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ORIGINAL SCIENTIFIC REPORT

Propensity Score-Matched Analysis of Pure Laparoscopic Versus Hand-Assisted/Hybrid Major Hepatectomy at Two Western Centers

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Abstract

Background Laparoscopic major hepatectomy is expanding, but little data exist comparing surgical approaches. The aim of this study was to test the hypothesis that pure laparoscopic liver resection (PLAP) has advantages over hand-assisted (HALS) or hybrid (HYB) resection for major hemi-hepatectomy at two western centers.

Methods Using propensity score matching, 65 cases of HALS + HYB (18 hand-assisted and 47 hybrid) were matched to 65 cases of PLAP. Baseline characteristics were well matched for gender, age, ASA score, Childs A cirrhosis, right/left hepatectomy, malignancy, tumor size, and type between the groups.

Results The HALS + HYB group had 27 right and 38 left major hepatectomies ($n = 65$) versus 29 right and 36 left ($n = 65$) in the PLAP group (p = NS). The median number of lesions resected was 1 in each group, with median size 5.6 cm (HALS + HYB) versus 6.0 cm (PLAP), (p = NS). The HALS + HYB group had shorter OR time (240 versus 330 min, $p < 0.01$), and less blood loss (EBL 150 ml vs. 300 ml, $p < 0.01$) versus the PLAP group, respectively. Median length of stay (LOS) was 4 days with HALS + HYB versus 5 days in the PLAP group ($p = 0.02$). There were no significant differences in use of the Pringle maneuver, transfusion rate, ICU stay, post-op morbidity, liver-specific complications, or R0 resection. Pain regimen/usage in each group is provided. There were no 30/90-day deaths in either group.

Conclusion This is the first reported series of propensity score matching of HALS + HYB versus PLAP for major hepatectomy. The HALS + HYB group had non-inferior OR time, blood loss, and LOS versus the PLAP group, while the other perioperative parameters were comparable. We conclude that minimally invasive liver resection with either PLAP or HALS + HYB technique yields excellent results.

Introduction

Laparoscopic liver resection (LLR) is rapidly expanding with over 10,000 cases reported in the literature [1]. Compared to open liver resection (OLR), clinical benefits of LLR include smaller incisions, less blood loss, decreased perioperative morbidity, and shorter hospital length of stay [1–4]. While early LLR studies consisted mostly of nonanatomic or minor liver resections, several teams have now reported large series of laparoscopic major hepatectomy, although this constitutes only about 20–25% of total LLR cases performed [5–19]. Much controversy

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remains regarding indications, techniques, learning curve, and long-term cancer outcomes with laparoscopic major hepatectomy [20–27]. From the 2014 Second International Laparoscopic Liver Consensus Conference in Morioka, the jury concluded that laparoscopic major hepatectomy is still an innovative procedure in the exploration phase [27].

Different technical approaches for major LLR include pure laparoscopic liver resection (PLAP), hand-assisted (HALS), or hybrid (HYB) resection where the liver is mobilized laparoscopically, and then, the hilar dissection and/or parenchymal transection is done through a small open incision [28, 29]. Selection of approach depends on tumor size and location, background liver, extent of resection, and surgeon preference/experience with pros and cons to each approach. Some teams advocate starting with a PLAP approach and converting to HALS or HYB if bleeding or technical difficulties are encountered, while others prefer to start with the HALS if a laparoscopic hepatic lobectomy is planned [28–33].

Given the lack of consensus and relatively sparse data comparing technical approaches to laparoscopic major hepatectomy, the purpose of this study was to use propensity score matching to compare PLAP versus HALS or HYB resection for major hemi-hepatectomy at two western centers. Our hypothesis was that the PLAP technique would offer clinical patient benefits over the HALS or HYB approach given the smaller incisions.

Materials and methods

Study population

For the present investigation, a study population arising from two high volume western liver centers was identified from a prospectively maintained database at each site. Cases of minimally invasive right and left hepatectomies were selected, encompassing both benign and malignant disease. The first group was identified from University of Pittsburgh Medical Center (UPMC), Pittsburgh, USA, retrospectively reviewing a database of 1062 laparoscopic liver procedures between years 2001 and 2017. Hand-assisted (HALS) and hybrid (HYB) right and left major hepatectomies were identified. The second group of pure laparoscopic (PLAP) major hepatectomy patients was identified from 706 laparoscopic liver procedures from the San Raffaele Hospital (HSR) in Milan, Italy, between the years of 2005 and 2017. The decision to perform PLAP versus HALS or HYB was at the discretion of the surgeon. In general, it is the practice of the Milan team to try and complete all laparoscopic major hepatectomies with a pure laparoscopic approach, while it is the preference of the Pittsburgh team to perform minimally invasive major hepatectomy using a handport or hybrid approach upfront.

Data collection

Demographic data were collected for each patient including gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, presence of cirrhosis, tumor type, tumor size, and number of lesions. Operative details including type of hepatectomy, operative time, estimated blood loss (EBL), use of Pringle maneuver, blood transfusion, and conversion to open rate were also assessed. Postoperative data regarding minor and major complications according to Clavien-Dindo classification, liver-specific complications (bile leakage, ascites, transient partial liver failure), intensive care unit (ICU), length of stay (LOS), and 30-day and 90-day mortality were reported. Pathologic diagnosis, tumor size, number of lesions, and resection margin status were ascertained from the final pathology report. Primary endpoint was the comparison of intraoperative and postoperative short-term outcomes.

