**Original article**

**Bile leakage after laparoscopic and open liver resection; incidence and clinical impact: an international multicenter propensity score-matched study of 13,379 patients**

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# ABSTRACT

**Background** Despite many developments, postoperative bile leakage (POBL) remains a relatively common postoperative complication after laparoscopic liver resection (LLR) and open liver resection (OLR). This study aimed to assess the incidence and clinical impact of POBL in patients undergoing LLR and OLR in a large international multicenter cohort using a propensity score matched analysis.

**Study Design** Patients undergoing LLR or OLR for all indications between January 2000 and October 2019 were retrospectively analyzed using a large, international multicenter liver database including data from 15 tertiary referral centers. Primary outcome was clinically relevant POBL (CR-POBL), defined as Grade B/C POBL.

**Results** Overall, 13,379 patients met the inclusion criteria and were included in the analysis (6,369 LLR and 7,010 OLR), with 6.0% POBL. After PSM, a total of 3,563 LLR patients were matched to 3,563 OLR patients. In both groups, PSM accounted for similar extent and types of resections. The incidence of CR-POBL was significantly lower in patients after LLR as compared to patients after OLR (2.6% vs. 6.0%; *P*<0.001). Among the subgroup of patients with CR-POBL, patients after LLR experienced less severe (non-POBL) postoperative complications (10.1% vs. 20.9%; *P*=0.028), a shorter hospital stay (12.5 vs. 17 days; *P*=0.001), and a lower 90-day/in-hospital mortality (0% vs. 5.4%; *P*=0.027) as compared to patients after OLR with CR-POBL.

**Conclusion** Patients after LLR seem to experience a lower rate of CR-POBL as compared to the open approach. Our findings suggest that in patients after LLR, the clinical impact of CR-POBL is less than after OLR.

**Keywords:** liver surgery, laparoscopic liver surgery, minimally invasive liver surgery, postoperative bile leakage

**Abbreviations and Acronyms:**

LLR = Laparoscopic liver resection

LOS = Length of hospital stay

OLR = Open liver resection

POBL = Postoperative bile leakage

CR-POBL = Clinically relevant postoperative bile leakage

BMI = body mass index

ASA = American Society of Anesthesiologists

IQR = Interquartile range

SD = Standard deviation

PSM = Propensity score matching

SMD = Standardized mean difference

# INTRODUCTION

Recent refinements in surgical technique have expanded the use of laparoscopic liver resection (LLR). In fact, LLR has gained more acceptance as a feasible and safe procedure, even for some major and complex resections demonstrating similar advantages to those seen in minor resections including reduced intraoperative blood loss, reduced length of hospital stay (LOS) and less morbidity with equivalent oncological outcomes as compared to open liver resection (OLR)(1–7). Despite these impressive developments, LLR remains challenging with relevant rates of postoperative morbidity (4-48%) and mortality (0-10%), highlighting the need for a better understanding of the clinical impact and best perioperative management of surgical complications, especially when the short term advantages seen in LLR could be diluted when they occur(1, 2, 8, 9).

Postoperative bile leakage (POBL) is one of the most common postoperative complications following liver surgery with extremely variable reported incidence rates, ranging between 3.6% and 33%, depending on the type of resection(10–13). Despite a clear reduction in the incidence of POBL reported in recent studies, its occurrence has been shown to be a strong prognostic for poor postoperative outcomes(14, 15). In fact, POBL has been shown to be associated with a prolonged LOS, delayed removal of abdominal drains and the need for additional diagnostics and reinterventions(16–19). Furthermore, POBL is related to other postoperative complications such as intra-abdominal infection, gastrointestinal bleeding, impaired regeneration and thrombo-embolic events(20–22). It is hypothesized that a minimally invasive approach may limit tissue harm during liver surgery and subsequently benefit postoperative recovery with less POBL.

Data from previous studies have mainly focused on patients undergoing OLR(15, 23). Although some studies on LLR evaluated the incidence of POBL as part of their postoperative complication rate, there is no data regarding the clinical impact of POBL following LLR and furthermore no studies assessing whether this impact could be mitigated by the adoption of a minimally invasive approach. The aim of this study is to assess the incidence and the clinical impact of POBL in patients undergoing LLR and OLR in a large international multicenter cohort using a propensity score matched analysis.

# METHODS

## Study Design and Patient Selection

This retrospective cohort study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement(24). It represents the combined experience of 15 tertiary referral hepatobiliary centers: Amsterdam UMC, location Academic Medical Center, Amsterdam, the Netherlands; Hospital Josep Trueta, Girona, Spain; Groeninge Hospital, Kortrijk, Belgium; San Raffaele Hospital, Milan, Italy; Ospedale Mauriziano Umberto I, Torino, Italy; Moscow Clinical Research Center, Moscow, Russia; Oslo University Hospital, Oslo, Norway; Riuniti Hospital, Ancona, Italy; Clinica Universidad de Navarra, Pamplona, Spain; Institut Mutualiste Montsouris, Paris, France; Padova University Hospital , Padova, Italy; Catholic University of the Sacred Heart, Rome, Italy; Southampton University Hospital, Southampton, United Kingdom; University of Verona Medical School, Verona, Italy; Virginia Mason Medical Center, Seattle, WA, USA. Data were collected and registered anonymously, hence no written informed consent or no ethical approval by the Institutional Review Boards was required.

