Minor Hepatectomies: Focusing a Blurred Picture: Analysis of the Outcome of 4471 Open Resections in Patients Without Cirrhosis

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Minor hepatectomies: Focusing a blurred picture

Analysis of the outcome of 4471 open resections in patients without cirrhosis

Luca Viganò[1], PhD, Guido Torzilli[1], PhD, Roberto Troisi[2], MD, Luca Aldrighetti[3], MD, Alessandro Ferrero[4], MD, Pietro Majno[5,6], MD, Christian Toso[5], PhD, Joan Figueras[7], MD, Daniel Cherqui[8], MD, René Adam[8], MD, Norihiro Kokudo[9], MD, Kiyoshi Hasegawa[9], MD, Alfredo Guglielmi[10], MD, Marek Krawczyk[11], MD, Felice Giuliante[12], MD, Mohammad Abu Hilal[13], MD, José Costa-Maia[14], MD, Antonio Daniele Pinna[15], MD, Matteo Cescon[15], MD, Eduardo De Santibanes[16], MD, Lucio Urbani[17], MD, Timothy Pawlik[18], PhD, Guido Costa[1], MD, Daniela Zugna[19], PhD, on behalf of the CLISCO group*.

1. Division of Hepatobiliary and General Surgery, Department of Surgery, Humanitas Clinical and Research Center – IRCCS, Humanitas University, Rozzano - Milan, Italy; 2. Ghent University Hospital, Ghent, Belgium; 3. S. Raffaele Hospital, Milano, Italy; 4. Mauriziano Hospital, Torino, Italy; 5. University Hospital of Geneva, Geneva, Switzerland; 6. Ospedale Regionale di Lugano, Lugano, Switzerland; 7. Josep Trueta Hospital, Girona, Spain; 8. Paul Brousse Hospital, Villejuif, France; 9. University of Tokyo Hospital, Tokyo, Japan; 10. Policlinico Rossi, Verona, Italy; 11. Medical University of Warsaw, Warsaw, Poland; 12. Gemelli Hospital, Roma, Italy; 13. University Hospital Southampton, Southampton, UK; 14. Centro Hospitalier de Sao Joao, Oporto, Portugal; 15. S. Orsola Hospital, Bologna, Italy; 16. Hospital Italiano, Buenos Aires, Argentina; 17. Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; 18. The Ohio State University Wexner Medical Center, US; 19. Department of Medical Sciences, Cancer Epidemiology Unit, University of Torino and CPO-Piemonte, Torino, Italy.

* CLISCO group: *Classification of Liver Surgery on Complexity and Outcome Group*

Corresponding Author:

Guido Torzilli, MD, PhD, FACS, Professor of Surgery, Director Department of Surgery & Division of Hepatobiliary & General Surgery, Humanitas Clinical and Research Center– IRCCS, Humanitas University, Via A. Manzoni, 56, 20089, Rozzano, Milan, Italy; Tel: +39-02-8224-4769; Fax: +39-02-8224-4590. E-mail: guido.torzilli@hunimed.eu

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MINI-ABSTRACT

Minor hepatectomies encompass a wide range of procedures. The present study elucidated their outcomes analyzing 4471 patients. Mortality is low, but they can be stratified according to severe morbidity, bile leak, and liver failure rates. Most complex resections have outcomes similar to right hepatectomy.

ABSTRACT

Objective: To elucidate minor hepatectomy (MiH) outcomes

Summary Background Data: Liver surgery has moved toward a parenchyma-sparing approach, favoring MiHs over major resections. MiHs encompass a wide range of procedures.

Methods: We retrospectively evaluated consecutive patients that underwent open liver resections in 17 high-volume centers. Exclusion criteria: cirrhosis and associated digestive/biliary resections. Resections were classified as (Brisbane nomenclature): limited resections (LR); (mono)segmentectomies/bisegmentectomies (S/BS); right anterior and right posterior sectionectomies (RAS/RPS). Additionally, we defined: complex LRs (CLR=LRs with exposed vessels); postero-superior segmentectomies (PSS=segment (Sg)7, Sg8, and Sg7+Sg8 segmentectomies); and complex core hepatectomies (CCHs=Sg1 segmentectomies and combined resections of Sg4s+Sg8+Sg1). Left lateral sectionectomies (LLSs, n=442) and right hepatectomies (RHs, n=1042) were reference standards. Outcomes were adjusted for potential confounders.