Statistical analysis

Since patients belonging to the two groups were not randomized, propensity case matching was used to mitigate selection bias. Variables including gender, age, BMI, ASA status, and cirrhosis were utilized in the matching processes. Baseline characteristics of all major hepatectomy patients prior to matching are given in Table 1. A propensity score match was then performed to achieve similar baseline characteristics between the groups; three sub-analysis were conducted through propensity score matching:

1. HALS + HYB versus PLAP
2. HALS versus PLAP
3. HYB versus PLAP

Numeric variables were expressed as medians with interquartile range (IQR) and compared through student *t* test or Mann–Whitney *U* test. Nominal variables were expressed as number and percentages and compared with Chi-squared test or Fisher's exact test. Analysis of variance (ANOVA) was used to analyze the differences among groups for mean length of stay, while linear regression analysis was applied to assess variables potentially affecting duration of hospital stay.

Independent variables potentially influencing length of staying were identified using linear regression model. In all analysis, p value <0.05 was considered statistically significant. Statistical analysis was conducted using IBM SPSS 20 (Chicago, IL, USA).

Table 1 Baseline demographic characteristics of the whole series

	Whole series			
	HALS (n = 18)	HYB (n = 47)	Pure LAP (n = 182)	p
Demographic characteristics HALS, HYB and PLAP				
Gender M/F, n (%)	3/15 (17/83)	14/33 (30/70)	94/86 (52/48)	<0.01
Age, median (IQR), year	56.5 (33–70)	50 (33–61)	68 (59–76)	<0.01
BMI, median (IQR), kg/m^2	25.1 (22.1–29.7)	28 (24.8–31)	25 (23–27)	<0.01
ASA score, n (%)				0.049
1	3 (16.7)	2 (4.3)	13 (7.1)	
2 + 3	15 (83.3)	45 (95.7)	169 (92.9)	
4	0	0	0	
Child A cirrhosis, n (%)	0	3 (6.4)	49 (26.9)	<0.01
Major hemi-hepatectomies, n (%)				0.024
Right	4 (22.2)	23 (48.9)	101 (55.5)	
Left	14 (77.8)	24 (51.1)	81 (44.5)	
Tumor type, n (%)				<0.01
Malignant	6 (33)	26 (55)	150 (82)	
HCC	4 (22)	5 (11)	55 (30)	
CRC	2 (11)	11 (23)	57 (31)	
Others	0	10 (21)	38 (21)	
Benign	12 (67)	21 (45)	32 (18)	

HALS Hand-assisted; *HYB* hybrid; *PLAP* pure laparoscopic

Operative technique

UPMC hand-assisted approach

For HALS approach, the patient is in the supine position and trocar setup for right and left hepatectomy is shown in Fig. 1a and b, respectively. For each operation, two 12-mm trocars and two 5-mm trocars are used, along with a gelport (Applied Medical). For right hepatectomy, the surgeon stands on the patient's left side and first assistant on the right side. For left hepatectomy, the surgeon stands on the patient's right side and first assistant on the left side. The second assistant stands on the patients left side and works the camera. The handport is placed at the start of the operation. For the left hepatectomy, the midline hand-assisted port incision is lower compared to the right hepatectomy, thus minimizing conflict of the hand with the instruments. When the hand is not being utilized, an additional 12-mm trocar can be inserted through the gelport. Liver mobilization is performed similar to open hepatectomy, and the short hepatic veins are divided with 5-mm locking hemoclips. After liver mobilization, vessels are dissected at the hilum. The right/left hepatic artery is divided with locking hemoclips. The right/left portal vein is divided with a vascular stapler extra-parenchymally. Parenchymal transection is conducted by use of an energy device for the superficial parenchyma. The crossing middle hepatic vein branches are divided with vascular stapler. The right or left hepatic duct is stapled intra-parenchymally once the liver has been open-booked. An intermittent Pringle maneuver is utilized during parenchymal transection with an intra-corporeal bulldog clamp inserted via the handport. The right and left/middle hepatic veins are divided as the last step using vascular stapler. Hemostasis is achieved with saline-cooled radiofrequency device (Aquamantys or floating ball). The hepatic lobe is extracted through the handport incision.

UPMC hybrid technique

With the hybrid (HYB) approach, the handport and trocar positions are shown in Fig. 1c and d for right and left hepatectomy, respectively. The main difference between the HYB and HALS approach described above is that with HYB, the liver is mobilized under pneumoperitoneum, but the hilar dissection and parenchymal slice are performed through a small open incision made by connecting the handport incision to the 12-mm trocar as shown. The final incision size is about half the size of a full open incision.

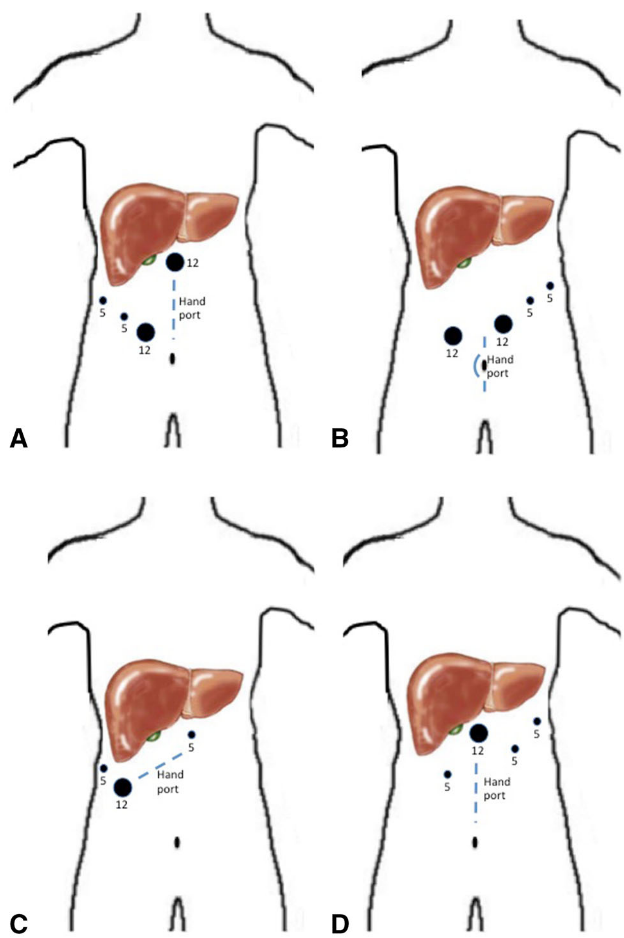

Fig. 1 Operative setup at University of Pittsburgh Medical Center. **a** Hand-assisted right hepatectomy; **b** hand-assisted left hepatectomy; **c** hybrid right hepatectomy; **d** hybrid left hepatectomy