All participating centers performed a retrospective review of their prospectively collected databases. Data of all consecutive patients who underwent LLR or OLR for all liver diseases between January 2000 and October 2019 were included. Patients were excluded when no formal resection was performed (i.e. in the case of cyst fenestration/deroofing, biopsies, diagnostic laparoscopy) , when emergency liver surgery was performed or when a bilio-enteric anastomosis was needed.

## Data collection, Definitions and Outcome

POBL was defined according to the 2010 ISGLS Definition and was primarily diagnosed based on increased drain bile levels from the third postoperative day onwards (i.e. three times the upper limit of the normal serum total bilirubin level) in case of an intraoperatively placed abdominal drain, or POBL related symptoms (fever, right upper quadrant pain, increasing systemic bilirubin) in case of no intraoperatively placed abdominal drain(25). If indicated, an abdominal ultrasonography or computed tomography was performed to determine the severity and most adequate treatment of POBL. POBL was categorized in three grades of severity: grade A requires no change in patient management and intraoperatively placed drains were left no longer than 7 days; grade B consists of POBL requiring a change in the clinical management (additional diagnostic or interventional procedures) or POBL lasting longer than 7 days regardless of the impact on the clinical management; and grade C includes POBL requiring a relaparotomy. The primary outcome of the current study was the incidence and clinical impact (i.e. postoperative outcomes) of clinically relevant POBL (CR-POBL), defined as grade B and C POBL(25).

Patient characteristics consisted of age, sex, body mass index (BMI, kg/m2), American Society of Anesthesiologists (ASA) grade, cirrhosis, neoadjuvant chemotherapy, previous extrahepatic abdominal surgery and previous liver surgery. Tumor and procedure characteristics included histological diagnosis, number of lesions, size of the largest lesion, distribution of lesions (i.e. uni- or bilobar), year of surgery, type of resection (i.e. non-anatomical, anatomical or combined non-anatomical/anatomical) and extent of resection (minor resection anterior/left lateral segments, minor resection posterior/superior segments, anatomically major resection), respectively.

Postoperative outcomes included 30-day overall postoperative complications (defined according to the Clavien-Dindo classification; severe complications were defined as Clavien-Dindo three or higher(26)), postoperative liver failure (defined according to ISGLS definition(27)), postoperative pulmonary complications, postoperative surgical site infection (defined according to the “Guideline for Prevention of Surgical Site Infection, 1999” by the Centers for Disease Control and Prevention(28, 29)), postoperative hemorrhage (defined as a drop in hemoglobin level >3 g/dL postoperatively compared to the postoperative baseline level and/or any postoperative transfusion of packed red blood cells for a decreasing hemoglobin and/or the need for radiological intervention and/or re-laparotomy to stop bleeding (30)), 30-day readmission, 30-day reoperation, postoperative LOS and 90-day or in hospital mortality.

Anatomically major liver resection was defined as a resection of three or more Couinaud’s segments(31).

Anatomical liver resection was defined as the complete removal of at least one Couinaud’s segment which contains the tumor together with the related portal vein branch, hepatic vein and the corresponding hepatic territory(32). Non-anatomical resection, also known as parenchymal-sparing resection, involves a less extensive liver resection compared to anatomical resection and aims to achieve minimum sufficient margins while preserving as much liver parenchyma as possible, regardless of the border of the anatomical segments(32).

## Surgical Technique

To assess surgical technique and intraoperative management per center, a short survey was sent to all participating centers (Supplementary Material 1). Operative techniques among the participating centers were largely comparable for both approaches. Intraoperative ultrasound was used in all centers to assess the number, location, size and proximity of the lesions to major vascular structures. In 13 centers (86.7%), parenchymal transection was performed with an energy device for the superficial part of the liver and ultrasonic aspirator for the deep parenchyma, whilst 2 centers (13%) used an energy device only for the superficial and deeper parenchyma. In all centers, vascular and biliary structures were divided between metal clips, Hem-o-Lok clips (Weck Closure Systems, Research Triangle Park, USA) or endoscopic staplers, as required. Anesthetic management was similar in all centers and involved a restrictive intravenous fluid approach during liver transection combined with a low central venous pressure. An abdominal drain was placed selectively in 10 centers (66.7%), while in 5 centers (33.3%) all patients received an abdominal drain, regardless of the surgical approach and extend of resection.

## Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous, not normally distributed variables were expressed as median with interquartile range (IQR). In case variables were normally distributed, they were reported as mean with standard deviation (SD). A Mann-Whitney U test was used to compare continuous, not normally distributed variables between groups. Normally distributed, continuous variables were compared using an independent samples T-test, as appropriate. Categorical variables were reported as frequencies and proportions and compared between groups using a chi-square test. Propensity score matching (PSM) was applied to decrease selection bias in the comparison of the incidence and postoperative outcomes of patients with CR-POBL who underwent LLR and OLR.(33) PSM was performed in R Studio version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) using a multivariable logistic regression model. Multiple imputation was used to impute missing baseline variables by creating 5 datasets. Variables entered in the propensity model were age, gender, BMI, ASA grade, previous liver surgery, neoadjuvant chemotherapy, histological diagnosis, size of the largest lesion, number of lesions, distribution of lesions, year of surgery, type of resection and extent of resection. Based on these propensity scores, LLR were matched with OLR in a 1:1 ratio with a standard caliper width of 0.2. The standardized mean difference (SMD) was calculated to assess the balance at baseline between both groups, with SMD of 0.1 or below being considered to indicate optimal balance. LLR procedures who were converted to open surgery were analyzed in the LLR group, according to intention-to-treat principles. Postoperative outcomes of CR-POBL have been analyzed subsequently using paired tests by directly comparing postoperative outcomes of patients with CR-POBL in LLR and OLR and by comparing postoperative outcomes in patients with and without CR-POBL in OLR and LLR separately. A sensitivity analysis was performed to eliminate any time effect by excluding all patients who underwent LLR and OLR before 2011. Two-sided P< 0.050 was considered statistically significant.

