Original Article

# The differential benefit of laparoscopic over open minor liver resection for lesions situated in the anterolateral or posterosuperior segments

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**Background:** It is well known that laparoscopic liver surgery can offer advantages over open liver surgery in selected patients. However, what type of procedures can benefit most from a laparoscopic approach has been investigated poorly thus far. The aim of this study is thus to define the extent of advantages of laparoscopic over open liver surgery for lesions in the anterolateral (AL) and posterosuperior (PS) segments.

**Methods:** In this international multicentre retrospective cohort study, laparoscopic and open minor liver resections for lesions in the AL and PS segments were compared after propensity score matching. The

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differential benefit of laparoscopy over open liver surgery, calculated using bootstrap sampling, was compared between AL and PS resections and expressed as a Delta of the differences.

**Results:** After matching, 3,040 AL and 2,336 PS resections were compared, encompassing open and laparoscopic procedures in a 1:1 ratio. AL and PS laparoscopic liver resections were more advantageous in comparison to open in terms of blood loss, transfusion rate, complications, and length of stay. However, AL resections benefitted more from laparoscopy than PS in terms of overall and severe complications (D-difference were 4.8%, P=0.046 and 3%, P=0.046) and blood loss (D-difference was 195 mL, P<0.001). Similar results were observed in the subset for high-volume centres, while in recent years no significant differences were found in the differential benefit between AL and PS segments.

**Conclusions:** The advantage of laparoscopic over open liver surgery is greater in the AL segments than in the PS segments.

**Keywords:** Liver neoplasms; hepatectomy; laparoscopic liver resection; open liver resection

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## Introduction

The field of hepatobiliary surgery has evolved significantly over the last three decades. In this context, an important development has been the adoption and wide implementation of minimally invasive liver surgery (MILS). Nowadays, a substantial proportion of the liver resections is performed laparoscopically in expert centers (1). During the implementation process of MILS, resections in the anterolateral (AL) segments (segment 2, 3, 4b, 5 and 6) have traditionally been considered technically easier to perform compared to those in the posterosuperior (PS) segments (segment 1, 4a, 7, 8) (2-7). During the latest consensus conference on MILS it was emphasized that PS resections are highly complex, require advanced expertise in MILS and are associated with greater operative time and blood loss than resections in the AL segments (4). With increasing experience, laparoscopic resections of the PS segments are now widely performed in expert centres (1). This practice is supported by observational studies showing that the laparoscopic approach can also offer benefits over the open approach for these challenging procedures, in terms of less blood loss, fewer postoperative complications, lower analgesic needs, a shorter hospital stay and a shorter interval to the initiation of adjuvant chemotherapy (8-11). Importantly, oncological outcomes comparable with the open approach have been reported (4,8,12). Recently, it has been suggested that the merits of the minimally invasive approach may be even greater for resections in the PS segments, as in these cases patients are spared a large incision for a liver resection of limited extent. One single-centre study, performed at a high volume MILS centre, has provided evidence supporting this theory (13). However, if these results are representative of the current situation on a wider scale remains to be defined. Therefore, the aim of this study is to investigate whether the benefits of laparoscopic over open liver surgery differ for resections in the AL and PS segments in a large international multicentre cohort. We present this article in accordance with the STROBE

### Highlight box

**Key findings**

- Laparoscopic surgery offers several benefits over open surgery when adopted for minor liver resections in the anterolateral (AL) and posterosuperior (PS) segments. The advantage of laparoscopy is however greater in the AL segments.

**What is known and what is new?**

- Laparoscopic resections in the PS segments have traditionally been deemed technically complex, but recently a single center study from a high-volume center demonstrated a greater benefit of laparoscopy in the PS than in the AL segments.
- This study provides insight into the efficacy profile that a laparoscopic approach may confer to different type of liver resections in the current era.

**What is the implication, and what should change now?**

- In centers with the appropriate experience, the minimally invasive approach should increasingly be adopted to perform minor liver resections irrespective of the location of the lesion(s).

reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-494/rc) (14).

## Methods

This is a retrospective analysis of an international multicentre database comprised of the prospectively maintained databases of 17 hepato-biliary referral centres in nine countries (15).

### *Study design*

The data of consecutive patients who underwent a laparoscopic or open minor liver resection (≤ two contiguous Couinaud's segments) between January 2009 and December 2019 was reviewed. Patients aged younger than 18 years, patients who underwent an emergency procedure, a liver resection for gallbladder carcinoma, a major concurrent procedure (e.g., pancreatic, gastric, colorectal or diaphragmatic resections), pre-operative portal vein occlusion (PVO) or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) were excluded. Included patients were divided, according to the location of the resected tumour, into two groups: AL or PS segments. The perioperative outcomes of laparoscopic and open resections were compared after propensity score matching (PSM) in a 1:1 ratio. After PSM, utilized to mitigate the influence of selection bias, the differential benefit of laparoscopy in both the AL and PS groups was calculated. Subsequently, the differential benefits in both groups were compared to calculate a "Delta of the differences" (graphically depicted in Figure S1, the study flowchart). Two sensitivity analyses were conducted to assess the outcomes in recent years (time period 2016–2019) and in high volume MILS centres. The Declaration of Helsinki (as revised in 2013) was respected at all times during the conduct of this study. The medical ethical committee of Brescia approved this study and waived the need to obtain informed consent due to its retrospective nature and the use of pseudonymized data (Judgement's reference number: NP 5472).

### *Definitions*

The anatomical extent (minor versus major) and location of liver resections (AL versus PS segments) were defined according to the Brisbane 2000 nomenclature (16). Postoperative complications were defined and graded according to the Clavien-Dindo (CD) classification, and considered severe when grade 3a or higher (17). A microscopically free resection margin (R0) was defined as a resection margin ≥1 mm. Centres performing ≥50 laparoscopic resections per year were defined as high volume, as previously described (18).

### *Preoperative assessment and surgical technique*

The preoperative assessment of each patient included routine laboratory tests, imaging with thoraco-abdominal contrast-enhanced computed tomography scans and, when indicated, magnetic resonance imaging scans with liver-specific contrast. The indication for surgery was discussed during a multidisciplinary team meeting with oncologists, surgeons, hepatologists and radiologists. A questionnaire distributed among the chief surgeons involved confirmed that, generally, resections were performed using a similar technique, irrespective of the adopted approach. Firstly, major extrahepatic disease (e.g., peritoneal metastases) was excluded. Subsequently, intraoperative ultrasonography was used to assess the extent of liver disease and lesions' proximity to major vessels. Superficial parenchyma transection was mainly performed using an ultrasonic dissector or bipolar vessel sealer, deep parenchyma transection using an ultrasonic aspirator. Vascular and biliary structures were sealed and divided using a dissector device, between metallic or Hem-o-Lok clips (Weck Closure Systems, Research Triangle Park, USA), sutures, or closed and transected with staplers depending on their size. A restrictive fluid strategy was employed during the transection phase, preserving a low central venous pressure. An intermittent Pringle manoeuvre was applied at the surgeons' convenience.

### *Statistical analysis*

Categorical data were reported as counts and percentages, continuous data as the mean with its standard deviation when normally distributed and as the median with its range in case of a non-normal distribution. Categorical data were compared using a Chi-square or, when appropriate, Fisher's exact test. Continuous data were compared, when normally distributed, using an unpaired *t*-test when non-normally distributed, using a Mann-Whitney *U* test. The distribution of continuous data was assessed by visually inspecting histograms and Q-Q plots.