Results: 4471 MiHs were analyzed. Compared to RHs, MiHs had lower 90-day mortality (0.5%/2.2%), severe morbidity (8.6%/14.4%), and liver failure rates (2.4%/11.6%, p<0.001), but similar bile leak rates. LR and LLS had similar outcomes. CLR and S/BS of anterolateral segments had higher bile leak rates than LLS rates (OR=2.35/OR=3.24), but similar severe morbidity rates. CCHs had higher bile leak rates than RH rates (OR=1.94); the severe morbidity rate approached that of RH. PSS, RAS, and RPS had severe morbidity and bile leak rates similar to RH rates. MiHs had low liver failure rates, except RAS (vs. LLS OR=4.02).

Conclusions: MiHs had heterogeneous outcomes. Mortality was low, but MiHs could be stratified according to severe morbidity, bile leak, and liver failure rates. Most complex resections had outcomes similar to RH outcomes.

INTRODUCTION

In past decades, liver surgery has moved toward a parenchyma-sparing approach, favoring minor hepatectomies (MiHs) over major resections [1-5]. Compared to major hepatectomies, MiHs are associated with lower mortality and fewer liver failures, with the same oncologic results, when properly conducted [1-6]. In cases of recurrence, patients that received a parenchyma-sparing surgery at the first diagnosis were more frequently eligible for repeated treatment and, consequently, had a better prognosis than patients that received major hepatectomies [4,7,8]. With the acquisition of deep knowledge of liver anatomy and the systematic implementation of intraoperative ultrasonography guidance, MiHs have been extended for treating deep and ill-located tumors [9].

MiHs encompass a wide range of procedures, including peripheral liver resections, anatomic mono- or bisegmentectomies, and complex resections of tumors with major vascular contacts. Overall, a non-negligible proportion of MiHs (5-15%) have been associated with severe postoperative complications that might impact quality of life, limit access to adjuvant treatments, and compromise the oncologic prognosis [10-12]. Theoretically, different MiHs are associated with different outcomes. Therefore, the classes ‘major’ and ‘minor’ are no longer adequate descriptors for depicting modern hepatectomies. New classifications have been proposed [13-15], but they are based on resection complexity, which does not necessarily correspond to outcome, and do not adequately reflect MiH heterogeneity.

The present study aimed to elucidate the outcomes of different MiH types. We accessed a large multicenter database with data from high-volume hepato-biliary centers worldwide. Outcomes of different MiHs were compared with outcomes of the two most standardized liver resections: the right hepatectomy (RH) and the left lateral sectionectomy (LLS).

METHODS

We retrospectively collected data for all consecutive patients that underwent a first liver resection in 17 international high-volume centers (**Supplementary Table 1**) during 2004-2014. Data from some centers reflected a shorter enrollment period, due to difficulties in collecting less recent data. The study protocol was amended accordingly, but all inclusions comprised a series of consecutive patients. Exclusion criteria were: repeated hepatectomies; emergency resection, and digestive or biliary resection associated with liver surgery. The cohort included 10770 patients. For the present study, we applied the following additional exclusion criteria: liver cirrhosis, mini-invasive liver surgery, and staged hepatectomies. Thus, we considered 7312 patients without cirrhosis that underwent a first open liver resection.

The study was approved by the local ethical committees and the requirement of informed consent was waived.

Study design

The primary endpoint was the severe morbidity rate. Morbidity rates were compared between the different MiHs (n=4471) and RH, the most standardized major hepatectomy. RHs performed in the same centers during the same period were used as reference standard (n=1042). RHs of staged hepatectomies were excluded. Secondary endpoints were: (*i*) severe morbidity rates of different MiHs compared to that of LLS, the most standardized MiH; and (*ii*) comparisons between MiH and RH and between MiH and LLS for mortality, overall morbidity, comprehensive complication index (CCI), liver failures, bile leaks, blood transfusions, and hospital stay times. Again, LLSs performed in the same centers during the same period were used as reference standard (n=442). Blood loss was not analyzed, because the data were not available for all patients, and the method of computing blood loss differed among centers.

Two separate analyses were performed. First, we evaluated unadjusted associations between the different procedures and outcomes. Second, associations between resection types and outcome were adjusted for covariates (see Statistical Analyses). Adjusted associations were performed for overall and severe morbidity, bile leaks, and liver failure. Mortality was not included, due to the low number of events.