# RESULTS

## Baseline characteristics

Among 14,514 patients screened from 15 participating European and American centers, 345 patients were excluded for the reasons shown in Figure 1. Another 790 patients were excluded due to need for biliary reconstruction. In total, 13,379 patients met the inclusion criteria and were included in the analysis (6,369 LLR and 7,010 OLR). The overall median center volume was 302 LLR procedures (IQR 208.5 - 622.5 LLR procedures) and 364 OLR procedures (IQR 39 - 765.5 OLR procedures).

Baseline characteristics are shown in table 1. Prior to matching, there were more women in the LLR group as compared to the open group (44.4% vs. 39.4%; SMD= 0.10). Patients who underwent LLR received less neoadjuvant chemotherapy (32.3% vs. 41.6%; SMD= 0.19) and had less previous liver surgery (11.2% vs. 15.7%; SMD= 0.13) as compared to the open group. A benign histological diagnosis was observed more often in the LLR group, as compared to the OLR group (16.5% vs. 9.8%; SMD 0.14*)*. Tumors of patients who underwent LLR were smaller as compared to patients who underwent OLR (28.0 mm (IQR 17.0-45.0) vs 35.0 mm (IQR 20.0-60.0); SMD= 0.29). Among those who underwent LLR, anatomically major resections were less frequent (18.1% vs. 38.2%; SMD= 0.53), whilst non-anatomical resections were performed more often in the LLR cohort (47.8% vs. 32.6%; SMD= 0.18).

After PSM, a total of 3,563 LLR patients were matched to 3,563 OLR patients (Table 1). An adequate balance between both groups was achieved, showing comparable baseline characteristics. A sensitivity analysis excluding all patients with missing values confirmed the robustness of the imputation method (Supplementary table 1).

Stratification of baseline characteristics into patients with CR-POBL following LLR and OLR resulted in 90 patients in the LLR group and 195 patients in the OLR group (Table 2). Except histological diagnosis, all patient, tumor and procedure characteristics were comparable between both approaches.

## Incidence of Bile leak

Before PSM, 805 of 13,379 patients had POBL after liver surgery (6.0%), including 193 patients after LLR (3.1%) and 612 patients after OLR (9.4%) (*P*<0.001) (Table 1). LLR patients had less grade B/C POBL as compared to the open cohort (2.1% vs. 6.6%; all *P*<0.001). After PSM, the overall POBL rate reduced to 5.6%. The incidence of Grade B/C was still significantly lower in patients after LLR as compared to patients after OLR (2.6% vs. 6.0%; all P<0.001). Figure 2 shows the evolution of the total number of LLR and OLR and the rates of CR-POBL for LLR and OLR over the years.

The incidence of CR-POBL varied considerably between participating hospitals, with a median incidence rate of 2.1% (IQR 1.5 - 3.1%) for LLR and 5.7% (IQR 3.9 - 8.1%) for OLR per participating hospital. There was no evident correlation between hospital volume and incidence of CR-POBL for LLR (b coefficient = 0.225; *P*=0.44) as well as for OLR (b coefficient = 0.317; P=0.32).

Stratification into extent of resection showed a significantly lower incidence of CR-POBL after LLR for anatomically minor resections of the anterior/left lateral and posterior/superior segments as well as for anatomically major resections as compared to the open approach, even after PSM (Supplementary figure 1). Furthermore, when stratified for type of resection, patients who underwent an anatomical, non-anatomical or combined LLR had a significantly lower incidence rate of CR-POBL as compared to the open approach (Supplementary figure 2).

*Clinical impact of Bile leak*

Table 3 shows the postoperative outcomes of patients with CR-POBL after LLR and OLR. Patients with CR-POBL after LLR experienced less severe additional postoperative complications (10.1% vs. 20.9%; *P*=0.028) and less surgical site infections (4.4% vs. 17.9%; *P*=0.002) as compared to patients with CR-POBL after OLR. Furthermore, LLR patients with CR-POBL had a shorter LOS (12.5 vs. 17 days; *P*=0.001) and a significantly lower 90-day/in-hospital mortality (0% vs. 5.4%; *P*=0.027) as compared to OLR patients with CR-POBL.