Single imputation was used to impute missing baseline data, which was present in a missing at random pattern (Figure S2). After imputation, PSM was performed separately for the AL and PS segments subgroups using the MatchIt package in R for Mac OS X version 3.6.3. Variables that, based on subject-matter knowledge, were deemed to potentially influence treatment allocation (laparoscopic or open surgery) were entered as covariates in the multivariable logistic regression model calculating the propensity scores. These variables were: age, gender, American Society of Anesthesiology (ASA) score, presence of cirrhosis, treatment with neoadjuvant chemotherapy, previous hepatectomy, malignant disease, type of resection (wedge versus segmentectomy or bisegmentectomy) and the extent of liver disease (number of lesions, size of the largest lesion and uni- or bilobar disease). Laparoscopic resections were matched one-to-one to their "nearest-neighbour" open resection without replacement, using a caliper width ranging from 0.05 to 0.1 (19). The balance between the laparoscopic and open group was assessed using standardized differences (SD) after PSM, considering an SD ≤0.1 as optimal balance (20).

After PSM, categorical data were compared by means of the McNemar's test or, when appropriate, Marginal Homogeneity. Continuous data were compared by means of the Wilcoxon Signed Rank test. Non-parametric bootstrapping was applied on the matched cohorts to separately calculate the differential benefit of laparoscopy in the AL and PS segments, and thereafter the Delta of the differences (i.e., the difference in benefit in the AL and PS segments) (21). This process, starting from 1:1 PSM, was repeated for the two sensitivity analyses. All statistical analyses were performed following the intention-to-treat principle, wherein converted laparoscopic procedures were analysed in the laparoscopic group. IBM SPSS Statistics® version 27.0 (IBM, Armonk, New York, USA) and R for Mac OS X version 3.6.3 were used for the statistical analyses. The significance level was set at a two-tailed P value <0.05.

## Results

The complete cohort comprised 7,706 patients, of whom 4,695 patients underwent resections in the AL segments (two-thirds were laparoscopic and one third were open) and 3,011 patients underwent resections of the PS segments (almost equally proportioned between laparoscopic and open) (*Table 1*). Before PSM, several differences in the baseline characteristics of the open and laparoscopic group were identified in terms of sex, neoadjuvant chemotherapy status, previous abdominal surgery, and disease extent (number and size of lesions). The conversion rate was 5.2% in the AL segments and 10.2% in the PS segments (P<0.001).

After PSM, the baseline characteristics of patients that underwent laparoscopic and open resections were well balanced, both in patients who underwent resections in the AL and PS segments (Table S1). In the AL group, laparoscopic procedures, compared to open procedures, resulted in a shorter operative time (29.4 minutes difference, P<0.001), less blood loss (280 mL difference, P<0.001), a shorter length of stay (4 *vs.* 6 days) and lower rates of transfusions (2.9% *vs.* 6.5%, P=0.001), overall complications (19% *vs.* 32.6%, P<0.001) and severe complications (5.3% *vs.* 9.3%, P<0.001). The conversion rate was 6% (*Table 2*). Similar results were observed in the PS group, where laparoscopic procedures were characterized by a shorter operative time (22 minutes difference, P<0.001), less blood loss (85 mL, P=0.02), a shorter length of stay (4 *vs.* 7 days, P<0.001), lower rates of transfusions (7.5% *vs.* 11%, P=0.043) and overall complications (25.4% *vs.* 34.2% P<0.001). In this group, 11.5% of the laparoscopic procedures were converted (*Table 2*).

The observed differences between laparoscopic and open surgery in each group (AL and PS) were compared between each other, as discussed in the methods. The results of the differential benefit analyses are illustrated in *Figure 1*. Overall, laparoscopy had a larger benefit in the AL as compared to the PS segments for overall complications (Delta of the differences was 4.8%, P=0.046) and severe complications (Delta of the differences was 3%, P=0.046) (*Figure 1A*). A larger benefit in the AL segments was also observed in terms of blood loss (Delta of the differences was 195 mL, P<0.001) (*Figure 1C*). However, no substantial differences were observed for operative time and length of stay (*Figure 1B,1D*).

Table S2 shows the baseline characteristics after PSM in the high-volume MILS centres, and *Table 3* reports the peri-operative outcomes in this subgroup. While similar results as in the overall cohort were observed in terms of operative time and blood loss, the benefit of laparoscopy in the AL segments for overall complications and length of stay was further magnified (18.9%, P<0.001 and 3.7 days, P<0.001, respectively). In the PS segments, similar results as in the overall cohort were observed in terms of a slightly shorter operative time for laparoscopic procedures and comparable differences in the overall complication rate and length of stay. The differential benefit of laparoscopy in the AL versus PS segment, in the subgroup analysis of

 

**Table 1** Baseline characteristics stratified by surgical approach (laparoscopic and open) before propensity score matching

| Characteristics | Anterolateral segments (n=4,695) | | | | Posterosuperior segments (n=3,011) | | | |
|---|---|---|---|---|---|---|---|---|
| | Laparoscopic (n=3,104) | Open (n=1,591) | P | SD | Laparoscopic (n=1,435) | Open (n=1,576) | P | SD |
| Age, years | 64.2 [54, 72.1] | 63.6 [54.5, 71.3] | 0.14 | 0.017 | 65.5 [56, 73] | 65 [56, 72] | 0.22 | 0.029 |
| Sex, male | 1,727 (55.6) | 975 (61.3) | <0.001 | 0.115 | 841 (58.6) | 995 (63.1) | 0.01 | 0.093 |
| BMI, kg/m$^2$ | 26.3 [23.4, 28.9] | 26.2 [23.7, 29.6] | 0.057 | 0.063 | 26.2 [23.4, 29.1] | 26 [23.4, 29.3] | 0.96 | 0.017 |
| ASA 3&4 | 1,047 (33.7) | 558 (35.1) | 0.38 | 0.028 | 490 (34.1) | 542 (34.4) | 0.92 | 0.005 |
| Cirrhosis | 694 (22.4) | 401 (25.2) | 0.03 | 0.067 | 238 (16.6) | 324 (20.6) | 0.006 | 0.102 |
| Neoadjuvant chemotherapy | 735 (23.7) | 493 (31.0) | <0.001 | 0.165 | 500 (34.8) | 629 (39.9) | 0.005 | 0.105 |
| Previous abdominal surgery | | | | | | | | |
| Extrahepatic surgery | 1,065 (34.3) | 452 (28.4) | <0.001 | 0.127 | 689 (48.0) | 869 (55.1) | <0.001 | 0.143 |
| Liver surgery | 274 (8.8) | 201 (12.6) | <0.001 | 0.123 | 145 (10.1) | 230 (14.6) | <0.001 | 0.137 |
| Disease | | | <0.001 | 0.214 | | | 0.02 | 0.132 |
| CRLM | 1,216 (39.2) | 703 (44.2) | | | 771 (53.7) | 907 (57.6) | | |
| HCC | 778 (25.1) | 359 (22.6) | | | 287 (20.2) | 342 (21.7) | | |
| Cholangiocarcinoma | 171 (5.5) | 108 (6.8) | | | 39 (2.7) | 43 (2.7) | | |
| Benign | 616 (19.8) | 220 (13.8) | | | 141 (9.8) | 117 (7.4) | | |
| NCRLM | 247 (8.0) | 122 (7.7) | | | 148 (10.3) | 130 (8.2) | | |
| Other malignancy | 62 (2.0) | 62 (3.9) | | | 38 (2.6) | 31 (2.0) | | |
| Multiple lesions | 745 (24.0) | 667 (41.9) | <0.001 | 0.388 | 521 (36.3) | 789 (50.1) | <0.001 | 0.280 |
| Bilobar distribution | 278 (9.0) | 210 (13.2) | <0.001 | 0.136 | 299 (20.8) | 632 (40.1) | <0.001 | 0.428 |
| Largest lesion, mm | 30 [18, 50] | 35 [21, 57.9] | <0.001 | 0.190 | 27 [17, 42] | 30.8 [20, 50.1] | <0.001 | 0.247 |
| Type of resection performed | | | 0.03 | 0.081 | | | <0.001 | 0.182 |
| Wedge | 1,699 (54.7) | 874 (54.9) | | | 900 (62.7) | 866 (54.9) | | |
| Segmentectomy | 530 (17.1) | 313 (19.7) | | | 274 (19.1) | 314 (19.9) | | |
| Bisegmentectomy | 875 (28.2) | 404 (25.4) | | | 261 (18.2) | 396 (25.1) | | |

Values are expressed in counts (percentages) or in medians [interquartile range], counts may not add up due to missing data. SD, standardized difference; BMI, body mass index; ASA, American Society of Anesthesiologists; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; NCRLM, non-colorectal liver metastases.

high-volume centres are illustrated in Figure S3. In this subgroup, the differential benefit for overall complications was even wider, in favour of AL resections (Figure S3A). For blood loss, a Delta of the differences similar to the entire cohort was observed, while no significant differential benefit was observed in terms of operative time and length of stay (Figure S3B-S3D).

