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ORIGINAL ARTICLE

Trends in the characteristics and perioperative outcomes of patients undergoing laparoscopic and open resections for benign liver lesions

An international multicenter retrospective cohort study of 845 patients

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Abstract

Background: Solid benign liver lesions (BLL) are increasingly discovered, but clear indications for surgical treatment are often lacking. Concomitantly, laparoscopic liver surgery is increasingly performed. The aim of this study was to assess if the availability of laparoscopic surgery has had an impact on the characteristics and perioperative outcomes of patients with BLL.

Methods: This is a retrospective international multicenter cohort study, including patients undergoing a laparoscopic or open liver resection for BLL from 19 centers in eight countries. Patients were divided according to the time period in which they underwent surgery (2008–2013, 2014–2016, and 2017–2019). Unadjusted and risk-adjusted (using logistic regression) time-trend analyses were performed. The primary outcome was textbook outcome (TOLS), defined as the absence of intraoperative incidents $\geq$ grade 2, bile leak $\geq$ grade B, severe complications, readmission and 90-day or in-hospital mortality, with the absence of a prolonged length of stay added to define TOLS+.

Results: In the complete dataset comprised of patients that underwent liver surgery for all indications, the proportion of patients undergoing liver surgery for benign disease remained stable (12.6% in the first time period, 11.9% in the second time period and 12.1% in the last time period, $p = 0.454$). Overall, 845 patients undergoing a liver resection for BLL in the first ($n = 374$), second ($n = 258$) or third time period ($n = 213$) were included. The rates of ASA-scores$\geq$3 (9.9%–16%,$p < 0.001$), laparoscopic surgery (57.8%–77%,$p < 0.001$), and Pringle maneuver use (33.2%–47.2%,$p = 0.001$) increased, whereas the length of stay decreased (5 to 4 days,$p < 0.001$). There were no significant changes in the TOLS rate (86.6%–81.3%,$p = 0.151$), while the TOLS + rate increased from 41.7% to 58.7% ($p < 0.001$). The latter result was confirmed in the risk-adjusted analyses (aOR 1.849,$p = 0.004$).

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Conclusion: The surgical treatment of BLL has evolved with an increased implementation of the laparoscopic approach and a decreased length of stay. This evolution was paralleled by stable TOLS rates above 80% and an increase in the TOLS + rate.

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Introduction

Benign liver lesion (BLL) is the umbrella term which covers several groups of lesions with different cellular origins. Of these, hepatocellular adenomas (HCA), hemangiomas and focal nodular hyperplasia (FNH) are most commonly encountered.[1] Occasionally, these lesions cause symptoms which prompt a physician to order an imaging test, but increased use and significant improvements in the technology of medical imaging modalities have led to an increase in their incidental discovery.[2,3] Guidelines state that the majority of all newly diagnosed patients with a BLL should be treated conservatively.[1,4,5] While these guidelines provide clear recommendations on when to consider surgical treatment in patients with HCA at risk for malignant transformation or bleeding, this is not the case for hemangioma, FNH or symptomatic low risk HCA. In practice, surgery is also considered if patients experience symptoms thought to be caused by the lesion(s) or when the diagnosis is unclear. Liver surgery has witnessed several considerable developments over the past decades, including an increasing adoption and wide implementation of minimally invasive liver surgery (MILS).[6,7] This process has been stimulated by observational studies and randomized controlled trials that have extensively associated MILS with benefits over open liver surgery in different settings, in terms of less blood loss, postoperative complications, and a shorter length of hospital stay and time to functional recovery.[8−15] Nevertheless, little is known about the impact of this development on patients with BLL.[16,17] In fact, it was initially feared that the expansion of minimally invasive liver surgery may tempt surgeons to widen the indications for surgical treatment when dealing with benign disease.[18] Therefore, the aim of this multicenter study is to assess if the availability of MILS has had an impact on the characteristics and perioperative outcomes of patients with BLL. The composite endpoint 'textbook outcome' was used as a primary outcome, since composite endpoints may offer a better and more accurate reflection of overall surgical quality.[19−23]