We adopted the Brisbane nomenclature for the following hepatectomies [16]: limited resections (LR); (mono)segmentectomies (S); left lateral sectionectomies (LLS); right anterior sectionectomies (RAS); right posterior sectionectomies (RPS); and other bisegmentectomies (BS). In addition, we defined three types of resections to identify procedures that theoretically could be associated with different outcomes, but were not adequately identified by the Brisbane classification. These types were: complex LRs (CLR), defined as LRs with major intrahepatic vessels exposed; postero-superior segmentectomies (PSS), defined as segmentectomies of segment 8 (Sg8), segmentectomies of Sg7, and bisegmentectomies of Sg7-8; and complex core hepatectomies (CCH), defined as segmentectomies of Sg1 and combined resections of Sg4s+Sg8+Sg1 (e.g., minimesohepatectomy, upper transversal hepatectomy, and liver tunnel [17-19]). The groups were determined a priori, before explorative analyses. The different MiH types are illustrated in **Figure 1.** In patients that underwent multiple resections, the most complex procedure was considered.

Definitions and Statistical analysis

Operative mortality was defined as death within 90 days after surgery. Morbidity was graded according to the Dindo-Clavien classification; any complication of grade ≥3 was classified as severe morbidity [20]. CCI was defined according to Slankamenac et al. [21] and was computed with an online calculator [22]. Postoperative liver failure and bile leaks were defined according to the ISGLS definition [23,24].

Continuous variables were assessed graphically to determine distribution normality, and they were evaluated with parametric (unpaired *t*-test) or non-parametric (Mann-Whitney *U*-test) tests, accordingly. Categorical variables were assessed with the chi-square or Fisher's exact tests, as appropriate. A multivariable logistic-regression model was performed to analyze associations between different MiHs and outcomes, after adjusting for potential confounders. Potential confounders were: age; ASA score; HBV/HCV infection; preoperative chemotherapy; diagnosis; preoperative total bilirubin, albumin and AST values; and the enrolling center. Preoperative INR values were not included due to missing data (36%). The number of predictors included were limited to ensure model parsimony, as suggested by Harrell et al. [25]. Adjusted p-values (q-values) were computed with the Benjamini-Hochberg correction to assess the false discovery rate for multiple comparisons [26]. All analyses were performed with Stata 15 software.

RESULTS

Overall, we analyzed data for 5513 patients that underwent a first open liver resection in a non-cirrhotic liver: 4471 had undergone MiHs, including 442 LLSs, and 1042 had undergone RHs. Patient characteristics are reported in **Table 1.** Compared to the RH group, the MiH group included older patients with more HBV/HCV infections, less cholangiocarcinomas, and more liver metastases. Some liver function tests differed between groups, but most values were within the normal range. Procedures and outcomes are summarized in **Table 2**. Compared to the RH group, the MiH group had lower 90-day mortality (0.5 vs. 2.2%, $p<0.001$), overall morbidity (31.3 vs. 44.0%, $p<0.001$), severe morbidity (8.6 vs. 14.4%, $p<0.001$), and liver failure rates (2.4 vs. 11.6%, $p<0.001$), but a similar bile leak rate (6.2 vs. 6.7%). Among patients with liver failure, mortality after RH was about two-fold the mortality after MiH (10 vs. 5.7%).

Severe morbidity

Figure 2a-b summarizes the adjusted odds ratios for severe morbidity of different MiHs. The LLS was associated with a low severe morbidity rate (5.4%, vs. RH, odds ratio [OR]: 0.30, 95% confidence intervals [95%CI]: 0.16-0.55). The LR, CLR, and S/BS of anterolateral segments (Sg2-6) were associated with slightly higher severe morbidity rates than the LLS (7.3%, 8.6%, and 8.7%, respectively; ORs vs. LLS=1.46, 1.53, and 1.83, respectively; $p>0.05$), but lower than rates associated with RH (LR OR=0.44, 95%CI=0.31-0.62; CLR OR=0.45, 95%CI=0.30-0.68; and S/BS Sg2-6 OR=0.52, 95%CI=0.33-0.82). No differences were observed in severe morbidity rates between LRs of the antero-lateral and postero-superior segments. The PSS, RPS, RAS, and CCH were associated with higher severe morbidity rates than the LLS, particularly PSS and RAS (PSS: 15.5%, OR=4.14, 95%CI=2.03-8.44; RAS: 14.5%, OR=4.95, 95%CI=2.26-10.84; RPS: 11%, OR=2.83, 95%CI=1.38-5.79; CCH: 11.5%, OR=2.56, 95%CI=1.05-6.23), but these rates were similar to those associated with RH.