Additionally, table 4 shows the postoperative outcomes of patients with and without CR-POBL stratified for LLR and OLR. In the LLR group, the impact of CR-POBL on the postoperative course was limited to a prolonged LOS (12.5 vs. 5 days; *P*<0.001) and a higher readmission rate (42.3% vs. 4.1%; *P*<0.001) without affecting the postoperative complication rate and 90-day/in-hospital mortality rate. On the contrary, in the OLR group, patients with CR-POBL experienced significantly more postoperative complications (51.1% vs. 25.2%; *P*<0.001), including a higher rate of postoperative liver failure (20.9% vs. 9.9%; *P*<0.001), surgical site infection (17.9% vs. 4.0%; *P*<0.001) and postoperative hemorrhage (2.6% vs. 0.7%; *P*=0.004) as compared to patients without CR-POBL. Furthermore, OLR patients with CR-POBL had a longer LOS (17.0 vs. 7.0 days; *P*<0.001), higher readmission rate (36.0% vs. 6.5%; P<0.001) and a higher 90-day/in-hospital mortality rate (5.4% vs. 1.8%; *P*=0.001) as compared to OLR patients without CR-POBL.

After excluding all patients who underwent LLR or OLR before 2011, postoperative outcomes did not change considerably from the outcomes of the primary analysis (Supplementary Table 2 and 3).

# DISCUSSION

This international multicenter study assessed the incidence and clinical impact of CR-POBL in patients undergoing LLR and OLR. Our findings show less CR-POBL after LLR as compared to OLR, even after PSM (2.6% vs. 6.0%). Patients after LLR with CR-POBL had a more favorable postoperative recovery in terms of clinical short-term outcomes as compared to patients who underwent OLR and developed CR-POBL.

Studies comparing the incidence of overall POBL and in particular CR-POBL after LLR and OLR are scarce. To date, only one study focused specifically on the incidence of POBL in OLR and LLR(34). This study included 599 patients after LLR and 789 after OLR from three American tertiary referral centers and showed a slightly lower incidence rate of POBL after LLR as compared to OLR (2.2% vs. 3.3%; *P*=0.209). The rate of CR-POBL did not differ between both groups (1.5% vs. 1.5%; *P*=0.978). Of note, baseline variables between OLR and LLR differed significantly in that study. Although the incidence rates of POBL after LLR and OLR were higher in the current study, it is important to note that the current study has an international character joining different surgical practices and including more than 13,000 patients. Furthermore, even though PSM has been applied and the SMD was below 0.1 which indicates optimal balance, the larger size of lesion in the OLR group as compared to the LLR group might be a contributary factor to the higher incidence of CR-POBL in patients after OLR as compared to patients after LLR. This is also supported by several previously published studies in the field of laparoscopic and open liver surgery showing that an increasing tumor size is associated with worse outcomes(35, 36). The incidence of POBL in the open cohort was consistent with the findings of several recently published observational studies focusing on POBL, ranging from 7.7-15.6%(13, 15, 20, 23, 37, 38). In addition, several studies on LLR evaluated the incidence of POBL as part of their postoperative complication rate, showing an incidence rate of 2.0-5.3% which is comparable with the current results(39–41). However, these studies didn’t focus on the rate of CR-POBL.

Interestingly, while the incidence of POBL in the OLR group remained stable across the last two eras, the incidence of CR-POBL in the LLR group showed a slight increase in the last era (figure 2). The stable incidence in the era 2000-2010 and 2010-2015 in the LLR group may be associated with careful selection of patients, while in recent years surgeons started to perform more and more complex LLR procedures due to the increasing experience and surgical skills, which may explain the increased rate of CR-POBL in the last era. At the same time, the incidence of CR-POBL in the open group seems to reach a plateau after 2011. This might be explained by the fact that after 2011, patient selection and surgical experience for OLR were settled in participating centers.

An important finding of the present study is the difference in postoperative impact of CR-POBL in patients after LLR and OLR. In fact, this is the first study assessing the clinical relevance of CR-POBL between patients after LLR and OLR since previous studies didn’t stratify for approach. A retrospective single center study included 501 patients who underwent liver resection and assessed the risk factors and clinical impact of BL after liver surgery(23). In accordance with the current study, they reported increased rates of surgical site infection, postoperative liver failure and mortality in patients with CR-POBL as compared to patients without CR-POBL. Of note, only a small number of patients in that cohort underwent LLR. Similarly, a large nationwide study including 6,859 patients from the NSQIP dataset showed that patients with POBL experienced a worse postoperative course, including more postoperative complications, a prolonged LOS, more surgical site infections, more readmissions and a higher mortality rate as compared to patients without POBL(13). However, the number of patients after LLR was relatively small and a stratification into severity of POBL was lacking. In contrast, only one retrospective cohort study specifically focused on the clinical impact of POBL after LLR(42). That study included 230 patients who underwent major LLR from two French tertiary referral centers and, unlike the current study, showed that POBL was associated with more infectious complications, more pulmonary complications, more acute renal insufficiency and more multiorgan failure as compared to patients without POBL. Since that study focused only on patients after major LLR and didn’t stratify for the severity of POBL, their results are difficult to extrapolate. The findings of the current study suggest that refinements of the laparoscopic approach including the instrument used during parenchymal transection may be contributory in limiting tissue harm during surgery. In addition, laparoscopy may provide a better view of the resection bed, making it more feasible to notice small bile leaks which can be controlled easily with sealing or sutures.