Methods

This is a retrospective analysis of an international multicenter database, comprised of the prospectively maintained databases of 19 hepato-biliary referral centers from eight countries.[24] Initially, the population of patients that underwent liver surgery between January 2008 and December 2019 was divided into three groups based on the procedure dates: 2008−2013, 2014−2016 and 2017−2019, thus following the adoption and expansion of MILS after the development of the three international consensus guidelines in the field.[18,25,26] The proportion of patients that underwent surgery for malignant or benign disease during these time periods was reviewed. Thereafter, adult patients that underwent an elective laparoscopic or open resection of a solid BLL were included. Although rare for benign indications, patients that underwent preoperative portal vein embolization, portal vein ligation or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), major concurrent procedures (e.g., vascular or biliary reconstructions, colorectal, diaphragmatic or pancreatic resections), or procedures using a thoracoscopic, hand-assisted or robotic-assisted approach were excluded (See Fig. 1 for the study flow chart). Unadjusted and risk-adjusted time-trend analyses were performed. Subsequently, patients were stratified according to the chosen surgical approach (laparoscopic or open), and the indications and perioperative outcomes of both treatment groups were compared before and after propensity score matching (PSM). This study received approval from the medical ethical committee of Brescia, which waived the requirement for obtaining informed consent on the grounds of its retrospective design and use of pseudonymized

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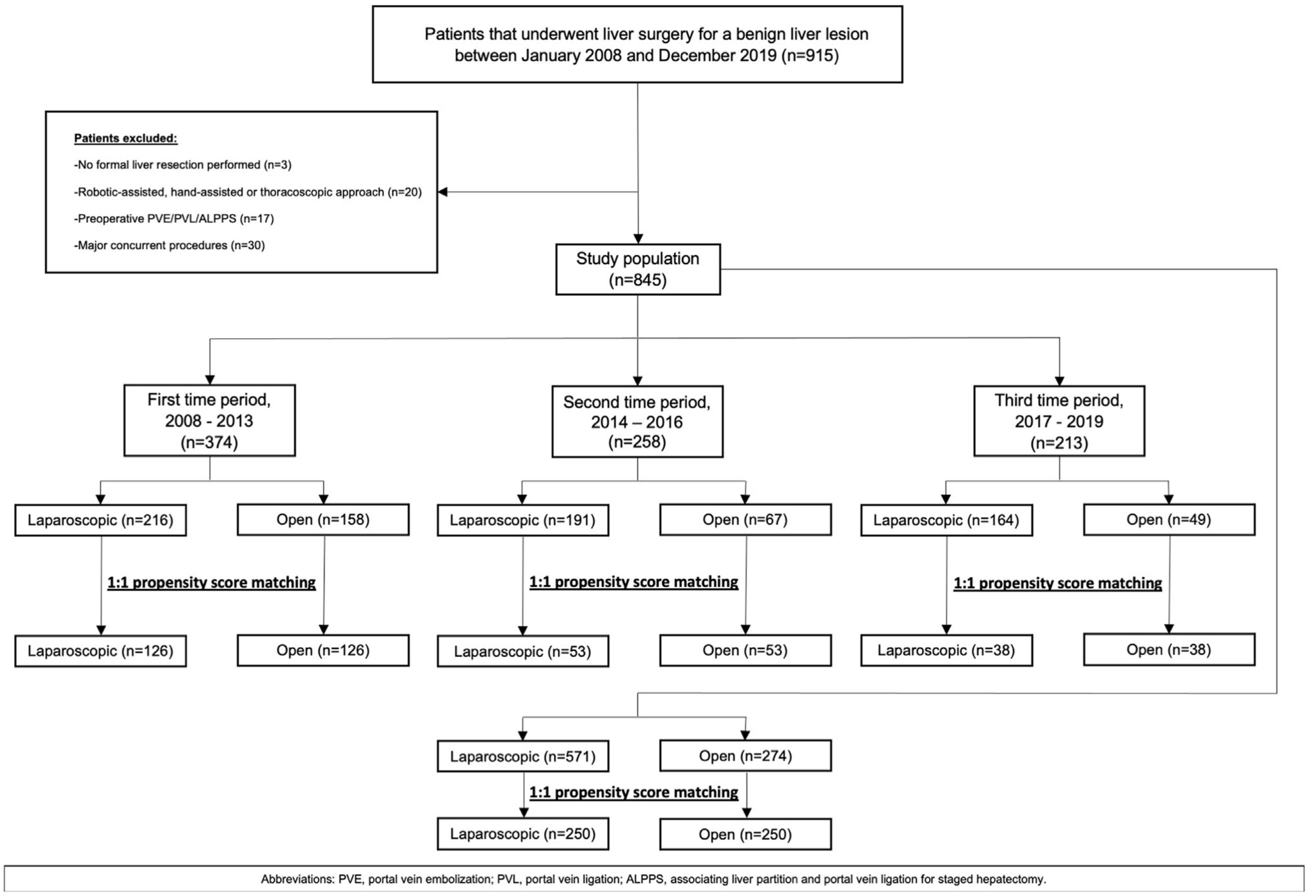