A time-dependent sensitivity analysis was also performed, to assess the results in the latter period [2016–2019]. Table S3 shows the baseline characteristics of this population after PSM, and the peri-operative outcomes are reported in *Table 4*. While comparing laparoscopic and open liver surgery in this period, the benefit of laparoscopy in terms of blood loss were even greater (differences were 280 mL in the AL group and 172 mL in the PS group). However, in this time period there were no statistically significant differences in the differential benefit of laparoscopy in the AL and PS segments (Figure S4).

 

**Table 2** Peri-operative outcomes stratified by surgical approach (laparoscopic and open) after propensity score matching

| Outcomes | Anterolateral segments (n=3,040) | | | | Posterosuperior segments (n=2,336) | | | |
|---|---|---|---|---|---|---|---|---|
| | Laparoscopic (n=1,520) | Open (n=1,520) | P | Difference (95% CI) | Laparoscopic (n=1,168) | Open (n=1,168) | P | Difference (95% CI) |
| Intraoperative outcomes | | | | | | | | |
| Operation duration, minutes | 179.4 [117, 240] | 205 [165, 260] | <0.001 | 29.4 (22.2–36.7) | 201 [140, 275] | 225 [180, 285] | <0.001 | 21.8 (13.2–31.2) |
| Estimated blood loss, mm | 200 [75, 350] | 350 [150, 700] | <0.001 | 279.5 (226.3–340.1) | 200 [100, 500] | 350 [185, 595] | 0.02 | 84.5 (24–153) |
| Pringle manoeuvre | 503 (35.2) | 413 (36.8) | 0.72 | 1.6% (−2.2% to 5.4%) | 477 (41.8) | 477 (45.6) | 0.08 | 3.8% (−0.3% to 7.9%) |
| Intraoperative PRBC transfusion | 37 (2.9) | 53 (6.5) | 0.001 | 3.6% (1.8–5.7%) | 76 (7.5) | 73 (11.0) | 0.043 | 3.5% (0.7–6.4%) |
| Conversion | 89 (6.0) | | | | 127 (11.5) | | | |
| Postoperative outcomes | | | | | | | | |
| Irradical resection (R1 or R2)* | 189 (17.1) | 248 (20.4) | 0.009 | 3.3% (0.2–6.5%) | 192 (19.8) | 207 (20.6) | 0.86 | 0.8% (−2.7% to 4.4%) |
| Overall complications | 285 (19.0) | 456 (32.6) | <0.001 | 13.6% (10.5–16.9%) | 294 (25.4) | 392 (34.2) | <0.001 | 8.8% (5.1–12.5%) |
| Severe complications | 79 (5.3) | 127 (9.3) | <0.001 | 4% (2.2–6%) | 86 (7.4) | 97 (8.5) | 0.44 | 1.1% (−1.1% to 3.3%) |
| Length of stay, days | 4 [3, 5] | 6 [5, 8] | <0.001 | 3.5 (3.1–4) | 4 [3, 6] | 7 [5, 9] | <0.001 | 3.1 (2.6–3.7) |
| 90-day or in-hospital mortality | 20 (1.3) | 13 (0.9) | 0.47 | −0.4% (−1.2% to 0.3%) | 12 (1.0) | 15 (1.4) | 0.56 | 0.4% (−0.5% to 1.3%) |

Values are expressed in counts (percentages) or in medians [interquartile range], counts may not add up due to missing data. *, analysis only performed for malignant lesions. PRBC, packed red blood cell; CI, confidence interval.

## Discussion

In this study, laparoscopic and open resections in the AL and PS segments were compared using a differential benefit, to quantify the advantages associated with laparoscopy during these procedures. The results confirm the benefit of the laparoscopic over the open approach for both AL and PS resections and demonstrate that laparoscopic AL resections provide slightly more clinical benefit than laparoscopic PS resections, when each of them is compared with the open approach. Nevertheless, the laparoscopic approach was associated with less blood loss, a lower morbidity rate and a shorter length of stay in both the AL and PS segments, while the advantages were more pronounced in the AL segments.

Several studies have previously compared the outcomes of laparoscopic and open liver resections in different settings (22). However, their separate analyses of AL or PS resections were often limited to single institutional series (6,12,23,24). In this context, the inclusion in the current study of thousands of procedures from a multitude of centres may achieve results more representative of reality. Additionally, the use of PSM to create well balanced cohorts may have mitigated the influence of allocation bias (25,26).

Traditionally, the operative time of laparoscopic procedures has been longer compared to open procedures in many surgical subspecialties. However, our results demonstrated that this limitation of laparoscopy is nowadays overcome, since laparoscopic procedures resulted shorter operative times than open surgery. Nevertheless, no differential benefit of laparoscopy was observed for operative time in both the AL and PS segments. Both laparoscopic AL and PS resections showed less blood loss and a lower need for transfusions in comparison to open procedures, in line with the known benefits of laparoscopy. However, laparoscopic AL resections were associated with

 

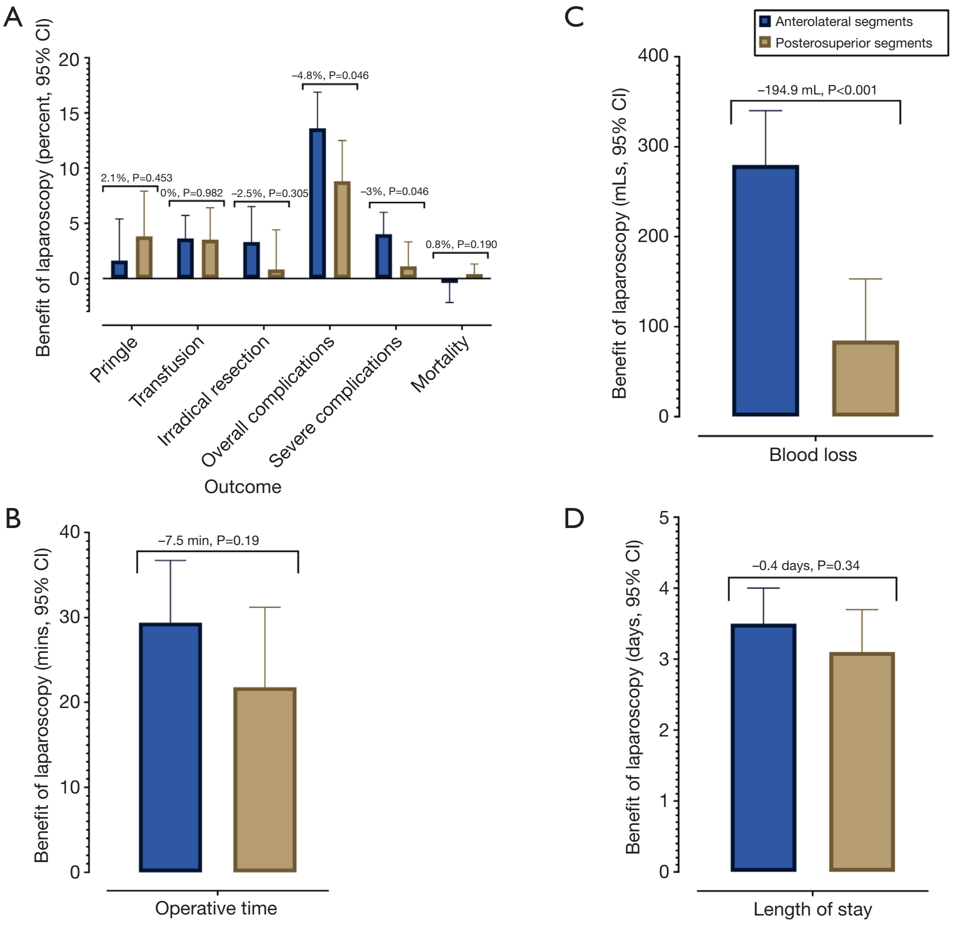


**Figure 1** Differential benefit of laparoscopy in the AL and PS segments in the complete cohort. CI, confidence interval; AL, anterolateral; PS, posterosuperior.

a greater benefit in this regard. This might be a reflection of the difficulty to obtain adequate exposure during liver resections of the PS segments; in addition, the rotation of the liver required during a complete liver mobilization can sometimes impair the liver outflow, contributing to more difficulty to control venous bleeding during laparoscopic resections (27).