Most of the hemi-hepatectomy cases done by the UPMC team use HALS or hybrid approach. When HALS is used, the handport serves as the extraction site. Typically, if the patients are obese with BMI > 30, then the hybrid approach is preferred. For BMI < 30, and whenever possible for left hemi-hepatectomy, the HALS approach is preferred.

San Raffaele hospital pure laparoscopic technique

A modified laparoscopic French position was adopted. Both inferior and superior limbs were abducted, seeing hips and knees slightly bent, thus conferring major stability in course of reverse-Trendelenburg tilting. First operator stands between the patient's legs, first assistant on the patient's left side, and second assistant on the right side of the patient. A standard setup consists of five operative 12-mm ports, placed in a rotated J-shape fashion (Fig. 2).

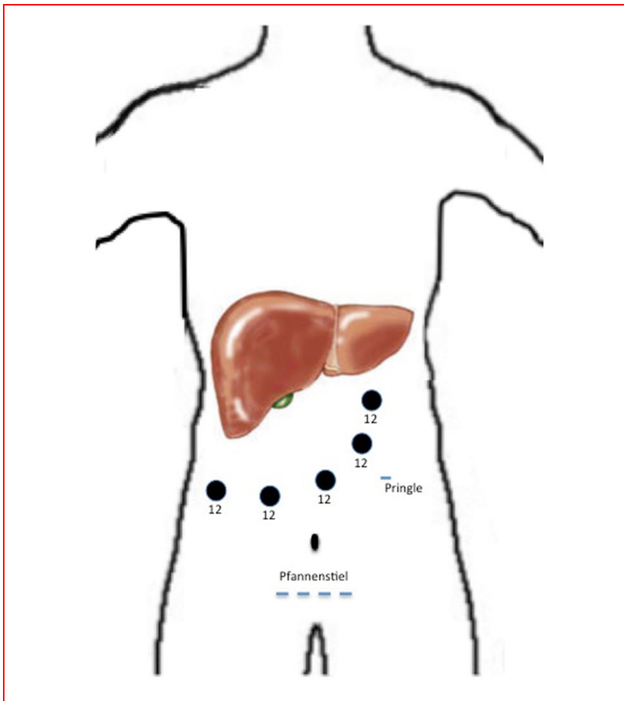

Fig. 2 Operative setup at San Raffaele Hospital for pure laparoscopic right and left hepatectomy. Oper = first operator trocar; Assist = first assistant trocar; C = optic trocar

An extra-corporeal Pringle maneuver is placed using a chest tube over an umbilical tape which exits in the left flank. Once the hemiliver is mobilized, the pedicle dissection is performed and the left or right portal vein and artery were sealed between hem-o-lock clips and cut extraparenchymally. The parenchymal transection is conducted along the Cantlie's line with the aid of an ultrasonic aspirator, while an energy device is used for more superficial layers. Lesser vascular structures are coagulated through wet bipolar forceps, while major structures are sealed through clip, hem-o-lock, or stapler, according to dimension. Ipsilateral hepatic duct is divided with vascular stapler. Hepatic veins are stapled intra-parenchymally. The specimen is extracted through a supra-pubic Pfannenstiel incision.

Results

Whole population

Baseline demographic data of the whole population among the three cohorts (HALS, HYB, and PLAP) are shown (Table 1). Significant differences were seen in baseline characteristics of gender, age, BMI, ASA score, the

Table 2 Propensity score-matching analysis between HALS + HYB versus PLAP

	1:1 ratio		
	HALS + HYB (*n* = 65)	Pure LAP (*n* = 65)	*p*
Demographic characteristics HALS + HYB versus PLAP			
Gender M/F, *n* (%)	17/48 (26/74)	25/40 (38/62)	0.094
Age, median (IQR), year	50 (33–65.8)	53 (45–61.5)	0.444
BMI, median (IQR), kg/m^2	27.2 (23.5–30.4)	24 (22–25)	**<0.01**
ASA score, *n* (%)			
1	5 (7.7)	11 (16.9)	0.090
2 + 3	60 (92.3)	54 (83.1)	0.090
4	0	0	NA
Child A cirrhosis, *n* (%)	3 (4.6)	3 (4.6)	0.660
Major hemi-hepatectomies, *n* (%)			0.430
Right	27 (41.5)	29 (44.6)	
Left	38 (58.5)	36 (55.4)	
Tumor type, *n* (%)			0.190
Malignant	32 (49)	38 (58)	
HCC	9 (14)	8 (12)	
CRC	13 (20)	17 (26)	
Others	10 (15)	13 (20)	
Benign	33 (51)	27 (42)	
Clinicopathological outcomes HALS + HYB versus PLAP			
N. lesions, median (IQR)	1 (1–2)	1 (1–2.2)	0.651
Largest tumor size, median (IQR), cm	5.6 (3–8.8)	6 (4.1–8.4)	0.614
R0 resection, *n* (%)	59 (92.2)	62 (95.4)	0.350
OR time min, median (IQR)	240 (212–282)	330 (270–390)	**<0.01**
Conversion to open, *n* (%)	2 (3.1)	2 (3.1)	0.690
EBL mL, median (IQR)	150 (50–350)	300 (250–400)	**<0.01**
Pringle maneuver, *n* (%)	59 (90.8)	61 (93.8)	0.372
Transfusion rate, *n* (%)	8 (12.3)	10 (15.4)	0.400
ICU stay, *n* (%)	4 (6.2)	1 (1.5)	0.183
Postoperative morbidity, *n* (%)			
Clavien-Dindo II–III	10 (15.4)	11 (17)	0.654
Clavien-Dindo IV–V	0	1 (1.5)	0.500
Pulmonary complications n (%)	3 (4.6)	3 (4.6)	0.690
Liver-specific complications, n (%)			
Bile leakage	0	1 (1.5)	0.500
Ascites	1 (1.5)	2 (3.1)	0.500
Transient partial liver failure	0	1 (1.5)	0.500
LOS day, median (IQR)	4 (3–5)	5 (4–5.5)	**0.002**
30-day mortality	0	0	NA
90-day mortality	0	0	NA