Figure 1 Study flowchart

data (Judgement's reference number: NP 5787). The guidelines outlined in the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) statement were followed to write the report of this study.[27]

Definitions and outcomes

Data were collected from electronic health records. Baseline characteristics consisted of patient demographics, American Society of Anesthesiologists (ASA) score, presence of cirrhosis, history of hepatic or extrahepatic abdominal surgery, disease characteristics (number of lesions, uni- or bilobar distribution, size of the largest lesion) and the extent and type of resection performed. Perioperative outcomes consisted of operative time in minutes, intraoperative blood loss in milliliters, utilization of the Pringle maneuver, perioperative blood transfusion, intraoperative unfavorable incidents, conversion to an open procedure (in case of a laparoscopic approach), postoperative 30-day morbidity, readmissions, length of stay, and 90-day or in-hospital mortality. The Brisbane 2000 terminology was used to define the extent and type of the liver resection performed, defining a resection of at least three contiguous segments as major.[28] However, minor liver resections in the anterolateral (Segment 2, 3, 4b, 5, and 6) or posterosuperior segments (Segment 1, 4a, 7, 8) were defined as minor and technically major, respectively, due to the risks associated with resections in the unfavorably located posterosuperior segments.[25,29] Intraoperative unfavorable incidents and postoperative morbidity were defined and graded according to the Oslo and Clavien-Dindo (CD) classification, respectively.[30,31] Postoperative morbidity was reported as overall and severe (CD $\geq$ 3a).

The data regarding textbook outcome was derived from the available perioperative outcome data, using the validated global survey-based definition of textbook outcome in liver surgery.[22] Since resection margins are less relevant for BLL, this item was excluded from the definition for this study, textbook outcome therefore comprised: the absence of intraoperative incidents of grade 2 or higher, postoperative bile leak grade B or C, severe morbidity, readmission, and 90-day or in-hospital mortality.[22] For open liver resections the intraoperative incident item was excluded from the definition since this relatively novel outcome measure is mainly used in minimally invasive surgery, and data were sparsely available for open procedures. To define textbook outcome+, the absence of a prolonged length of stay was included, using the cut-offs described previously (>4 days for

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minor and >7 days for major laparoscopic liver resections, >5 days for minor and >9 days for major open liver resections).[22] Of note, the addition of the variable 'absence of a prolonged length of stay' did not reach the 80% consensus cut-off for the standard definition, possibly related to the fact that a variability in length of stay exists due to geographic and health care setting factors. Therefore, this outcome requires a more nuanced interpretation.

Survey on liver surgery in patients with benign liver lesions

A survey developed by two of the authors (JS and GZ) was distributed among the chief liver surgeons of the participating centers using Qualtrics XM® (Qualtrics, Provo, Utah, USA). The survey included nine questions on preoperative imaging, indications for liver resection, contra-indications for usage of MILS and developments in the management of patients with BLL. Responses were analyzed anonymously.

Preoperative assessment and surgical technique

During the preoperative workup, patients routinely underwent routine blood tests, contrast-enhanced triphasic thoraco-abdominal computed tomography (CT) scans and magnetic resonance imaging (MRI) scans. The treatment plan for each patient was discussed by a multidisciplinary team of surgeons, radiologists and hepatologists.

Liver resections were generally performed using similar surgical techniques, irrespective of the chosen approach. First, the extent of hepatic disease and the proximity of lesions to major vascular structures was assessed using intraoperative ultrasound. Superficial parenchymal transection was mainly performed with an ultrasonic dissector or a bipolar vessel sealer and deep parenchymal transection with an ultrasonic aspirator. Vessels and biliary structures were sealed and divided with the used dissector device or between metallic clips, Hem-o-Lok clips (Weck Closure Systems, Research Triangle Park, USA), sutures, or closed and transected with staplers depending on their diameter. Intravenous fluids were restrictively administered during the parenchyma transection phase, to maintain a low central venous pressure. The Pringle maneuver was intermittently applied at the discretion of the operating surgeon.