Q-value analyses produced the same results, except for the higher rate of severe morbidity after CCH than after LLS (q-value=0.156, **Supplementary Table 2**).

Secondary end-points

Overall morbidity rates (**Figure 2c-d**) were low and similar among LLS, LR, and S/BS of antero-lateral segments (25.3%, 26.7%, and 28.9%, respectively). CLR had a slightly higher overall morbidity rate than LLS (37.6%, OR=1.27, 95%CI=0.90-1.79). PSS, RAS, RPS, and CCH were associated with higher overall morbidity rates than LLS (LLS: 25.3%; PSS: 37.7%, OR=1.79, 95%CI=1.16-2.75; RAS: 39.5%, OR=2.28, 95%CI=1.39-3.73; RPS 39.9%, OR=2.05, 95%CI=1.37-3.07; and CCH 45.1%, OR 2.44, 95%CI=1.44-4.13), but these rates were similar to those associated with RH.

LLS and LR had low bile leak rates (3.4% and 5.3%, respectively **Figure 3a-b**). CLR, S/BS of anterolateral segments, PSS, RPS, and RAS were associated with higher bile leak rates than LLS (CLR: 7.3%, OR=2.35, 95%CI=1.08-5.13; S/BS Sg2-6: 6.6%, OR=3.24, 95%CI=1.44-7.27; PSS: 6.3%, OR=2.56, 95%CI=1-6.63; RPS: 6.3%, OR=2.74, 95%CI=1.15-6.52; and RAS: 9.7%, OR=3.44, 95%CI=1.34-8.87), but similar to those associated with RH. CCH was associated with a higher bile leak rate than RH (13.3%, OR=1.94, 95%CI=1-3.84).

Most MiHs had low liver failure rates (**Table 2** and **Figure 3c-d**). RPS and CCH were associated with slightly higher liver failure rates than LLS (4.3% and 4.4%, respectively; OR=1.83 and 2.75, respectively; p>0.05). PSS and RAS were associated with even higher rates than LLS (PSS: 5.3%, OR=3.21, 95%CI=1.09-9.51; RAS: 9.7%, OR=4.02, 95%CI=1.34-12.06), but lower than those associated with RH (OR=0.40 and OR=0.57, respectively).

Q-value analyses produced the same results, except for the higher bile leak rate after CCH than after RH (q-value=0.324); the higher bile leak rates after CLR, PSS, and RPS than after LLS (q-values=0.096, 0.100, and 0.092, respectively); and the higher liver failure rates after PSS and RAS than after LLS (q-values=0.210 and 0.091, respectively), **Supplementary Table 3-5**).

Univariate analyses (**Table 2**) showed that all MiHs had lower mortality rates than RH. CLR, PSS, CCH, and RPS had higher transfusion rates than LLS (LLS=10.5%; CLR: 15.6%, p=0.022; PSS: 16.7%, p=0.021; CCH: 17.1%, p=0.060; and RPS: 17.5%, p=0.009), but lower than RH (23.2%). The CCI was similar among all procedures, but LR and CLR had lower values than RH. Hospital stays were similar for all MiHs, except that of RAS (15.1 days), which was similar to RH (13.4 days).

The classification proposed by Lee et al. [13,14] was applied to our series (**Supplementary Table 6**). Low-, intermediate-, and high-complexity groups (LR+LLS, RPS, and RAS, respectively) were associated with progressive increases in severe morbidity, liver failure, and bile leak rates. However, including RH in the intermediate-complexity group compromised the classification performance, because the RH outcome was similar to the RAS outcome.

DISCUSSION

The distinction between major and minor hepatectomies was based on the fact that major hepatectomies (but not minor hepatectomies) were associated with high risks of liver failure and liver failure-related mortality [3,4,6,27-30]. However, this difference is not sufficient to describe modern liver surgery. First, outcomes other than mortality and liver failure should be considered. For example, MiHs are associated with a non-negligible risk of severe morbidity (5-15%, 9% in present series) that could impact the quality of life, limit access to adjuvant treatments, and compromise oncologic prognoses [10-12]. Second, MiHs encompass a galaxy of different procedures for which different outcomes are expected. Progress in our understanding of liver anatomy, surgical techniques, and anesthesiology has led to the standardization of complex segmentectomies and right-sided sectionectomies. The implementation of enhanced intraoperative ultrasonography has led to the development of new types of MiH, such as CLRs, transverse hepatectomies, and CCHs (e.g., minimesohepatectomies or liver tunnels) [5,17-19,31-34].