Statistically significant values are given in bold ($p < 0.05$)

HALS Hand-assisted; *HYB* hybrid, *PLAP* pure laparoscopic

presence of cirrhosis, right versus left hepatectomy, and tumor type. Clinicopathological outcomes for the three series before propensity score matching are contained in supplementary Table 1.

HALS + HYB versus PLAP—1:1 ratio

To achieve a meaningful comparison of groups, propensity score matching was performed comparing HALS + HYB to PLAP with 65 patients in each group for a 1:1 analysis.

Table 3 Linear regression analysis for predictors impacting on length of stay (LOS)

Linear regression; dependent variable: length of stay (LOS)		
	Magnitude	*p*
Age	0.141	0.185
Gender	− 0.078	0.438
ASA	0.021	0.848
BMI	− 0.004	0.963
Method (HALS or HYB vs. PLAP)	0.315	**0.002**
Right or left hepatectomy	0.016	0.857

Statistically significant value is given in bold ($p < 0.05$)

HALS Hand-assisted; *HYB* hybrid, *PLAP* pure laparoscopic

The groups were well matched for gender, age, ASA score, the presence of Childs A cirrhosis, type of operation, tumor type, number of lesions, and largest tumor size (Table 2). The only slight but significant difference between the groups was a lower BMI of 24.0 in the PLAP group versus 27.2 in the HALS + HYB group ($p < 0.01$). This is most likely explained by the larger size/obesity of the American compared to the Italian patients. Approximately 50% of resections were for malignancy in each group, with the most common tumor type being metastatic colorectal cancer (CRC) and hepatocellular carcinoma (HCC).

Among intraoperative data, the HALS + HYB group had shorter operative time (240 vs. 330 min, $p < 0.01$) and estimated blood loss (150 vs. 300 mL, $p < 0.01$). There were no differences in use of Pringle maneuver between the groups (90.8% vs. 93.8%, p = NS). In spite of decreased blood loss in the HALS + HYB group, there was no statistically significant difference in pRBC transfusion rate (12.3 vs. 15.4%) compared to the PLAP group, respectively. Postoperatively, there was no significant differences in ICU stay (6.2 vs. 1.5%), postoperative minor (15.4 vs. 17%) or major complications (0 vs. 1.5%), bile leakage (0 vs. 1.5%), ascites (1.5 vs. 3.1%), or transient partial liver failure (0 vs. 1.5%), p = NS between the groups for each parameter.

Analysis of variance (ANOVA) showed shorter median length of stay for HALS + HYB group in comparison with PLAP (4 vs. 5 days, $p = 0.02$). Linear regression analysis assessing variables potentially affecting length of stay showed that surgical method (HALS + HYB vs. PLAP) was the only predictive variable impacting the LOS (Table 3). For pathological data, there were no differences in number of lesions resected (1 vs. 1), tumor size (5.6 vs. 6 cm), or R0 resection margin rate (92.2 vs. 95.4%, p = NS) between the two groups.

HALS versus PLAP—1:2 ratio

To better understand if the differences between the HALS + HYB versus PLAP group were due to features associated with HALS versus HYB approaches, a subset propensity score match was performed directly comparing HALS versus PLAP and HYB versus PLAP groups. Eighteen patients from the HALS group were propensity score-matched to 36 patients in the PLAP group for a 1:2 analysis. There were no differences in any of the baseline characteristics between the two groups, indicating that the patients were well matched (Table 4). Intraoperative data showed decreased blood loss in the HALS versus PLAP group (55 vs. 350 mL, $p = 0.01$). There were no differences in use of Pringle maneuver (94.4 vs. 91.7%, p = NS). Interestingly, operative time did not differ between the groups (305 vs. 308 min, p = NS).

Perioperatively, no significant differences were observed for transfusion rate (11 vs. 8.3%), minor (22 vs. 13.8%) or major complications (0 vs. 0), bile leakage (0 vs. 8.3%), ascites (0 vs. 0) or transient partial liver failure (0 vs. 0). Two patients of HALS cohort required intensive care unit stay (11% vs. 0, $p = 0.04$), while none did in the PLAP group. Despite such difference in ICU stay between the cohorts, the two patients of the HALS series were transferred to ICU nightly just for postoperative monitoring, rather than for clinical issues and, therefore, this was not accounted as a Clavien-Dindo IV grade complication.