The rate of overall complications was lower following laparoscopic resections, and again the differential benefit was greatest in AL resections. This finding might also be related to the relatively easy access to the AL segments. In fact, laparoscopic PS resections have been traditionally acknowledged as technically demanding. Many studies document a longer operative time and more frequent use of the Pringle manoeuvre than both their open counterparts and minimally-invasive resections in the AL segments (22,28). Some authors have described specific technical adjustments that can be adopted during resections in these unfavourable locations, aiming to facilitate their safe completion. Recently, techniques have also been elaborated and proposed in order to efficiently use the pure laparoscopic approach for centrally and deeply located tumours. Lastly, while the length of stay was shorter after laparoscopic procedures compared to open procedures, laparoscopy didn't have greater benefits in the AL or PS segments in this regard.

In addition, we explored the results in high-volume MILS centres (centres with a volume of at least 50 laparoscopic procedures per year). The comparison in this sub-setting resulted in a more pronounced differential benefit in AL resections regarding overall complications and blood loss. Concerning complications, the wider differential benefit between AL and PS resulted from a wider gap between laparoscopic and open procedures

**Table 3** Peri-operative outcomes stratified by surgical approach (laparoscopic and open) after propensity score matching, only high-volume centres (≥50 MI resections per year)

| Outcomes | Anterolateral segments (n=1,768) | | | | Posterosuperior segments (n=1,380) | | | |
|---|---|---|---|---|---|---|---|---|
| | Laparoscopic (n=893) | Open (n=893) | P | Difference (95% CI) | Laparoscopic (n=690) | Open (n=690) | P | Difference (95% CI) |
| Intraoperative outcomes | | | | | | | | |
| Operation duration, minutes | 170 [115, 240] | 210 [165, 265] | <0.001 | 31.9 (22–41.4) | 200 [141, 273] | 225 [180, 290] | 0.002 | 23.6 (11.3–36.3) |
| Estimated blood loss, mm | 200 [50, 350] | 320 [150, 600] | <0.001 | 171.6 (121.6–225.1) | 300 [100, 500] | 330 [200, 550] | 0.45 | –8.6 (–73.2 to 58.6) |
| Pringle manoeuvre | 304 (35.3) | 280 (44.3) | <0.001 | 9% (4.1–14.2%) | 281 (41.8) | 285 (47.1) | 0.09 | 5.4% (–0.2% to 10.7%) |
| Intraoperative PRBC transfusion | 19 (2.7) | 31 (4.7) | 0.11 | 2% (0.2–4.1%) | 51 (8.5) | 43 (7.6) | 0.32 | –0.9% (–4.1% to 2.2%) |
| Conversion | 34 (3.9) | | | | 86 (13.4) | | | |
| Postoperative outcomes | | | | | | | | |
| Irradical resection (R1 or R2)* | 163 (22.7) | 156 (21.7) | >0.99 | –1% (–5.4% to 3.2%) | 122 (21.5) | 130 (22.6) | 0.49 | 1.1% (–3.7% to 5.9%) |
| Overall complications | 180 (20.5) | 304 (39.4) | <0.001 | 18.9% (14.5–23.2%) | 185 (27.1) | 245 (36.4) | <0.001 | 9.3% (4.3–14.3%) |
| Severe complications | 54 (6.2) | 73 (9.7) | 0.03 | 3.6% (0.9–6.2%) | 53 (7.8) | 50 (7.5) | 0.84 | –0.3% (–3.2% to 2.5%) |
| Length of stay, days | 3.5 [2, 5] | 7 [5, 9] | <0.001 | 3.7 (3–4.4) | 4 [3, 6] | 7 [6, 9] | <0.001 | 3.4 (2.6–4.1) |
| 90-day or in-hospital mortality | 2 (0.2) | 8 (0.9) | 0.11 | 0.7% (0.1–1.5%) | 4 (0.6) | 5 (0.7) | >0.99 | 0.2% (–0.7% to 1%) |

Values are expressed in counts (percentages) or in medians [interquartile range], counts may not add up due to missing data. *, analysis only performed for malignant lesions. PRBC, packed red blood cell; CI, confidence interval.

within the AL group. An explanation to this might reside in the fact that within the reality of high-volume centres, the benefits of laparoscopy are even more magnified due to their extensive experience with this approach. In terms of length of stay, there was a benefit of laparoscopy in both AL and PS resections, and none of the two benefitted more than the other. Finally, a time-sensitivity analysis showed similar results in terms of better outcomes of laparoscopic surgery; nevertheless, the differential benefit of laparoscopy was not significantly greater in the AL or PS in this time period, as a remarkable difference with the analyses of the overall cohort where laparoscopy was revealing more advantages for AL resection. It is reasonable to think that the enhanced experience obtained prior to the latter period would result in improved outcomes for PS resections and thus in a flattened differential benefit—meaning both PS and AL resections benefit from minimally-invasiveness to a similar extent. This hypothesis is supported by a nationwide study from Italy which reported comparable perioperative outcomes following minimally invasive resections for HCC in the AL versus PS segments (29).

The latter result is somehow highlighted in a previous study from Cipriani *et al.*, where the authors investigated the differential benefit of laparoscopy in the AL and PS segments in a single, high-volume centre study (13). Interestingly, they found that the benefit of laparoscopy was greater in the PS segments, rather than the AL segments, in terms of blood loss, length of stay and morbidity. However, our analysis performed on a larger, multi-institutional cohort did not confirm this. Nevertheless, the study from Cipriani *et al.* might be representative for very high-volume centres. The more pronounced benefits of laparoscopic PS resections observed in this centre might be the result of extensive experience and a meticulous standardization and

**Table 4** Peri-operative outcomes stratified by surgical approach (laparoscopic and open) after propensity score matching, time period 2016–2019

