears to be extremely attractive.

In the present systematic review, a total number of 27 MIS-ALPPS subjects was identified in the literature. The small number of cases can be explained by the recent introduction of ALPPS procedure. In fact, the first case of ALPPS was described only in 2011.[1] Another reason for the small number of reported series may be related to the attitude around publishing only *positive* cases. No studies comparing MIS-ALPPS and open ALPPS coming from the international ALPPS registry (http://www.alpps.net/?q=registry) have been still published. Notwithstanding this limitation, the present results suggest that MIS-ALPPS is associated with better results with respect to open series.

Two main reasons may justify the better results observed in the MIS-ALPPS series: (a) better selection of the underlying pathology to treat and (b) no failures after the first stage.

As for the first aspect, the MIS-ALPPS approach has been preferred in managing particular liver tumors (i.e., CRLM or HCC) relative to others (CCA). For example, the open series described by Nadalin et al.[33] reported 9/15 CCA patients, showing the worst rates of complication (73%) and in-hospital mortality (27%). CCA showed a detrimental effect for the risk of first- to second-stage failures, complications, and death.[10] A study from the Italian ALPPS registry proposed the introduction of a moratorium for classic ALPPS in CCA and to abort ALPPS procedures in patients with an interstage increase in bilirubin, due to the higher risk of liver failure and mortality.[43] Only one case of CCA was treated with a MIS-ALPPS, precluding the possibility to define the role of MIS-ALPPS in the management of this tumor.[19]

When MIS-ALPPS cases were compared with open series exclusively focused on CRLM management,[31] it was interesting to observe that laparoscopic series still demonstrated better results. In the study reported by Machado et al.,[23] in which ten laparoscopic procedures were compared with 20 open cases, the latter showed higher rates of complication and in-hospital death, although 85% of patients had a CRLM.

The second important aspect to underline in favor of MIS-ALPPS is its ability to always consent to perform the second stage. In all the MIS-ALPPS patients, an absolute sFLR increase of > 30% after the first stage was observed. Thanks to the efficacy of the remnant liver growth, no failures for size were reported between the first and second stages. In contrast, patients included in the open series showed liver failure rates ranging 10–25%.[23,30] These failures were principally connected with post-first-stage complications more than with poor liver growth.

The results need to be considered with some interpretation as some statistical biases exist in the initial patient selection. Shortcomings of the data include the following: (a) ultra-selection of MIS-ALPPS patients, with CRLM and HCC cases almost exclusively reported; (b) no *negative* MIS-ALPPS subjects reported in the literature; and (c) selection by time, with MIS cases performed more recently (*learning curve* effect) with respect to open cases in the same center. After analyzing the data available in the literature, only one study that compared open and laparoscopic series was reported. As a consequence, it was impossible to construct a *balanced* comparison between MIS-ALPPS and open ALPPS in terms of liver pathology and initial sFLR. Large registry studies, meta-analyses, and meta-regressions may represent future ways to overcome these limitations. Currently, these approaches are impossible to be performed based on the literature currently available. Therefore, future studies that specifically compare the MIS versus open approach in the setting of ALPPS procedure will be needed.

Conclusions

MIS-ALPPS appears to be safe, with potentially lower morbidity and mortality relative to open series. However, these results should be considered with caution. Only a limited number of cases exist in the literature, and selection biases should be considered when comparing open versus MIS-ALPPS series. Therefore, registry studies are needed to better define the outcomes of MIS-ALPPS versus open ALPPS patients.

Contributors FM, FG, QL, and TMP designed the research; FM, FG, QL, and TMP collected and interpreted the data; FM, FG, QL, and TMP wrote the paper; RH, ZLL, FF, MR, and GM critically revised the paper; all the authors gave final approval of the article to be published.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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