Statistical analysis

Categorical variables were reported as counts and percentages, and compared between treatment groups (laparoscopic and open) using Chi-squared or Fisher's exact tests, when appropriate. Continuous variables with a normal distribution were reported as the mean with its standard deviation and compared between treatment groups using an unpaired T-test. Continuous variables with a non-normal distribution were reported as the median with its range and compared between treatment groups using the Mann−Whitney U test. Trends over time were analyzed using the Cochran−Armitage test for trend for the categorical variables, and using the Jonckheere−Terpstra test for continuous variables. Normality was assessed by visually inspecting histograms and Q−Q plots. For the risk-adjusted time-trend analyses, multivariable logistic regression models were used. The dependent variables were the primary endpoint (textbook outcome and textbook outcome+), and its subcomponents. Aside from the chosen time periods, variables with a $P < 0.10$ in the univariable analyses were entered in these models. Some of the independent variables contained missing data in a missing at random pattern (Supplementary figure 1). Therefore, a multiple imputation process was applied.[32] The data of the dependent variables of interest, namely textbook outcome and textbook outcome+, were not imputed.

Subsequently, PSM was applied in a 1:1 ratio without replacement on the multiply imputed data of the overall cohort and, as a subgroup analysis, the different time periods, using the within approach with a caliper width ranging from 0.1 to 0.2.[33,34] Factors that could possibly influence treatment allocation, in terms of laparoscopic or open surgery, were entered as covariates in the PSM model: age, gender, ASA-score, cirrhosis, history of previous hepatic surgery, type of BLL, location (anterolateral versus posterosuperior segments) and extent of resection (minor versus major), and the disease extent, in terms of number of lesions, size of the largest lesions, and uni- or bilobar distribution.

After PSM, balance was assessed by computing standardized differences in the matched datasets. A standardized difference (SD) ≤ 0.1 is deemed as optimal balance.[35] Descriptive statistics were generated by averaging the values across the imputed datasets according to Rubin's rules, P-values were computed by applying logistic regression models on the imputed datasets and subsequently pooling the causal effect estimates.[36] All analyses were performed on an intention-to-treat basis. A two-sided P-value <0.05 was considered statistically significant. Data were analyzed using R for Mac OS X version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 1.973 of the 14.852 patients that underwent liver surgery during the study period were operated for benign disease (13.3%). Over time, the proportion of patients undergoing liver surgery for benign disease remained stable, namely 12.6% in the first time period, 11.9% in the second time period and 12.1% in the last time period ($p = 0.454$) (Fig. 2). Of the patients undergoing surgery for benign disease, 915 patients (46.4%) underwent surgery for solid lesions. After applying the exclusion criteria, the study population consisted of 845 patients, of which 374 were operated in the first, 258 in the second and 213 in the third time period (Fig. 1).

Trends in the baseline, procedural and disease characteristics

The baseline, procedural and disease characteristics are summarized in Table 1. Most patients were relatively young (median

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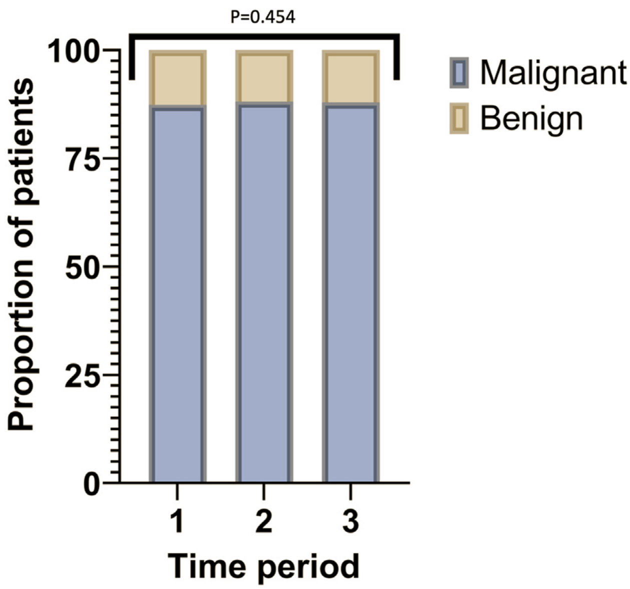