| Outcomes | Anterolateral segments (n=660) | | | | Posterosuperior segments (n=962) | | | |
|---|---|---|---|---|---|---|---|---|
| | Laparoscopic (n=330) | Open (n=330) | P | Difference (95% CI) | Laparoscopic (n=481) | Open (n=481) | P | Difference (95% CI) |
| Intraoperative outcomes | | | | | | | | |
| Operation duration, minutes | 180 [124.3, 251.8] | 215.5 [169.4, 270] | 0.04 | 25.5 (9–41.1) | 230 [150, 300] | 240 [190, 304.2] | <0.001 | 20.4 (5.9–34.3) |
| Estimated blood loss, mm | 156 [100, 350] | 400 [100, 713] | <0.001 | 280.3 (183.2–406) | 200 [100, 425] | 340 [170, 600] | <0.001 | 172.6 (93.2–288.6) |
| Pringle manoeuvre | 136 (42.9) | 80 (32.9) | 0.009 | −10.4% (−18.4% to −2.3%) | 246 (52.2) | 226 (49.8) | 0.42 | −2.4% (−8.8% to 4%) |
| Intraoperative PRBC transfusion | 4 (1.5) | 8 (6.0) | 0.046 | 4.5% (1–9.9%) | 25 (6.2) | 30 (12.0) | 0.03 | 5.9% (1.5–11%) |
| Conversion | 21 (6.5) | | | | 46 (10.0) | | | |
| Postoperative outcomes | | | | | | | | |
| Irradical resection (R1 or R2)* | 52 (20.2) | 64 (23.7) | 0.51 | 3.5% (−3.4% to 10.7%) | 96 (24.2) | 108 (26.0) | 0.86 | 1.8% (−4.3% to 7.6%) |
| Overall complications | 63 (19.4) | 97 (30.6) | 0.002 | 11.5% (4.7–18.4%) | 122 (25.6) | 189 (39.6) | <0.001 | 14% (8.2–20%) |
| Severe complications | 21 (6.5) | 31 (10.0) | 0.18 | 3.8% (−0.4% to 8.1%) | 30 (6.3) | 50 (10.5) | 0.02 | 4.2% (0.6–7.7%) |
| Length of stay, days | 4 [3, 6] | 6 [5, 8] | <0.001 | 3.2 (2.2–5.1) | 4 [3, 6] | 7 [5, 9] | <0.001 | 3.4 (2.6–4.2) |
| 90-day or in-hospital mortality | 3 (0.9) | 1 (0.3) | 0.62 | −0.2% (−1.6% to 1.1%) | 2 (0.4) | 9 (2.0) | 0.03 | 1.6% (0.4–3.2%) |

Values are expressed in counts (percentages) or in medians [interquartile range], counts may not add up due to missing data. *, analysis only performed for malignant lesions. PRBC, packed red blood cell; CI, confidence interval.

refining of the technique, resulting in a greater benefit of laparoscopy in the most challenging procedures.

The above-mentioned results are innovative and add to the body of evidence on the efficacy of laparoscopic liver resections. After the first guidelines meeting on laparoscopic liver surgery, the laparoscopic approach has been recommended as standard practice for resections in the left lateral section, and as the preferred approach for minor liver resections in the AL segments (2). Our study provides insight into the efficacy profile that a laparoscopic approach may confer to different type of liver resections in the current era, demonstrating several benefits of laparoscopy when adopted for minor liver resections in both the AL and PS segments. These results are thus encouraging and support a wider adoption of MILS in selected patients requiring a minor liver resection, irrespective of the location.

Some limitations need to be kept in mind when reading this study. First, this study has the well-known limitations of a retrospective study. Patients were allocated to a surgical technique (laparoscopic or open) without randomization, hence with a possible influence of selection bias on its results. We attempted to mitigate this influence by only including specific, well-defined, procedures (minor resections in the AL and PS segments), and performing a propensity score matched analysis, using factors which may have an effect on treatment allocation as covariates in the PSM model. Nevertheless, the data of some possible confounding factors embedded in difficulty scores (such as the distance to major vessels or the type of previous liver resection) were unfortunately not available, and PSM does not account for unknown confounders (30). Second, the learning curve, centre and surgeon volumes might also have an influence on the investigated outcomes. We addressed this issue by performing the sensitivity analysis. Conversely to the findings in the overall cohort, we found no difference in the differential benefit in the AL and PS segments in the time-dependent analysis. Therefore, it could be that, with increasing experience, the benefits of laparoscopy even become greater in the PS segments, as demonstrated in the earlier mentioned single-centre study (12). Third, a standardized intra and postoperative management protocol was not a prerequisite for participation in the present retrospective study, which may also introduce a certain degree of bias. Our aim was however to conduct a pragmatic study which depicts a "real world image" of the contemporary practices and outcomes in a multitude of Western tertiary referral centres. Nevertheless, it is desirable to confirm these findings in a well-designed multicentre randomized trial, with a certain degree of standardization of peri-operative management, in order to minimize the effect of confounding. The results of the ORANGE Segments trial, which recently finished accrual, are expected soon (31). Acknowledging these shortcomings, we believe that the interest should now be focused on fine-tuning the knowledge of the advantages on mini-invasiveness for selected procedures and in specific settings.

## Conclusions

The advantage of laparoscopic over open liver surgery is greater in the AL segments. However, advantages of laparoscopy were also widely observed in the PS group. Despite their technical difficulty, selected patients requiring a PS resection should be allocated to a laparoscopic approach, whenever the expertise of the surgical team is adequate.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-494/rc

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-494/coif). M.A.H. and L.A.A. serve as unpaid editorial board members of *HepatoBiliary Surgery and Nutrition*. Outside of the submitted work, S.L.B. reported payment or honoraria from Baxter, Olympus, Siemens and Johnson & Johnson, and A.A.F. reported speaker's honoraria from Bayer and Olympus. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Declaration of Helsinki (as revised in 2013) was respected at all times during the conduct of this study. The medical ethical committee of Brescia approved this study and waived the need to obtain informed consent due to its retrospective nature and the use of pseudonymized data (Judgement's reference number: NP 5472).