In recent years, several nationwide registry studies showed an increased implementation of LLR into daily clinical practice(43–46). According to the most recent Southampton consensus guidelines, LLR is now considered the standard approach for minor liver resections, while major LLR is considered feasible, safe and effective in selected patients and in experienced hands(47). The current study suggests that LLR has potential advantages in patients with CR-POBL as compared to patients after OLR, especially in terms of severe additional postoperative complications, surgical site infections and LOS. These potential benefits in short term outcomes may also affect long term prognosis, as proposed by several previous studies(48–51). Therefore, as stated by the Southampton guidelines, the further implementation of LLR may be encouraged by starting LLR programs in all liver surgery centers in a stepwise fashion and disseminating LLR on a national scale.(47) However, OLR will remain of paramount importance in the treatment of liver diseases. Complex LLR procedures such as resection of lesions of 3 cm or more, repeat liver resection and resection of lesions in the posterior/superior segments are namely all safe and feasible, but are considered technically difficult procedures(52–57). Increased operative time, blood loss and postoperative complications have been acknowledged for complex and difficult LLR procedures, and therefore, a great emphasize should be put on selecting suitable patients for LLR. To this end, risk factor assessment for CR-POBL in patients with an indication for liver surgery is crucial to finetune the surgical strategy including the choice of approach. The French Association of Hepatopancreatobiliary Surgery and Transplantation (ACHBT) developed a score to predict CR-POBL after liver surgery(58). This prediction model includes blood loss, remnant ischemia, anatomical resection of segment 8, transection along right aspect of left intersectional plane and associating liver partition and portal vein ligation for staged hepatectomy and has been recently externally validated for LLR patients(59). Of note, the ACHBT score has been developed and validated upon a national French cohort and its international application remains questionable. Further international studies focusing on prediction models such as the ACHBT score may be of clinical value in the preoperative assessment of patients with an indication for liver surgery.

The current study has several limitations. First, the retrospective design of the study could introduce selection bias since more complex procedures were performed in the open group. Hence, PSM has been applied to limit this effect and ensure a more reliable comparison between LLR and OLR. Second, results in the current study were obtained from 15 international tertiary referral centers with a large experience in minimally invasive liver surgery and where OLR was mainly reserved for cases where LLR was not indicated. Therefore, a cautious interpretation of these data regarding generalizability is required. However, this is the largest multicenter series so far comparing LLR and OLR and in particular investigating the occurrence and clinical impact of CR-POBL of patients after LLR and OLR. Third, the long study period of 19 years may be subject to bias due to changes in technology, perioperative management and patient care over time. However, a sensitivity analysis was performed to eliminate any time effect by excluding all patients before 2011 and showing comparable results as in the entire cohort. Fourth, although the multicenter nature of the cohort was a strength, there may be some variation in the perioperative management of patients at the individual center level such as the routine use of a leakage test. At last, previous literature showed that intraoperative drain placement was associated with increased diagnosis of POBL, especially in bile leaks not requiring an intervention (60). Although all participating centers reported that intraoperative drain placement occurred selectively after LLR and OLR, individual patient data on intraoperative drain placement were not collected. Future studies on LLR and OLR with data on intraoperative drain placement may be valuable to gain further insights in the incidence rates of POBL after LLR and OLR.

# CONCLUSIONS

This international multicenter propensity-score matched study shows that LLR seems to have a lower incidence rate of CR-POBL as compared to the open approach. Our findings suggest that CR-POBL negatively affects outcomes after both LLR and OLR , but that patients after LLR with CR-POBL experience less impactful postoperative clinical outcomes as compared to patients after OLR with CR-POBL. Future international studies focusing on risk factor assessment for CR-POBL may be useful in selecting the most suitable operative approach on a per-patient base.

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### TABLES

**Table 1.** Baseline and procedure characteristics and incidence of postoperative bile leakage (POBL) following laparoscopic and open liver surgery, before and after propensity score matching