Figure 2 Proportion of patients undergoing liver surgery for benign and malignant disease

age 46 years), female (73%), and had an ASA-score of 1 or 2 (87.2%). When comparing patients' characteristics over time, body mass indices gradually decreased (from median 26.8 to 24.7 kg/m^2, p = 0.008), while an ASA-score of 3 or 4 became more common (from 9.9% to 16%, p < 0.001). The use of the laparoscopic approach increased from 57.8% in the first time period to 77% in the last time period (p < 0.001). The proportion of patients undergoing a major liver resection also increased, from 17.1% in the first time period to 26.3% in the last time period, although this increase was not statistically significant (p = 0.087). Lastly, the proportion of patients undergoing a resection for HCA decreased from 35% to 24.9%, while the proportion of patients undergoing a resection for hemangioma increased from 36.9% to 43.7% (p = 0.023).

Unadjusted trends in perioperative outcomes

Despite the mentioned increase in the number of laparoscopic procedures and major liver resections over time, relatively stable intraoperative outcomes were observed, in terms of operative times (median 170–182.1 min, p = 0.098), rates of transfusion (4.8%–3.3%, p = 0.457), intraoperative incidents (8.9%–6.4%, p = 0.403) and conversion (4.9%–7.6%, p = 0.292) (Table 2). However, a significant increase in the use of the Pringle maneuver was noted (33.2%–47.2%, p = 0.001), paralleled by a slight decrease in blood loss (First time period, 200 mL [range 100–450], second time period, 200 [100–350], third time period 200 [50–400], p = 0.052) (Table 2).

Concerning postoperative outcomes, the severe morbidity and mortality rates increased slightly, although this increase did not reach statistical significance (from 5% to 9.1%, p = 0.060 and from 0.5 to 2.4%, p = 0.060, respectively). The median length of stay decreased significantly (from 5 to 4 days, p = 0.002), paralleled by a decrease in the prolonged length of stay rates (from 41.7% to 26.6%, p < 0.001). These results were accompanied by relatively stable textbook outcome rates, ranging from 86.6% in the first time period to 83.8% in the second, and 81.3% in the last time period (p = 0.151), and a gradually increasing textbook outcome + rate, from 41.7% in the first time period to 54.9% in the second, and finally 58.7% in the last time period (p < 0.001) (Table 2).

Risk-adjusted time-trend analyses for textbook outcome and its subcomponents

The results of the univariable analyses are reported in supplementary table 1. In the risk-adjusted analyses, undergoing surgery during the different time periods was not independently associated with the textbook outcome rate, while undergoing surgery for larger lesions and undergoing a major liver resection was independently associated with lower textbook outcome rates (adjusted odds ratio (aOR) 0.994, p = 0.036 and 0.396, p < 0.001; respectively) (Table 3). The gradual increase in the textbook outcome + rate over time was confirmed in the risk-adjusted analyses, with an aOR of 1.680 (p = 0.014) of achieving textbook outcome+ in the last time period, compared to the first time period. Usage of the minimally invasive approach was also independently associated with a higher textbook outcome + rate (aOR 1.951, p < 0.001), while the presence of liver cirrhosis and undergoing a technically major resection were independently associated with lower textbook outcome + rates (aOR 0.337, p = 0.042 and 0.619, p = 0.019; respectively) (Table 3).

Assessing risk-adjusted time trends in subcomponents of textbook outcome+, the third time period was independently associated with a higher severe morbidity rate (aOR 2.159, p = 0.038). Conversely, usage of the minimally invasive approach was independently associated with a lower severe morbidity rate (aOR 0.382, p = 0.003) (Table 3). The risk of a prolonged length of stay gradually decreased over time, with an aOR of 0.691 in the second time period (p = 0.050) and 0.596 in the third time period (p = 0.013) (Table 3). Independently of this time trend, usage of the minimally invasive approach and undergoing a major hepatectomy were also associated with a lower prolonged length of stay rate (aOR 0.331, p < 0.001). On the contrary, cirrhosis and undergoing a technically major resection were associated with a higher prolonged length of stay rate (aOR 3.782, p = 0.004 and aOR 1.713, p = 0.006; respectively). Due to low event rates, analyses of the other subcomponents of textbook outcome+ were not performed, since results of these analyses would likely not be reliable (<40 events for each subcomponent).[37]

Patient characteristics and perioperative outcomes stratified by the chosen surgical approach, before PSM