Similar to the combined HALS + HYB group, the HALS alone group had a median 4 day LOS vs. 5 days in the PLAP group which was significant ($p = 0.043$). For pathological data, there were no differences in the number of lesions harvested (1 vs. 1, p = NS), tumor dimension (7.3 vs. 6.5 cm, p = NS), or R0 resection margins (94.4% vs. 97.2%, p = NS).

HYB versus PLAP–2 ratio

Forty-seven patients of the hybrid cohort were propensity score-matched to ninety-four laparoscopic cases, resulting in a 1:2 matching ratio (Table 5). The two groups were well matched for baseline demographic characteristics for gender (29.8 vs. 41.5%, p = NS), ASA score, number of right (48.9 vs. 47.9%, p = NS) and left (51.1 vs. 52.1%, p = NS) hepatectomies, and tumor type. However, age (50.5 vs. 56.5, $p = 0.014$) and BMI (28 vs. 24, $p < 0.01$) showed younger and heavier patients in the HYB cohort. There was no difference in use of Pringle maneuver (89.4 vs. 95.7%, p = NS). Similar to the HALS + HYB group, the HYB group alone showed shorter operative time versus the PLAP group (200 vs. 300 min, $p < 0.01$).

Perioperatively, no significant differences were observed for transfusion rate (12.8 vs. 14.9%, p = NS),

Table 4 Propensity score-matching analysis between HALS versus PLAP

	1:2 ratio		
	HALS (n = 18)	Pure LAP (n = 36)	p
Demographic characteristics HALS versus PLAP			
Gender M/F, n (%)	3/15 (17/83)	15/21 (42/58)	0.066
Age, median (IQR), year	56.5 (33–70.5)	62.5 (40.5–72.7)	0.359
BMI, median (IQR), kg/m^2	25.1 (22–29.7)	24 (21–26)	0.128
ASA score, n (%)			
1	3 (16.7)	9 (25)	0.389
2 + 3	15 (83.3)	27 (75)	0.487
4	0	0	NA
Child A cirrhosis, n (%)	0	0	NA
Major hemi-hepatectomies, n (%)			0.999
Right	4 (22)	8 (22)	
Left	14 (78)	28 (78)	
Tumor type, n (%)			0.999
Malignant	6 (33)	12 (33)	
HCC	4 (22)	2 (5)	
CRC	2 (11)	4 (11)	
Others	0	6 (17)	
Benign	12 (67)	24 (67)	
Clinicopathological outcomes HALS versus PLAP			
N. lesions, median (IQR)	1 (1–1)	1 (1–1)	0.349
Largest tumor size, median (IQR), cm	7.3 (5–12)	6.5 (4.1–8.7)	0.211
R0 resection, n (%)	17 (94.4)	35 (97.2)	0.610
OR time min, median (IQR)	305 (270–360)	308 (247–360)	0.912
Conversion to open, n (%)	1 (5.6)	3 (8.3)	0.713
EBL mL, median (IQR)	55 (50–162)	350 (300–400)	**0.010**
Pringle maneuver, n (%)	17 (94.4)	33 (91.7)	0.713
Transfusion rate, n (%)	2 (11)	3 (8.3)	0.740
ICU stay, n (%)	2 (11)	0	**0.042**
Postoperative morbidity, n (%)			
Clavien-Dindo II-III	4 (22)	5 (13.8)	0.343
Clavien-Dindo IV-V	0	0	NA
Pulmonary complications n (%)	1 (5.6)	2 (5.6)	0.730
Liver-specific complications, n (%)			
Bile leakage	0	3 (8.3)	0.208
Ascites	0	0	NA
Transient partial liver failure	0	0	NA
LOS day, median (IQR)	4 (3–4)	5 (4–5)	**0.043**
30-day mortality	0	0	NA
90-day mortality	0	0	NA

Statistically significant values are given in bold ($p < 0.05$)

HALS Hand-assisted; *PLAP* pure laparoscopic

postoperative minor (12.8 vs. 13.8%, p = NS) or major complications (0 vs. 1.1%, p = NS), bile leakage (0 vs. 1.1%, p = NS), ascites (2.1 vs. 1.1%, p = NS), transient partial liver failure (0 vs. 1.1%, p = NS), and ICU stay (4.3 vs. 1.1, p = NS). Similar to the HALS + HYB or HALS alone groups, the HYB group had a shorter LOS compared to the PLAP group (4 vs. 5 days, $p < 0.01$).

Table 5 Propensity score-matching analysis between HYB versus PLAP

	1:2 ratio		
	HYB (n = 47)	Pure LAP (n = 94)	p
Demographic characteristics HYB versus PLAP			
Gender M/F, n (%)	14/33 (30/70)	39/55 (42/58)	0.176
Age, median (IQR), year	50 (33.7–61)	59 (47–66)	**0.014**
BMI, median (IQR), kg/m^2	28 (24.8–31)	24 (22–26)	**<0.01**
ASA score, n (%)			
1	2 (4.3)	13 (13.8)	0.082
2 + 3	45 (95.7)	81 (86.2)	0.082
4	0	0	NA
Child A cirrhosis, n (%)	3 (6.4)	9 (9.6)	0.522
Major hemi-hepatectomies, n (%)			0.905
Right	23 (48.9)	45 (47.9)	
Left	24 (51.1)	49 (52.1)	
Tumor type, n (%)			0.080
Malignant	26 (55)	66 (70)	
HCC	5 (11)	15 (16)	
CRC	11 (23)	30 (32)	
Others	10 (21)	21 (22)	
Benign	21 (45)	28 (30)	
Clinicopathological outcomes HYB versus PLAP			
N. lesions, median (IQR)	1 (1–2)	1 (1–3)	0.956
Largest tumor size, median (IQR), cm	5 (3–7)	5.8 (4–8.1)	0.205
R0 resection, n (%)	43 (91.5)	89 (94.7)	0.465
OR time min, median (IQR)	225 (203–247)	330 (300–388)	**<0.01**
Conversion to open, n (%)	1 (2.1)	6 (6.4)	0.273
EBL mL, median (IQR)	200 (100–400)	300 (262–400)	**<0.01**
Pringle maneuver, n (%)	42 (89.4)	90 (95.7)	0.144
Transfusion rate, n (%)	6 (12.8)	14 (14.9)	0.733
ICU stay, n (%)	2 (4.3)	1 (1.1)	0.216
Postoperative morbidity, n (%)			
Clavien-Dindo II–III	6 (12.8)	13 (13.8)	0.672
Clavien-Dindo IV–V	0	1 (1.1)	0.478
Pulmonary complications n (%)	2 (4.3)	4 (4,3)	0.688
Liver-specific complications, n (%)			
Bile leakage	0	1 (1.1)	0.478
Ascites	1 (2.1)	1 (1.1)	0.615
Transient partial liver failure	0	1 (1.1)	0.478
LOS day, median (IQR)	4 (3–5)	5 (4–5)	**<0.01**
30-day mortality	0	0	NA
90-day mortality	0	0	NA