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## Supplementary

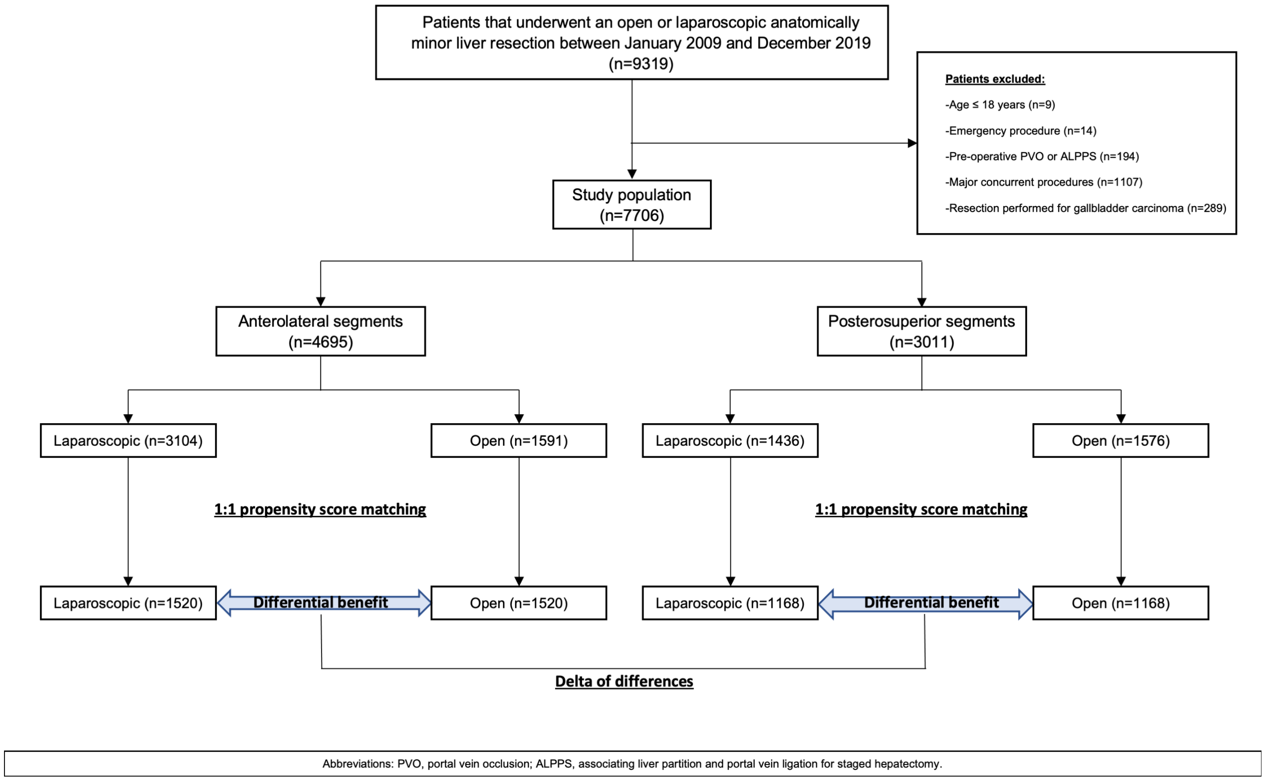


**Figure S1** Study flowchart.

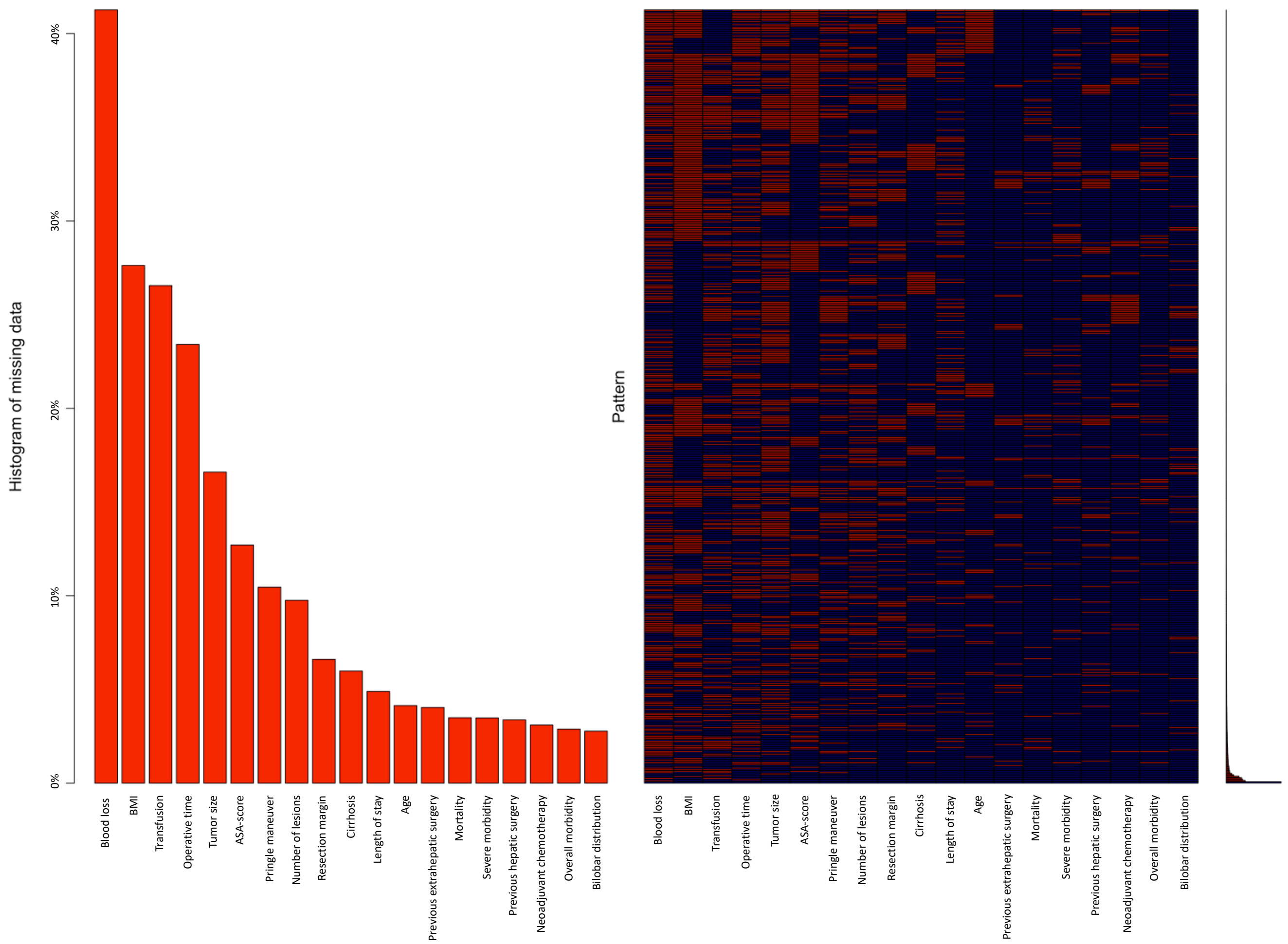


**Figure S2** Overview of missing data.


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**Table S1** Baseline characteristics stratified by surgical approach (Laparoscopic and open) after propensity score matching

| Characteristics | Anterolateral segments (n=3,040) | | | | Posterosuperior segments (n=2,336) | | | |
|---|---|---|---|---|---|---|---|---|
| | Laparoscopic (n=1,520) | Open (n=1,520) | P | SD | Laparoscopic (n=1,168) | Open (n=1,168) | P | SD |
| Age, years | 65 [53, 71] | 64 [54.6, 71.4] | 0.004 | 0.082 | 64.5 [55, 72] | 65.7 [55.8, 71.9] | 0.764 | 0.031 |
| Sex, male | 853 (56.1) | 922 (60.7) | 0.006 | 0.092 | 723 (61.9) | 748 (64) | 0.228 | 0.044 |
| BMI, kg/$m^2$ | 26.3 [23.3, 28.9] | 26.2 [23.7, 29.7] | 0.028 | 0.060 | 26.5 [23.4, 29.3] | 26.2 [23.5, 29.4] | 0.974 | 0.002 |
| ASA 3&4 | 546 (35.9) | 530 (34.9) | 0.542 | 0.022 | 451 (38.6) | 400 (34.2) | 0.016 | 0.091 |
| Cirrhosis | 294 (19.3) | 366 (24.1) | 0.002 | 0.115 | 231 (19.8) | 222 (19.0) | 0.634 | 0.019 |
| Neoadjuvant chemotherapy | 440 (28.9) | 448 (29.5) | 0.771 | 0.012 | 394 (33.7) | 426 (36.5) | 0.126 | 0.057 |
| Previous abdominal surgery | | | | | | | | |
| Extrahepatic surgery | 547 (36.0) | 441 (29.0) | <0.001 | 0.149 | 532 (45.5) | 638 (54.6) | <0.001 | 0.182 |
| Liver surgery | 229 (15.1) | 184 (12.1) | 0.011 | 0.086 | 138 (11.8) | 133 (11.4) | 0.764 | 0.013 |
| Disease | | | 0.345 | 0.195 | | | 0.010 | 0.112 |
| CRLM | 648 (42.6) | 669 (44.4) | | | 593 (50.8) | 656 (56.2) | | |
| HCC | 343 (22.6) | 348 (23.1) | | | 271 (23.2) | 250 (21.4) | | |
| Cholangiocarcinoma | 74 (4.9) | 98 (6.4) | | | 32 (2.7) | 34 (2.9) | | |
| Benign | 304 (20.0) | 218 (14.3) | | | 113 (9.7) | 101 (8.6) | | |
| NCRLM | 119 (7.8) | 116 (7.6) | | | 116 (9.9) | 98 (8.4) | | |
| Other malignancy | 28 (1.8) | 58 (3.8) | | | 34 (2.9) | 26 (2.2) | | |
| Multiple lesions | 555 (36.5) | 596 (39.2) | 0.007 | 0.056 | 458 (39.2) | 503 (43.1) | 0.019 | 0.078 |
| Bilobar distribution | 223 (14.7) | 190 (12.5) | 0.050 | 0.063 | 298 (25.5) | 305 (26.1) | 0.534 | 0.014 |
| Diameter largest lesion, millimetres | 35 [20, 60] | 35 [20.6, 55] | 0.571 | 0.021 | 28 [17, 47] | 30 [20, 47] | 0.009 | 0.086 |
| Type of resection performed | | | 0.015 | 0.149 | | | 0.027 | 0.101 |
| Wedge | 914 (60.1) | 826 (54.3) | | | 687 (58.8) | 643 (55.1) | | |
| Segmentectomy | 223 (14.7) | 303 (19.9) | | | 247 (21.1) | 243 (20.8) | | |
| Bisegmentectomy | 383 (25.2) | 391 (25.7) | | | 234 (20.0) | 282 (24.1) | | |

Values are expressed in counts (percentages) or in medians [interquartile range]. SD, standardized difference; BMI, body mass index; ASA, American Society of Anesthesiologists; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; NCRLM; non-colorectal liver metastases.