When assessing treatment allocation in the overall cohort, in terms of the chosen surgical approach, patients in the

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Table 1 Unadjusted trends in the baseline, procedural and disease characteristics

	Overall	2008–2013	2014–2016	2017–2019	P
	n = 845	n = 374	n = 258	n = 213	
Baseline characteristics					
Age (years)	46 [36.8, 57]	45.6 [37, 56.4]	46 [37, 58.1]	47 [35.8, 56.7]	0.960
Gender, male	226 (27)	100 (26.7)	66 (25.9)	60 (28.8)	0.643
BMI	25.8 [22.3, 28.7]	**26.8 [23.5, 29.6]**	**26 [22.5, 28]**	**24.7 [21.4, 28.4]**	**0.008**
ASA-score 3&4	100 (12.8)	**34 (9.9)**	**34 (14.3)**	**32 (16)**	**<0.001**
Cirrhosis	20 (2.6)	8 (2.3)	7 (2.8)	5 (2.6)	0.789
Previous abdominal surgery					
Extrahepatic	126 (15)	50 (13.5)	36 (14)	40 (18.9)	0.102
Hepatic	16 (1.9)	10 (2.7)	2 (0.8)	4 (1.9)	0.371
Procedural characteristics					
Laparoscopic approach	571 (67.6)	**216 (57.8)**	**191 (74)**	**164 (77)**	**<0.001**
Type of resection					0.087
Minor	505 (59.8)	238 (63.6)	157 (60.9)	110 (51.6)	
Wedge	242 (47.9)	109 (45.8)	79 (50.3)	54 (49.1)	
Segmentectomy	105 (20.8)	55 (23.1)	32 (20.4)	18 (16.4)	
Bisegmentectomy	158 (31.3)	74 (31.1)	46 (29.3)	38 (34.5)	
Technically major	175 (20.7)	72 (19.3)	56 (21.7)	47 (22.1)	
Wedge	102 (58.3)	39 (54.2)	30 (53.6)	33 (70.2)	
Segmentectomy	36 (20.6)	14 (19.4)	18 (32.1)	4 (8.5)	
Bisegmentectomy	37 (21.1)	19 (26.4)	8 (14.3)	10 (21.3)	
Major	165 (19.5)	64 (17.1)	45 (17.4)	56 (26.3)	
Trisegmentectomy	8 (0.9)	4 (1.1)	1 (0.4)	3 (1.4)	
Hemi hepatectomy	137 (16.2)	55 (14.7)	36 (14)	46 (21.6)	
Extended hemi hepatectomy	14 (1.7)	3 (0.8)	6 (2.3)	5 (2.3)	
Central hepatectomy	5 (0.6)	2 (0.5)	1 (0.4)	2 (0.9)	
Other anatomically major	1 (0.1)	0	1 (0.4)	0	
Disease characteristics					
Number of lesions	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	0.772
Bilobar distribution	91 (11)	33 (9.1)	29 (11.6)	29 (13.7)	0.089
Size largest lesion, millimeters	50 [30, 80]	50 [30, 80]	55 [30, 80]	55 [27, 90]	0.400
Type of benign liver lesion					**0.023**
Hemangioma	347 (41.1)	**138 (36.9)**	**116 (45)**	**93 (43.7)**	
Focal Nodular Hyperplasia	225 (26.6)	**98 (26.2)**	**67 (26)**	**60 (28.2)**	
Hepatocellular adenoma	250 (29.6)	**131 (35)**	**66 (25.6)**	**53 (24.9)**	
Other	23 (2.7)	**7 (1.9)**	**9 (3.5)**	**7 (3.3)**	

Values are expressed in percentages or in median (IQR).
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

laparoscopic group were younger (median age 45 vs 47.1 years, p = 0.017), more often female (75.5% vs 67.9%, p = 0.020), without a history of previous hepatic surgery (98.8% vs 96.6%, p = 0.038) (Supplementary table 2). Additionally, patients allocated to the laparoscopic approach generally underwent less technically complex procedures (Technically or anatomically major resections), for less extensive disease, in terms of the number of lesions, their distribution and size (Supplementary table 2).