Statistically significant values are given in bold ($p < 0.05$)

HYB Hybrid, *PLAP* pure laparoscopic

For pathological data, there were no differences in the number of lesions harvested (1 vs. 1, p = NS), tumor size (5 vs. 5.8 cm, p = NS), or R0 resection margins (91.5 vs. 94.7%, p = NS).

Pain medications–narcotic and non-narcotic use

The pain regimens varied between the two centers. The Milan group (HSR) that used the PLAP approach used a

Table 6 Pain medications use

	HALS + HYB	PLAP
Patients with IV PCA	93%	5%
IV PCA #days, median (IQR)	2.5 (2–3)	0 (0–0)
Patients with paravertebral block anesthesia	0%	89%
Paravertebral block #days, median (IQR)	NA	3 (3–4)
IV narcotic #doses, median (IQR)	0 (0–0)	0 (0–0)
PO narcotic #doses, median (IQR)	12 (8.8–14)	4 (3–4)
IV non-narcotic #doses, median (IQR)	11.5 (6–14)	6 (4–7)
PO non-narcotic #doses, median (IQR)	0 (0–4)	14 (3–16)

HALS + HYB Hand-assisted and hybrid, *PLAP* pure laparoscopic
PCA Patient controlled analgesia; *IV* intravenous; *PO* per os

POD / Analgesia	1		2		3		4		5	
	UPMC	HSR	UPMC	HSR	UPMC	HSR	UPMC	HSR	UPMC	HSR
Paravertebral	✗	✓	✗	✓	✗	✓				
Acetaminophen IV	✓	✓								
Acetaminophen P.O.				✓	p.r.n.	✓	p.r.n.	✓	p.r.n.	✓
NSAIDs IV	✓	p.r.n.	✓	p.r.n.		p.r.n.				
NSAIDs P.O.	✗	✗	✗	✗	p.r.n.	✗	p.r.n.	✗	✗	✗
Opioids IV	✓	✗	✓	✗						
Opioids P.O.			✓	p.r.n.	✓	p.r.n.	p.r.n.	p.r.n.	p.r.n.	p.r.n

Fig. 3 Pain regimen used at University of Pittsburgh Medical Center (UPMC) and San Raffaele Hospital (HSR)

combination of unilateral paravertebral catheter with sufentanil + naropine along with paracetamol IV and PO. Intravenous non-steroid antiinflammatory drugs (NSAIDs IV) were used as pro re nata (prn) for break-through pain. They did not use IV narcotics, and PO narcotics were used sparingly prn for break-through pain (Table 6). The paravertebral catheter was typically removed on POD #3–4 (Fig. 3). Foley catheter was removed on POD #2. Patients were discharged with paracetamol PO and narcotic (tapentadol) PO prn.

In contrast, the Pittsburgh group (UPMC) with a HALS or HYB approach did not use paravertebral catheters. Acetaminophen was given IV in the OR and q12 h × 2 doses post-op. Toradol (ketorolac) was given IV in the OR and continued q6 h × 48 h post-op. A dilaudid PCA was given for the first 1–2 days post-op and switched to PO oxycodone POD #2–3. Foley catheter was removed on POD #1. Patients were discharged with ibuprofen PO and narcotic (oxycodone) PO prn. Oral narcotic doses were greater in the HALS + HYB patients, while total non-narcotic doses were greater in the PLAP patients (Table 6).

Discussion

Laparoscopic major hepatectomy is increasing and accounts for approximately 25% of overall cases in a recent world review of nearly 10,000 cases of LLR [1]. In spite of hundreds of publications in the field, there is no consensus as to which surgical approach (PLAP, HALS, HYB, or robotic) is superior. In contrast to a large amount of data and many published studies comparing laparoscopic to open liver resection [1–3], there is a scant amount of data comparing the different technical approaches of LLR, let alone for laparoscopic major hepatectomy. While each technique has pros and cons, there are advocates or defenders for each approach that are convinced of their ways. Given the sparse amount of data, the purpose of this study was to use propensity score matching to compare PLAP versus HALS or HYB resection for major hemi-hepatectomy at two western centers. The western centers were selected to mitigate against potential bias and cultural differences in patient expectations if an eastern center was used for comparison. Moreover, within the western centers to minimize selection bias of "cherry-picking" better outcome cases, the two centers were selected that preferentially perform all laparoscopic major hepatectomies with a PLAP approach (Milan) or HALS/HYB approach (Pittsburgh).