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Before PSM** | | | | **After PSM** | | | |
|  | **Laparoscopic**  **(N = 6369)** | **Open**  **(N = 7010)** | ***P*** | **SMD** | **Laparoscopic**  **(N = 3565)** | **Open**  **(N = 3565)** | ***P*** | **SMD** |
| **Patient characteristics** |  |  |  |  |  |  |  |  |
| Age, years, median (IQR)  *Missing (%)* | 64.5 (55.0 – 72.5)  543 (8.5) | 64.0 (55.0 – 71.0)  528 (7.5) | **0.001** | 0.03 | 64.0 (55.1 – 72.0) | 64.0 (56.0 – 71.0) | 0.127 | 0.00 |
| Sex, male (%)  *Missing (%)* | 3503 (55.6)  67 (1.1) | 4250 (60.6)  2 (0.0) | **<0.001** | 0.10 | 2090 (58.6) | 2084 (58.5) | 0.885 | 0.00 |
| BMI, kg/m2, median(IQR)  *Missing (%)* | 26.0 (23.3-28.4)  1678 (26.3) | 25.4 (22.8 – 28.4)  3097 (44.2) | **<0.001** | 0.07 | 26.0 (23.8-28.0) | 25.7 (23.7 – 27.9) | **0.033** | 0.03 |
| ASA grade  ASA 1 (%)  ASA 2 (%)  ASA 3 (%)  ASA 4 (%)  *Missing (%)* | 433 (7.9)  3243 (59.2)  1753 (32.0)  53 (1.0)  889 (14.0) | 632 (11.4)  2880 (51.8)  1955 (35.2)  87 (1.6)  1455 (20.8) | **<0.001** | 0.01 | 324 (9.1)  1996 (56.0)  1204 (33.8)  41 (1.2) | 331 (9.3)  2010 (56.4)  1186 (33.3)  38 (1.1) | 0.946 | 0.01 |
| Cirrhosis (%)  *Missing (%)* | 1061 (17.8)  411 (6.5) | 947 (17.1)  1463 (20.9) | 0.299 | 0.02 | 519 (14.6) | 535 (15.0) | 0.593 | 0.01 |
| Neoadjuvant chemotherapy (%)  *Missing (%)* | 1928 (32.3)  391 (6.1) | 2659 (41.6)  620 (8.8) | **<0.001** | 0.19 | 1351 (37.9) | 1377 (38.6) | 0.526 | 0.01 |
| Previous extrahepatic abdominal surgery (%)  *Missing (%)* | 1980 (32.2)  211 (3.3) | 1957 (30.9)  673 (9.6) | 0.126 | 0.03 | 1160 (32.5) | 1133 (31.8) | 0.494 | 0.02 |
| Previous liver surgery (%)  *Missing (%)* | 557 (11.2)  1402 (22.0) | 841 (15.7)  1651 (23.6) | **<0.001** | 0.13 | 396 (11.1) | 393 (11.0) | 0.910 | 0.00 |
| **Tumor characteristics** |  |  |  |  |  |  |  |  |
| Histological Diagnosis  CRLM (%)  HCC (%)  Intrahepatic Cholangiocarcinoma (%)  Gallbladdercarcinoma (%)  Non-CRLM (%)  Other malignancy (%)  Benign (%)  *Missing (%)* | 2882 (45.4)  1289 (20.3)  292 (4.6)  69 (1.1)  613 (9.7)  158 (2.5)  1049 (16.5)  17 (0.3) | 3227 (47.5)  1274 (18.8)  684 (10.1)  198 (2.9)  564 (8.3)  181 (2.7)  665 (9.8)  217 (3.1) | **<0.001** | 0.14 | 1731 (48.6)  634 (17.8)  250 (7.0)  65 (1.8)  317 (8.9)  114 (3.2)  454 (12.7) | 1756 (49.3)  647 (18.1)  229 (6.4)  69 (1.9)  309 (8.7)  102 (2.9)  453 (12.7) | 0.908 | 0.01 |
| Number of lesions   * 0 (%) * 1 (%) * 2 (%) * 3 (%) * ≥ 4 (%) * *Missing (%)* | 148 (3.1)  3149 (66.7)  762 (16.1)  342 (7.2)  322 (6.8)  1646 (25.8) | 74 (1.9)  2009 (51.0)  625 (15.9)  401 (10.2)  834 (21.2)  3067 (43.8) | **<0.001** | 0.45 | 77 (2.2)  2415 (67.7)  482 (13.5)  264 (7.4)  327 (9.2) | 80 (2.2)  2421 (67.9)  468 (13.1)  255 (7.2)  341 (9.6) | 0.949 | 0.00 |
| Size of largest lesion, mm, median (IQR)  *Missing (%)* | 28.0 (17.0-45.0)  1390 (21.8) | 35.0 (20.0-60.0)  2365 (33.7) | **<0.001** | 0.29 | 35.7 (23.0-53.8) | 40.0 (23.0-60.0) | **<0.001** | 0.02 |
| Distribution of lesions  Unilobar (%)  Bilobar (%)  *Missing (%)* | 5173 (83.6)  1018 (16.4)  178 (2.8) | 4745 (70.4)  1999 (29.6)  266 (3.8) | **<0.001** | 0.32 | 2812 (78.9)  751 (21.1) | 2790 (78.3)  775 (21.7) | 0.496 | 0.02 |
| **Procedure characteristics** |  |  |  |  |  |  |  |  |
| Year of surgery | 2015 (2012-2017) | 2012 (2009-2015) | **<0.001** | 0.60 | 2014 (2010-2017) | 2013 (2010-2016) | **0.003** | 0.00 |
| Type of resection  Anatomical (%)  Non-anatomical (%)  Combined non-anatomical/anatomical (%)  Missing (%) | 2858 (44.9)  3042 (47.8)  469 (7.4)  0 | 4080 (58.2)  2285 (32.6)  645 (9.2)  0 | **<0.001** | 0.18 | 1814 (50.9)  1446 (40.6)  303 (8.5) | 1840 (51.6)  1410 (39.6)  315 (8.8) | 0.647 | 0.01 |
| Extent of resection  *Anterior/left lateral segments (2,3,4b,5,6)*  Wedge (%)  Segmentectomy (%)  Bisegmentectomy (%)  *Posterior/superior segments (4a,7,8,1)*  Wedge (%)  Segmentectomy (%)  Bisegmentectomy (%)  *Anatomically Major*  Trisegmentectomy (%)  Hemihepactectomy (%)  Extended hemihepatectomy (%)  Other major hepatectomy (%)  *Missing (%)* | 1991 (31.3)  641 (10.1)  984 (15.4)  1051 (16.5)  279 (4.4)  272 (4.3)  96 (1.5)  928 (14.6)  107 (1.7)  20 (0.3)  0 | 1275 (18.2)  502 (7.2)  713 (10.2)  1010 (14.4)  424 (6.0)  409 (5.8)  222 (3.2)  1640 (23.4)  680 (9.7)  135 (1.9)  0 | **<0.001** | 0.53 | 847 (23.8)  314 (8.8)  446 (12.5)  599 (16.8)  213 (6.0)  199 (5.6)  87 (2.4)  732 (20.5)  107 (3.0)  19 (0.5) | 857 (24.0)  331 (9.3)  457 (12.8)  553 (15.5)  188 (5.3)  199 (5.6)  83 (2.3)  742 (20.8)  137 (3.8)  18 (0.5) | 0.543 | 0.01 |
| Pringle manoeuvre (%)  Missing (%) | 2391 (43.3)  843 (13.2) | 2627 (46.2)  1321 (18.8) | **0.002** | 0.06 | 1542 (43.3) | 1578 (44.3) | 0.162 | 0.02 |
| **Postoperative bile leakage**  Overall (%)  Grade A (%)  Grade B (%)  Grade C (%) | 193 (3.1)  39 (0.6)  115 (1.7)  27 (0.4) | 612 (9.4)  105 (1.6)  370 (5.7)  58 (0.9) | **<0.001**  **<0.001**  **<0.001**  **<0.001** |  | 121 (3.4)  23 (0.7)  68 (2.0)  22 (0.6) | 284 (8.8)  55 (1.7)  172 (5.3)  23 (0.7) | **<0.001**  **<0.001**  **<0.001**  0.696 |  |