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**Table S2** Baseline characteristics stratified by surgical approach (laparoscopic and open) after propensity score matching, only high-volume centres (≥50 laparoscopic resections per year)

| Characteristics | Anterolateral segments (n=1,786) | | | | Posterosuperior segments (n=1,380) | | | |
|---|---|---|---|---|---|---|---|---|
| | Laparoscopic (n=893) | Open (n=893) | P | SD | Laparoscopic (n=690) | Open (n=690) | P | SD |
| Age, years | 63 [52.6, 69.8] | 64 [55, 71.8] | 0.003 | 0.166 | 64.8 [54.9, 71.8] | 65.3 [55, 71] | 0.483 | 0.052 |
| Sex, Male | 544 (60.9) | 552 (61.8) | 0.741 | 0.018 | 424 (61.4) | 439 (63.6) | 0.392 | 0.045 |
| BMI, $kg/m^2$ | 26.3 [23.3, 28.4] | 26.1 [23.4, 29.4] | 0.143 | 0.053 | 26.6 [23.6, 29] | 25.6 [23.2, 29] | 0.064 | 0.084 |
| ASA 3&4 | 363 (40.6) | 349 (39.1) | 0.515 | 0.032 | 232 (33.6) | 258 (37.4) | 0.089 | 0.079 |
| Cirrhosis | 243 (27.2) | 276 (30.9) | 0.079 | 0.081 | 138 (20.0) | 154 (22.3) | 0.256 | 0.057 |
| Neoadjuvant chemotherapy | 330 (37.0) | 332 (37.2) | 0.957 | 0.005 | 275 (39.9) | 285 (41.3) | 0.566 | 0.030 |
| Previous abdominal surgery | | | | | | | | |
| Extrahepatic surgery | 318 (35.6) | 194 (21.7) | <0.001 | 0.311 | 346 (50.1) | 343 (49.7) | 0.911 | 0.009 |
| Liver surgery | 137 (15.3) | 117 (13.1) | 0.190 | 0.064 | 111 (16.1) | 105 (15.2) | 0.685 | 0.024 |
| Disease | | | 0.729 | 0.195 | | | 0.604 | 0.205 |
| CRLM | 383 (42.9) | 387 (43.3) | | | 367 (53.2) | 375 (54.3) | | |
| HCC | 231 (25.9) | 207 (23.2) | | | 136 (19.7) | 153 (22.2) | | |
| Cholangiocarcinoma | 53 (5.9) | 71 (8.0) | | | 22 (3.2) | 25 (3.6) | | |
| Benign | 117 (13.1) | 94 (10.5) | | | 81 (11.7) | 65 (9.4) | | |
| NCRLM | 87 (9.7) | 85 (9.5) | | | 71 (10.3) | 54 (7.8) | | |
| Other malignancy | 13 (1.5) | 35 (3.9) | | | 3 (0.4) | 16 (2.3) | | |
| Multiple lesions | 374 (41.9) | 388 (43.4) | 0.272 | 0.032 | 305 (44.2) | 308 (44.6) | 0.886 | 0.009 |
| Bilobar distribution | 133 (14.9) | 98 (11) | 0.017 | 0.117 | 184 (26.7) | 193 (28) | 0.448 | 0.029 |
| Largest lesion, millimetres | 30 [17, 50] | 35 [20.4, 55] | <0.001 | 0.216 | 30 [18, 50] | 32 [20, 50] | 0.075 | 0.090 |
| Type of resection performed | | | 0.576 | 0.219 | | | 0.349 | 0.051 |
| Wedge | 526 (58.9) | 489 (54.8) | | | 361 (52.3) | 345 (50.0) | | |
| Segmentectomy | 115 (12.9) | 187 (20.9) | | | 165 (23.9) | 168 (24.3) | | |
| Bisegmentectomy | 252 (28.2) | 217 (24.3) | | | 164 (23.8) | 177 (25.7) | | |

Values are expressed in counts (percentages) or in medians [interquartile range]. SD, standardized difference; BMI, body mass index; ASA, American Society of Anesthesiologists; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; NCRLM, non-colorectal liver metastases.


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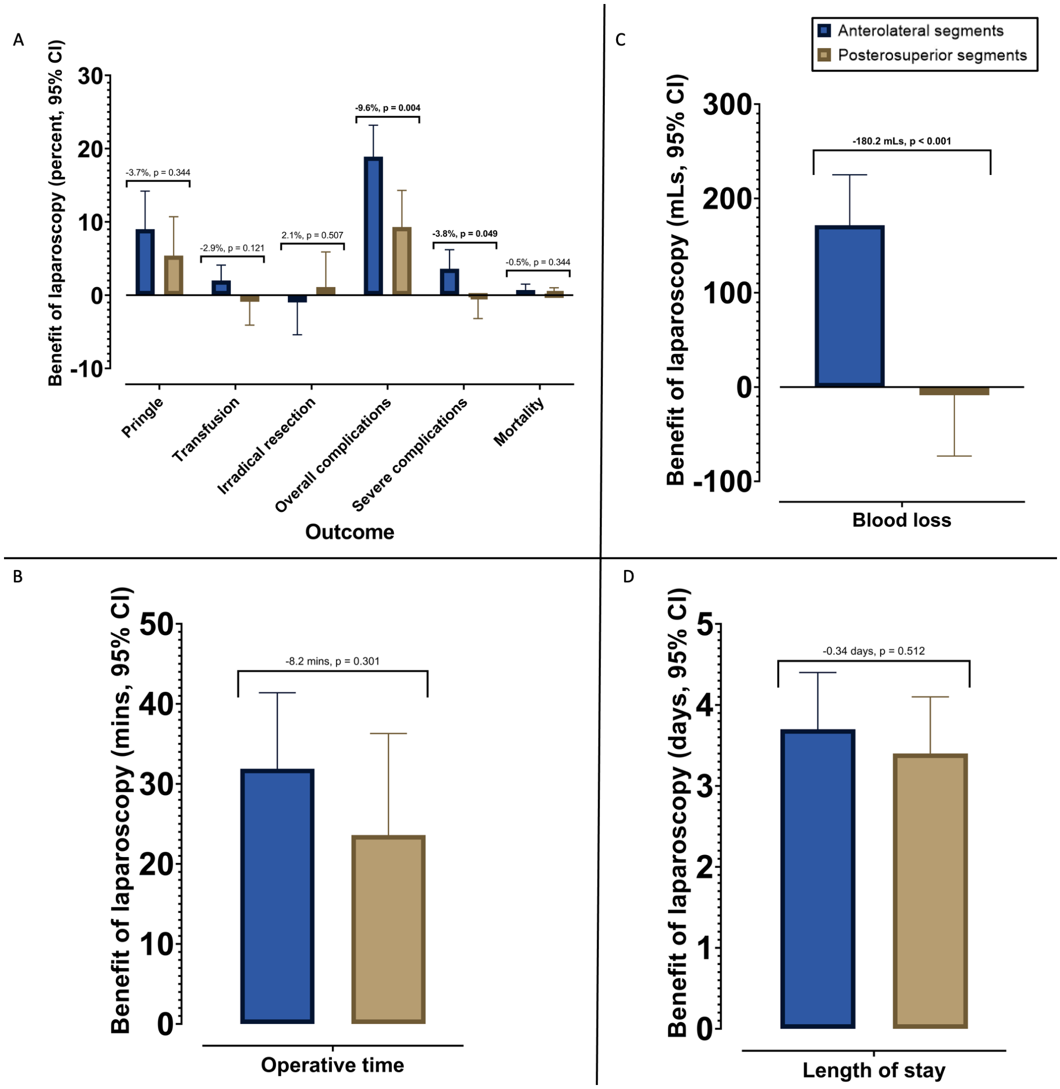


**Figure S3** Differential benefit of laparoscopy in the AL and PS segments in high-volume centers. CI, confidence interval; AL, anterolateral; PS, posterosuperior.