The major and novel findings of this propensity score-matched study are: (1) the HALS + HYB versus PLAP group had non-inferior OR time (240 vs. 330 min, $p < 0.01$), blood loss (150 vs. 300 ml, $p < 0.01$), and LOS (4 vs. 5 days); (2) a detailed pain regimen and usage for each group is provided (Fig. 3 and Table 6) and neither group was able to claim superiority with regard to narcotic use; 3) there were no differences in use of the Pringle maneuver, transfusion rate, ICU stay, post-op morbidity, liver-specific complications, mortality, or R0 resection rate between the groups.

A finding in the current study was significantly less blood loss (EBL) (150 vs. 300 ml) with use of a HALS + HYB group compared to the PLAP group. While many studies have showed decreased blood loss with laparoscopic versus open liver resection [1–3], few have compared blood loss amongst different MIS techniques of liver resection. One explanation commonly asserted for the decreased blood loss with a laparoscopic approach is the benefit of pneumoperitoneum during parenchymal transection with pneumoperitoneal pressures of 14–15 mmHg and low CVP of <5 mmHg [1–3]. However, the significantly less blood loss in the HYB versus PLAP group where the liver transection in the HYB group is done without pneumoperitoneum argues against the necessity of pneumoperitoneum to achieve a low blood loss.

An additional finding in the current study was a significantly shorter OR time (240 vs. 330 min) with use of a HALS + HYB group compared to the PLAP group. There are many factors that influence operating room time, which include extent of resection, nature of background liver, time required to open and close an incision, speed of hilar dissection and parenchymal transection, experience and learning curve of the operative team, and time associated with the training of residents and fellows. When considering the added time required to open and close an incision with the HALS or HYB approach, it could be expected that this would increase overall OR time compared to a PLAP approach. On the other hand, use of a HALS or HYB approach might shorten the OR time needed for the hilar dissection and parenchymal transection. Our data shows a significantly shorter OR time with use of a HALS + HYB group compared to the PLAP group indicating that a HALS + HYB approach can shorten the overall OR time. Since nearly all of the Pittsburgh HALS + HYB cases were done by a HPB fellow with attending surgeon assisting, the shorter OR time with HALS + HYB is most likely attributed to the shorter time needed for hilar dissection and parenchymal transection facilitated by HALS or HYB access rather than time attributed to training of fellows. Also, the baseline patient characteristics of gender, age, ASA score, background liver, type of resection, diagnosis, tumor number and size were comparable between the HALS + HYB versus PLAP groups, so the baseline characteristics do not account for the differences in OR times. Although the median BMI (24 vs. 27) was less in the Italian compared to the American patients, it is generally accepted that increased BMI with obese patients typically increases OR time, so the shorter OR time in the HALS + HYB (American) cases is not attributable to the slight but significant differences in BMI. It is possible that the OR times in the HALS + HYB cases would be even shorter if performed in patients with BMI < 25, although this study does not provide the data to assert such a claim.

To better understand if the shorter OR time between the HALS + HYB versus PLAP group was specifically due to use of HALS versus HYB approaches, a subset propensity score match was performed directly comparing HALS versus PLAP and HYB versus PLAP groups. Interestingly, the OR times were comparable (305 vs. 308 min) when directly comparing HALS to PLAP cases, while the HYB vs. PLAP maintained a shorter OR time (225 vs. 330 min). This suggests that the shorter overall OR time with HYB approach is explained by increased ease and speed of hilar dissection and/or parenchymal transection. This makes sense because those portions of the case are done through a small open incision rather than under pneumoperitoneum with HALS or PLAP techniques.

In one of the earliest studies comparing HYB to HALS or PLAP approaches, Koffron et al. analyzed ten patients undergoing laparoscopic lobectomy in each group. In contrast to our finding of shorter OR time in the HYB group, his study showed the HYB patients had double the OR time versus HALS or PLAP groups [28]. However, data were not provided as to right versus left hemi-hepatectomy, and no explanation for differences in OR times was provided.

It could be argued that the PLAP group in this study was disadvantaged from the presence of patients at the beginning of the laparoscopic experience. To answer this question, ancillary analyses have been performed, comparing the early cohort versus the late cohort of the PLAP group only (Supplementary Table 2), observing how operative time and bleeding did improve in the late series. Early cohort was defined choosing the first forty hemi-hepatectomies, number which is required for the completion of the learning curve in laparoscopic major liver resections.

We then compared the late PLAP cohort to the HALS/hybrid cases (Supplementary Table 3), and, again, a moderate higher OR time and EBL were seen for the PLAP group. However, PLAP group was characterized from a higher rate of patients with chronic liver disease, more right lobectomies and cases operated for malignancy, potentially explaining the previous findings and accounting for a higher complexity of the patients in this group, other than the faster dissection in the hybrid approach.

In a multicenter study of laparoscopic major hepatectomy in 210 patients at 6 centers (3 European, 2 USA, and 1 Australian), the MIS surgical approach was HALS in 57% of cases, and PLAP in 43% [7]. Technique was selected at the discretion of the surgeon with the European centers generally preferring a PLAP approach, while the U.S. teams used a HALS approach. While the overall median OR time for laparoscopic hemi-hepatectomy was 250 min (and within the range of OR time in the present study), no breakdown of OR time between HALS and PLAP was provided.

In a questionnaire survey conducted in 2009 of 32 hospitals of the Japanese Endoscopic Liver Study Group, 106 laparoscopic major hepatectomies were reported [34]. 88% of the cases were HYB, 4% HALS, and 8% PLAP. Overall OR times were not reported, so no direct comparison can be made to the current study.