Values in parentheses are percentages unless mentioned otherwise. Percentages may not add up due to rounding and missing data. SMD = Standardized Mean Difference, IQR = inter quartile range, BMI = body mass index, ASA = American Society of Anesthesiology, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma

**Table 2.** Baseline and procedure characteristics of patients with clinically relevant postoperative bile leakage (CR-POBL) following laparoscopic and open liver surgery, after propensity score matching

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CR-POBL after laparoscopic surgery**  **(N = 90)** | **CR-POBL after open surgery**  **(N = 195)** | ***P*** |
| **Patient characteristics** |  |  |  |
| Age, years, median (IQR) | 65.5 (57.0 – 74.0) | 65.0 (57.0 – 72.0) | 0.608 |
| Sex, male (%) | 54 (60.0) | 120 (61.5) | 0.804 |
| BMI, kg/m2, median(IQR) | 24.9 (23.1-27.0) | 25.1 (22.9 – 28.0) | 0.751 |
| ASA grade  ASA 1 (%)  ASA 2 (%)  ASA 3 (%)  ASA 4 (%) | 5 (5.6)  54 (60.0)  31 (34.4)  0 (0) | 17 (8.7)  94 (48.2)  81 (41.5)  3 (1.5) | 0.202 |
| Cirrhosis (%) | 14 (15.6) | 22 (11.3) | 0.313 |
| Neoadjuvant chemotherapy (%) | 37 (41.1) | 72 (36.9) | 0.499 |
| Previous extrahepatic abdominal surgery (%) | 37 (41.1) | 65 (33.3) | 0.203 |
| Previous liver surgery (%) | 16 (17.8) | 30 (15.4) | 0.610 |
| **Tumor characteristics** |  |  |  |
| Histological Diagnosis  CRLM (%)  HCC (%)  Intrahepatic Cholangiocarcinoma (%)  Gallbladdercarcinoma (%)  Non-CRLM (%)  Other malignancy (%)  Benign (%) | 52 (57.8)  16 (17.8)  6 (6.7)  2 (2.2)  3 (3.3)  1 (1.1)  10 (11.1) | 81 (41.5)  25 (12.8)  26 (13.3)  4 (2.1)  20 (10.3)  6 (3.1)  33 (16.9) | **0.043** |
| Number of lesions   * 0 (%) * 1 (%) * 2 (%) * 3 (%) * ≥ 4 (%) | 2 (2.2)  58 (64.4)  12 (13.3)  9 (10.0)  9 (10.0) | 8 (4.1)  140 (71.8)  24 (12.3)  7 (3.6)  16 (8.2) | 0.208 |
| Size of largest lesion, mm, median (IQR) | 40.0 (28.0-60.0) | 41.4 (26.0-63.1) | 0.948 |
| Distribution of lesions  Unilobar (%)  Bilobar (%) | 56 (62.2)  29 (32.2) | 147 (75.4)  46 (23.6) | 0.055 |
| **Procedure characteristics** |  |  |  |
| Type of resection  Anatomical (%)  Non-anatomical (%)  Combined non-anatomical/anatomical (%) | 58 (64.4)  23 (25.6)  9 (10.0) | 130 (66.7)  40 (20.5)  25 (12.8) | 0.558 |
| Extent of resection  *Anterior/left lateral segments (2,3,4b,5,6)*  Wedge (%)  Segmentectomy (%)  Bisegmentectomy (%)  *Posterior/superior segments (4a,7,8,1)*  Wedge (%)  Segmentectomy (%)  Bisegmentectomy (%)  *Anatomically Major*  Trisegmentectomy (%)  Hemihepactectomy (%)  Extended hemihepatectomy (%)  Other major hepatectomy (%) | 10 (11.1)  4 (4.4)  9 (10.0)  13 (14.4)  7 (7.8)  4 (4.4)  3 (3.3)  28 (31.1)  12 (13.3)  0 (0) | 24 (12.3)  11 (5.6)  15 (7.7)  16 (8.2)  7 (3.6)  24 (12.3)  8 (4.1)  73 (37.4)  13 (6.7)  4 (2.1) | 0.096 |
| Pringle manoeuvre (%) | 43 (52.4) | 84 (43.1) | 0.841 |