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**Table S3** Baseline characteristics stratified by surgical approach (laparoscopic and open) after propensity score matching, time period 2016–2019

| Characteristics | Anterolateral segments (n=660) | | | | Posterosuperior segments (n=962) | | | |
|---|---|---|---|---|---|---|---|---|
| | Laparoscopic (n=330) | Open (n=330) | P | SD | Laparoscopic (n=481) | Open (n=481) | P | SD |
| Age, years | 65.1 [52, 69.1] | 65.8 [54.9, 71.4] | <0.001 | 0.194 | 65.7 [56, 72] | 66 [56, 72.1] | 0.523 | 0.016 |
| Sex, Male | 200 (60.6) | 191 (57.9) | 0.200 | 0.056 | 311 (64.7) | 300 (62.4) | 0.457 | 0.048 |
| BMI, kg/m$^2$ | 26 [23.2, 29.1] | 25.6 [23, 29.2] | 0.862 | 0.005 | 25.7 [23, 28.7] | 25.9 [23.4, 29.3] | 0.091 | 0.106 |
| ASA 3&4 | 117 (35.5) | 109 (33.0) | 0.201 | 0.051 | 167 (34.7) | 174 (36.2) | 0.680 | 0.030 |
| Cirrhosis | 87 (26.4) | 81 (24.5) | 0.345 | 0.042 | 93 (19.3) | 95 (19.8) | 0.932 | 0.010 |
| Neoadjuvant chemotherapy | 82 (24.8) | 80 (24.2) | 0.850 | 0.014 | 178 (37.0) | 152 (31.6) | 0.044 | 0.114 |
| Previous abdominal surgery | | | | | | | | |
| Extrahepatic surgery | 106 (32.1) | 98 (29.7) | 0.533 | 0.052 | 218 (45.3) | 261 (54.3) | 0.007 | 0.180 |
| Liver surgery | 30 (9.1) | 33 (10.0) | 0.505 | 0.031 | 55 (11.4) | 53 (11.0) | 0.908 | 0.013 |
| Disease | | | | 0.233 | | | 0.975 | 0.077 |
| CRLM | 125 (37.8) | 129 (39.1) | | | 258 (53.6) | 260 (54.1) | | |
| HCC | 99 (30.0) | 87 (26.4) | | | 110 (22.9) | 112 (23.3) | | |
| Cholangiocarcinoma | 24 (7.3) | 28 (8.5) | | | 12 (2.5) | 14 (2.9) | | |
| Benign | 40 (12.1) | 46 (13.9) | | | 47 (9.8) | 42 (8.7) | | |
| NCRLM | 30 (9.1) | 17 (5.2) | | | 38 (7.9) | 36 (7.5) | | |
| Other malignancy | 9 (2.7) | 19 (5.8) | | | 11 (2.3) | 16 (3.3) | | |
| Multiple lesions | 105 (31.8) | 106 (32.1) | 1 | 0.006 | 227 (47.2) | 218 (45.3) | 0.565 | 0.038 |
| Bilobar distribution | 43 (13.0) | 43 (13.0) | 1 | 0 | 171 (35.6) | 172 (35.8) | >0.99 | 0.004 |
| Largest lesion, millimetres | 30 [20, 53.8] | 36 [23, 55] | <0.001 | 0.227 | 28 [16, 50] | 32 [22, 50] | 0.001 | 0.160 |
| Type of resection performed | | | 0.634 | 0.142 | | | 0.673 | 0.027 |
| Wedge | 192 (58.2) | 180 (54.5) | | | 269 (55.9) | 263 (54.7) | | |
| Segmentectomy | 51 (15.5) | 69 (20.9) | | | 99 (20.6) | 100 (20.8) | | |
| Bisegmentectomy | 87 (26.4) | 81 (24.5) | | | 113 (23.5) | 118 (24.5) | | |

Values are expressed in counts (percentages) or in medians [interquartile range]. SD, standardized difference; BMI, body mass index; ASA, American Society of Anesthesiologists; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; NCRLM, non-colorectal liver metastases.

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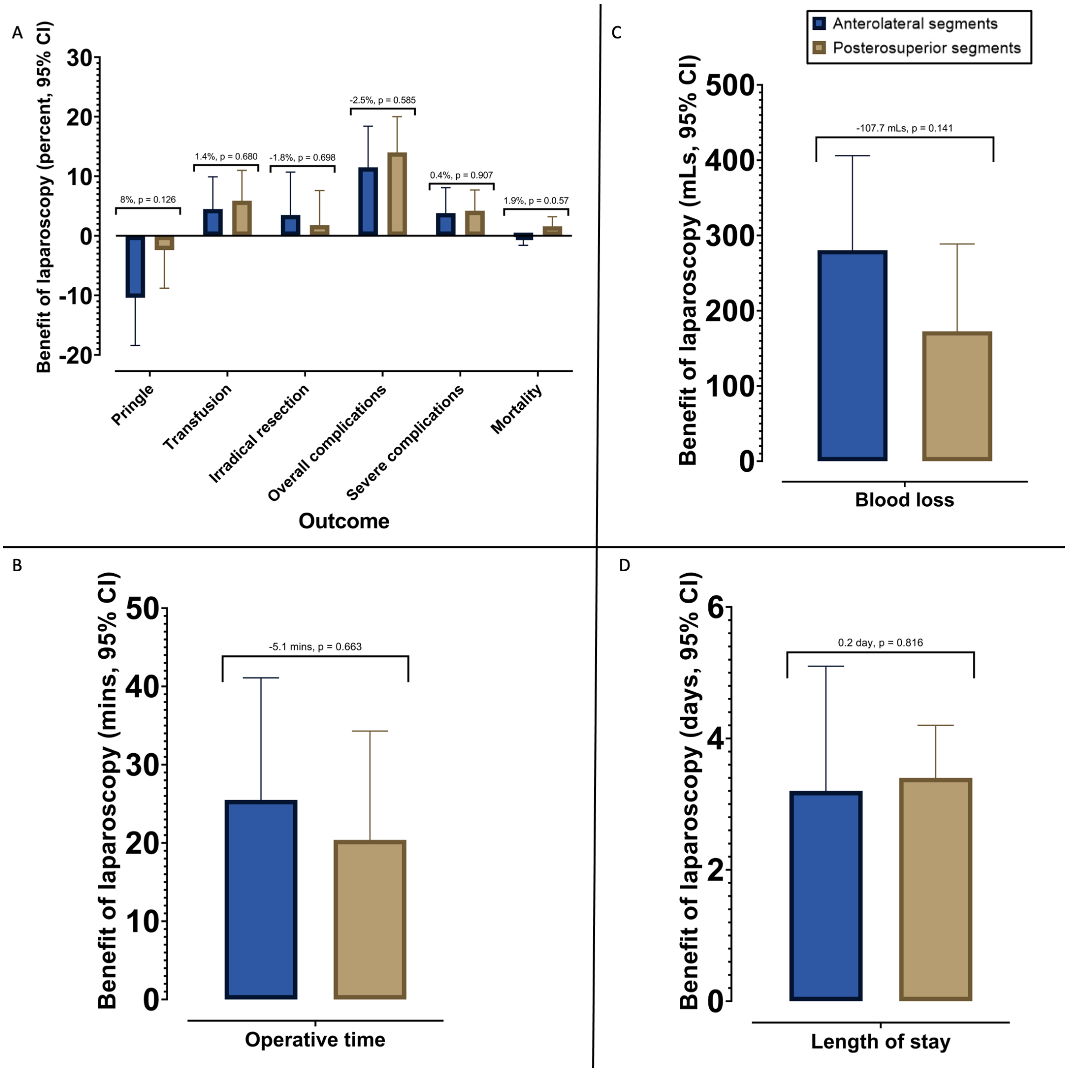


**Figure S4** Differential benefit of laparoscopy in the AL and PS segments in the last time period [2016–2019]. CI, confidence interval; AL, anterolateral; PS, posterosuperior.


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