Despite major interest and progress, MiHs remain a blurred picture. Previous analyses that compared MiHs and major hepatectomies have confirmed better results with MiHs, but no study has stratified different procedures to analyze outcomes [4-6,27-30]. On the other hand, studies that focused on single MiHs have reported detailed outcomes [8,17-19,30-39]. However, those studies involved single centers with a limited number of patients, and they reported feasibility and safety of the procedure, rather than its position in surgical practice. The present analysis was the first to provide a broad perspective on different MiHs. We adopted two separate reference standards; i.e. the most standardized major hepatectomy (RH) and the most standardized MiH (LLS), to evaluate every MiH in an appropriate context. Moreover, we highlighted graded outcomes.

Our results showed that LR outcomes were similar to LLS outcomes, independent of the resected segment. CLR and S/BS of Sg2-6 had slightly higher severe morbidity rates than LLS, and bile leak rates were similar to rates with RH. These results reflected the deep parenchyma transection required for CLR and S/BS, combined with vessel exposure or a pedicle section at the origin [40-42]. The severe morbidity rates of the remaining MiHs (RPS, CCH, PSS, and RAS) were similar to those of RH, particularly PSS and RAS. Bile leaks were the most relevant issue; bile leaks were even more common with CCH than with RH. Sections of large pedicles at their origin, and, for CCHs, dissection of the perihilar area with multiple Sg1 ducts were probably the main determinants of those outcomes [19, 40-42]. Furthermore, “central” bile leaks are those that more frequently require interventional procedures to heal (severe morbidity) [42-44].

All MiHs had lower liver failure rates than RHs, but some MiHs had slightly higher (RPS, PSS, CCH) or substantially higher (RAS) liver failure rates than LLSs. These findings could be explained by the increasing complexity of resections and of volumes of parenchyma removed in patients with preoperative chemotherapy and/or metabolic disorders [45-48]. However, liver failures were less severe with MiHs than with RHs, as demonstrated by the mortality rates among patients with liver failure.

The present results suggested that a new classification of hepatectomies is needed to replace the major/minor classification. Based on an international survey of experts, Lee et al. proposed a new classification system [13,14]. They classified LLS and LR as low-complexity resections, RPS as a medium-complexity resection (like RH), and RAS as a high-complexity resection. However this system described the difficulty/complexity of resections, which did not necessarily correspond to outcomes. In fact, Jang et al. demonstrated that the proposed classification was equivalent to the standard major/minor classification in predicting severe morbidity [49]. We found similar results when that classification was applied to the present series. Furthermore, some MiHs, such as PSS, CCH, and CLR were not included, then lacking the specific complications highlighted in the present study. A new hepatectomy classification should reflect the complexity of surgery, separately considering different procedures. The implemented version of the Brisbane classification we used could be a starting point.

The main strength of this study was its clinical relevance. The elucidation of different MiH outcomes provided a basis for efficient, reliable comparisons of the experiences and outcomes between different centers; for the identification of procedure-related risks and their specific solutions; for better communication of risks to patients; and for better stratification of reimbursements. Some limitations could be argued. Inherent limitations included the retrospective design and the heterogeneous cohort of patients from different centers. However, we included a large number of resections, and only high-volume centers participated the study. Moreover, we adjusted outcomes for potential confounders, including differences among centers. We adopted the standard classification of hepatectomies, (i.e., the Brisbane), with a few additional groups to focus on procedures with specific anticipated risks. This assumption was supported by the results. The most standardized hepatectomies (LLS/RH) were used as references. Another limitation was that some procedures were grouped together (e.g., CCH or PSS groups) to achieve an adequate number of cases and events. Thus, considerations about single procedures were precluded, and should be investigated further. Finally, the heterogeneity of the procedures and patients did not allow a benchmark to be defined for MiHs. However, our large number of patients from highly experienced centers favored reliable reference outcomes and guaranteed adequate outcome stratification.