Values in parentheses are percentages unless mentioned otherwise. Percentages may not add up due to rounding and missing data. CR-POBL = clinically relevant postoperative bile leakage, IQR = inter quartile range, BMI = body mass index, ASA = American Society of Anesthesiology, CRLM = colorectal liver metastasis, HCC = hepatocellular carcinoma

**Table 3.** Postoperative outcomes of patients with clinically relevant postoperative bile leakage following laparoscopic and open liver surgery, after propensity score matching.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CR-POBL after laparoscopic surgery**  **(N = 90)** | **CR-POBL after open surgery**  **(N = 195)** | ***P*** |
| Any additional postoperative complication (%)  Severe, grade 3-5 | 16 (17.8)  9 (10.1) | 93 (51.1)  37 (20.9) | **<0.001**  **0.028** |
| Liver failure (%) | 1 (1.1) | 9 (4.6) | 0.135 |
| Pulmonary complications (%) | 6 (6.7) | 7 (3.6) | 0.247 |
| Surgical site infection (%)  Superficial  Deep  Organ/Space | 4 (4.4)  0  0  4 (4.4) | 35 (17.9)  2 (1.0)  2 (1.0)  31 (15.9) | **0.002**  0.574  0.574  **0.006** |
| Hemorrhage (%) | 2 (2.2) | 5 (2.6) | 0.862 |
| Length of hospital stay, days, median (IQR) | 12.5 (5.8-23.3) | 17.0 (10.0-30.0) | **0.001** |
| Readmission (%)  Reoperation within 30 days (%) | 22 (42.3)  24 (27.0) | 31 (36.0)  32 (17.9) | 0.464  0.085 |
| 90-day/ in-hospital mortality (%) | 0 (0) | 10 (5.4) | **0.027** |

Values in parentheses are percentages unless mentioned otherwise. CR-POBL = clinically relevant postoperative bile leakage, IQR = inter quartile range

**Table 4.** Postoperative outcomes of patients with and without clinically relevant postoperative bile leakage following laparoscopic and open liver surgery, after propensity score matching.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **LAPAROSCOPIC** | | | **OPEN** | | |
|  | **No CR-POBL**  **(N=3377)** | **CR-POBL**  **(N=90)** | ***P*** | **No CR-POBL**  **(N=2843)** | **CR-POBL**  **(N=195)** | ***P*** |
| Any postoperative complication (%)  Severe, grade 3-5 | 669 (19.8)  220 (6.5) | 16 (17.8)  9 (10.0) | 0.633  0.178 | 714 (25.2)  281 (9.9) | 93 (51.1)  37 (20.9) | **<0.001**  **<0.001** |
| Liver failure (%) | 16 (0.5) | 1 (1.1) | 0.393 | 38 (1.3) | 9 (4.6) | **<0.001** |
| Pulmonary complications (%) | 135 (4.0) | 6 (6.7) | 0.206 | 170 (6.0) | 7 (3.6) | 0.168 |
| Surgical site infection (%) | 76 (2.3) | 4 (4.4) | 0.171 | 115 (4.0) | 35 (17.9) | **<0.001** |
| Hemorrhage (%) | 45 (1.3) | 2 (2.2) | 0.471 | 19 (0.7) | 5 (2.6) | **0.004** |
| Length of hospital stay, days, median (IQR) | 5.0 (3.0-7.0) | 12.5 (5.8-23.3) | **<0.001** | 7.0 (6.0-10.0) | 17.0 (10.0-30.0) | **<0.001** |
| Readmission (%) | 97 (4.1) | 22 (42.3) | **<0.001** | 85 (6.5) | 31 (36.0) | **<0.001** |
| 90-day/ in-hospital mortality (%) | 78 (2.3) | 0 (0) | 0.149 | 47 (1.8) | 10 (5.4) | **0.001** |

Values in parentheses are percentages unless mentioned otherwise. CR-POBL = clinically relevant postoperative bile leakage, IQR = inter quartile range

### FIGURES LEGENDS

**Figure 1** Flow chart of patient selection

**Figure 2.** Incidence of clinically relevant postoperative bile leakage per era, 2000–2019

### SUPPLEMENTARY MATERIAL LEGENDS

**Supplementary material 1.** Survey to assess surgical technique and intraoperative management among the participating centers.

**Supplementary Table 1.** Sensitivity analysis of baseline and procedure characteristics and incidence of postoperative bile leakage (POBL) following laparoscopic and open liver surgery, before and after propensity score matching excluding all patients with missing values.

**Supplementary Table 2.** Postoperative outcomes of patients with clinically relevant postoperative bile leakage after excluding patients who underwent laparoscopic and open liver surgery before 2011.

**Supplementary Table 3.** Postoperative outcomes of patients with and without clinically relevant postoperative bile leakage after excluding patients after excluding patients who underwent laparoscopic and open liver surgery before 2011.

**Supplementary Figure 1.** The incidence ofclinically relevant postoperative bile leakage following laparoscopic and open liver resection stratified for extent of resection, before and after propensity score matching

**Supplementary Figure 2.** The incidence ofclinically relevant postoperative bile leakage following laparoscopic and open liver resection stratified for type of resection, before and after propensity score matching