Another finding in the current study was the similar median LOS (4 vs. 5 days) in the HALS + HYB versus PLAP group. This is somewhat counter-intuitive, as most surgeons would predict a shorter LOS with use of PLAP versus the larger incisions associated with HALS or HYB approaches. Although both surgical teams were at western centers (USA and Italy), the most likely explanation for the one day longer LOS in the Milan patients with a PLAP technique is differences in patient expectations and healthcare systems between USA and Italy. The Italian NHS lacks adequate support for outpatients, and this creates a difference between the concept of "ready-to-discharge" and "real discharge." Given the cultural differences, we conclude similar (non-inferior) LOS comparing the HALS + HYB to the PLAP group.

Similar to the 4- and 5-day median LOS reported for MIS major hepatectomy at two western centers in the current study, Medbery et al. reported on 48 patients that underwent HALS right lobectomy at a single western center with a 5-day median LOS [35]. However, this study did not have any comparison between HYB or PLAP cases. In an earlier series from the Pittsburgh group, Cardinal et al. reported a shorter LOS in PLAP (2.5 days) versus HALS (3.5 days) or HYB (3.8 days) cases; however, this study included 72/113 (64%) of patients that had a laparoscopic left lateral sectionectomy (LLS) operation [31]. Hence, it was not restricted to laparoscopic major hepatectomy cases as in the current study and likely accounts for the shorter overall LOS regardless of surgical technique used.

In comparison with the reported LOS in the western centers, a study from Nitta et al. reported on laparoscopic-assisted major hepatectomy (HYB) in 42 patients at an eastern center in Japan [29]. They had median LOS of 13.5 days which is much longer than the LOS from the two western centers in the current study. This comparison certainly highlights the major impact that cultural differences in patient and healthcare expectations can have on hospital length of stay. It is important to mention that the LOS did decrease from 17 to 9 days in the Japanese study comparing their early versus later cohort. Although not the focus of our current study, it has been shown that laparoscopic versus open liver resection results in an approximately 50% reduction in LOS across the board regardless of cultural expectations [3].

An important contribution from this study is the detailed perioperative pain regimen provided for each group. Although the pain regimens were center specific and significantly different, not permitting any kind of statistic comparison, there is little in the literature on this topic for minimally invasive liver surgery. A common belief is that a PLAP approach to major hepatectomy would result in less pain and less narcotic use compared to the HALS/HYB groups. However, in the current study, we were not able to identify superiority of one pain regimen over the other in the PLAP versus HALS/HYB groups.

Between the groups, total narcotic doses were difficult to compare because narcotic was used continuously in the paravertebral catheter for 3 days in the PLAP group, while the HALS + HYB used a dilaudid PCA for 2 days post-op along with IV non-narcotics and then converted to po narcotics. Also, the pain management protocols varied considerably with regards to the use of paravertebral catheter, IV and PO narcotic use.

Of note, both a local anesthetic (naropine) and narcotic (sufentanil) were routinely used in the paravertebral catheter in the PLAP patients, and it was typically discontinued on post-op day #3–4. At this point, most patients in their cohort were transitioned to oral non-narcotics rather than the oxycodone that was commonly used in the Pittsburgh patients. It is difficult to tell if regional use of narcotic in the paravertebral catheter had less adverse effect on ileus than the dilaudid PCA for the first few post-op days in the HALS/HYB patients. While the paravertebral catheter may have a positive benefit for the patient, the time, cost, efficacy, and potential complications have to be considered. In addition, the Foley catheter was typically continued an extra day (POD#2) in patients with the paravertebral catheter. While no randomized clinical trial has been performed assessing the role of paravertebral catheters in the setting of minimally invasive liver resection, there was a recent RCT comparing bilateral thoracic paravertebral to thoracic epidural catheter for open liver resection [36]. The results showed a modest benefit for the epidural group; however, the epidural patients did exhibit a greater amount of relative hypotension.

A meta-analysis on the role of HALS and HYB v. PLAP techniques were recently reported [37]. The differences between that study and our current study are that most of the reports examined in the meta-analysis included laparoscopic minor hepatectomies, while our study consisted entirely of laparoscopic major hepatectomies (right or left formal hepatectomies). Moreover, the conclusion from the meta-analysis published in 2015 was that there was insufficient evidence to conclude any single approach is superior to the others. Hence, this conclusion supports the rationale and need for our propensity score match analysis.

A limitation of this study is that the PLAP (Milan) versus HALS and HYB (Pittsburgh) approaches were performed at two different centers in different countries. We acknowledge the inherent cultural differences in LOS between the two countries and therefore only claim “non-inferiority” for the clinical parameters measured, based on the data. Since there is such scant literature on hand-assisted or hybrid versus pure laparoscopic approach for MIS major hepatectomy, and the general assumption in the field that PLAP is better, we felt this study was warranted to compare the two approaches with the best data possible which are propensity score matching at the two western centers. Another limitation of this study was the differences among the baseline population; in fact, PLAP group had a higher percentage of cirrhosis (26.9 vs. 6.4%), fewer left hepatectomies (44 vs. 59%) and a higher percentage of cancer cases (82 vs. 49%), compared to HALS/hybrid groups. Propensity score match was chosen to mitigate such differences.

Finally, hand-assisted and hybrid approach can be considered as intermediate steps for the completion of the learning curve of surgeons in training, while some surgeons preferentially favor these techniques for any hemi-epatectomy case with the handport site serving as the extraction site.

Conclusion

Laparoscopic major hepatectomy performed with HALS or HYB techniques is not inferior to pure laparoscopic liver resection (PLAP) for perioperative short-term outcomes. In addition, an important finding of this study is that were no significant differences in use of the Pringle maneuver, transfusion rate, ICU stay, post-op morbidity, liver-specific complications, mortality, or R0 resection between the groups. Hence, minimally invasive liver resection with either PLAP or HALS + HYB techniques yields excellent clinical results.

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