In conclusion, MiHs encompass procedures with different outcomes. Although mortality was low after all MiH procedures, MiHs could be stratified according to the risks of severe morbidity, bile leaks, and liver failure. Waiting for an external validation of these results, anyhow it seems that most complex resections had outcomes similar to RH outcomes.

Clinical Investigators who collected the data: *Eloisa Franchi, Humanitas Clinical and Research Center – IRCCS, Rozzano - Milan, Italy; Giammauro Berardi, Ghent University Hospital, Ghent, Belgium; Francesca Ratti, S. Raffaele Hospital, Milano, Italy; Serena Langella, Mauriziano Hospital, Torino, Italy; Fariba Abbassi, University Hospital of Geneva, Geneva, Switzerland; Santi López-Ben, Josep Trueta Hospital, Girona, Spain; Maite Albiol, Josep Trueta Hospital, Girona, Spain; Andrea Laurenzi, Paul Brousse Hospital, Villejuif, France; Takashi Kokudo, University of Tokyo Hospital, Tokyo, Japan; Andrea Ruzzenente, Policlinico Rossi, Verona, Italy; Simone Conci, Policlinico Rossi, Verona, Italy; Michal Grat, Medical University of Warsaw, Warsaw, Poland; Francesco Ardito, Gemelli Hospital, Roma, Italy; Majd Rawashdesh, University Hospital Southampton, Southampton, UK; Arab Rawashdeh, University Hospital Southampton, Southampton, UK; Renato Bessa de Melo, Centro Hospitalier de Sao Joao, Oporto, Portugal; Vanessa de Pace, Orsola Hospital, Bologna, Italy; Julio Lazarte, Hospital Italiano, Buenos Aires, Argentina; Nicolò Roffi, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Fabio Bagante, The Ohio State University Wexner Medical Center, US.*

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Figures legend

Figure 1. Types of minor hepatectomies. *LR, limited resection; CLR, complex LR, defined as LR with major intrahepatic vessels exposed; LLS, left lateral sectionectomy; S/BS Sg2-6, mono-/bisegmentectomy of antero-lateral segments; PSS, postero-superior segmentectomy, defined as segmentectomy of segment 8 (Sg8), segmentectomy of Sg7, and bisegmentectomy of Sg7-8; RPS, right posterior sectionectomy; RAS, right anterior sectionectomy; CCH, complex core hepatectomy, defined as segmentectomy of Sg1 and combined resection of Sg4s+Sg8+Sg1.*

Figure 2. Adjusted odds ratios for severe and overall morbidity of different minor hepatectomies. Adjusted odds ratios for severe morbidity, vs. left lateral sectionectomy (a), and vs. right hepatectomy (b). **A**djusted odds ratios for overall morbidity, vs. left lateral sectionectomy (c), and vs. right hepatectomy (d). *LLS, left lateral sectionectomy; RH, right hepatectomy; LR, limited resection; CLR, complex LR, defined as LR with major intrahepatic vessels exposed; S/BS Sg2-6, mono-/bisegmentectomy of antero-lateral segments; PSS, postero-superior segmentectomy, defined as segmentectomy of segment 8 (Sg8), segmentectomy of Sg7, and bisegmentectomy of Sg7-8; RPS, right posterior sectionectomy; RAS, right anterior sectionectomy; CCH, complex core hepatectomy, defined as segmentectomy of Sg1 and combined resection of Sg4s+Sg8+Sg1.*

Figure 3. Adjusted odds ratios for bile leak and postoperative liver failure of different minor hepatectomies. Adjusted odds ratios for bile leak, vs. left lateral sectionectomy (a), and vs. right hepatectomy (b). Adjusted odds ratios for postoperative liver failure, vs. left lateral sectionectomy (c), and vs. right hepatectomy (d). *LLS, left lateral sectionectomy; RH, right hepatectomy; LR, limited resection; CLR, complex LR, defined as LR with major intrahepatic vessels exposed; S/BS Sg2-6, mono-/bisegmentectomy of antero-lateral segments; PSS, postero-superior segmentectomy, defined as segmentectomy of segment 8 (Sg8), segmentectomy of Sg7, and bisegmentectomy of Sg7-8; RPS, right posterior sectionectomy; RAS, right anterior sectionectomy; CCH, complex core hepatectomy, defined as segmentectomy of Sg1 and combined resection of Sg4s+Sg8+Sg1.*