Patients allocated to an open approach more often underwent surgery for a hemangioma (48.2% vs 37.7%, p < 0.001). Over time, the differences in the baseline and procedural characteristics of patients allocated to the laparoscopic or open approach became less distinct, in terms of patients with a history of

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Table 2 Unadjusted trends in the intra- and postoperative outcomes

	Overall n = 845	2008–2013 n = 374	2014–2016 n = 258	2017–2019 n = 213	P
Intraoperative outcomes					
Operative time, minutes	174 [120, 243.4]	170 [120, 230]	170 [110.8, 251.1]	182.1 [130, 260.1]	0.098
Blood loss, milliliters	200 [100, 400]	200 [100, 450]	200 [100, 350]	200 [50, 400]	0.052
Perioperative blood transfusion	30 (4.4)	14 (4.8)	10 (4.6)	6 (3.3)	0.457
Pringle maneuver	302 (38.9)	**108 (33.2)**	**100 (39.7)**	**94 (47.2)**	**0.001**
Intraoperative incidents					0.403
Grade 1	10 (2)	4 (2.2)	3 (1.6)	3 (2.1)	
Grade 2	27 (5.3)	12 (6.7)	9 (4.8)	6 (4.3)	
Grade 3	1 (0.2)	0	1 (0.5)	0	
Conversion (in case of lap. approach)	31 (5.7)	10 (4.9)	9 (4.9)	12 (7.6)	0.292
Postoperative outcomes					
Overall morbidity	149 (18)	64 (17.6)	44 (17.3)	41 (19.6)	0.596
Severe morbidity	51 (6.2)	18 (5)	14 (5.5)	19 (9.1)	0.060
Length of stay, days	4 [3, 6]	**5 [4, 7]**	**4 [3, 6]**	**4 [3, 6]**	**0.002**
Prolonged length of stay[a]	277 (34.6)	**146 (41.7)**	**77 (31.2)**	**54 (26.6)**	**<0.001**
90-day or in-hospital mortality	11 (1.3)	2 (0.5)	4 (1.6)	5 (2.4)	0.060
Readmission	31 (4.5)	9 (3)	13 (6.4)	9 (5)	0.208
Textbook outcome	505 (84.3)	213 (86.6)	166 (83.8)	126 (81.3)	0.151
Textbook outcome+	336 (50.1)	**120 (41.7)**	**118 (54.9)**	**98 (58.7)**	**<0.001**

Values are expressed in percentages or in median (IQR).
Abbreviations: lap., laparoscopic.
[a] Defined as > 4 days for minor and >7 days for major laparoscopic liver resections, >5 days for minor and >9 days for major open liver resections.

previous hepatic surgery and patients undergoing a major liver resection (Supplementary table 2).

In the unmatched cohort, the laparoscopic approach offered several significant benefits over the open approach, in terms of shorter operative times, less blood loss, a shorter length of stay, and lower rates of transfusions, Pringle usage, prolonged length of stay, overall and severe morbidity (Supplementary table 3). This was accompanied by comparable textbook outcome rates of 85.6% for laparoscopic procedures and 82.3% for open procedures (p = 0.345), while the textbook outcome + rate was significantly higher when patients were allocated to the laparoscopic approach (57.4% vs 38%, p < 0.001) (Supplementary table 3). Assessing trends over time, the benefits of the laparoscopic approach over the open approach seemed greater in the later time periods, in terms of operative time, morbidity, length of stay and textbook outcome+. Comparable textbook outcome rates were observed in all time periods (Supplementary table 3).

Patient characteristics and perioperative outcomes stratified by the chosen surgical approach, after PSM

After applying PSM in order to mitigate selection bias, 250 patients could be matched in the overall cohort and 126 (2008–2013), 53 (2014–2016), and 38 (2017–2019) patients in the three time periods. In both the overall cohort and the subgroups, the covariates were well balanced after PSM (All SD $\leq$ 0.12) (Table 4). Intraoperatively, the laparoscopic approach continued to be associated with lower rates of transfusions (2.4% versus 9.6%, p = 0.006) and intraoperative incidents (7.6% versus 15.2%, p = 0.014), compared to the open approach (Table 5). During the postoperative course, patients in the laparoscopic group had lower overall and severe morbidity rates (14% versus 26%, p = 0.002 and 4.4% versus 10%, p = 0.048, respectively) and a shorter length of stay (4 versus 6 days, p < 0.001). This was paralleled by a lower prolonged length of stay rate (26.3% versus 50.6%, p < 0.001), and higher textbook outcome + rates (55.4% versus 38.4%, p < 0.001). Nevertheless, comparable textbook outcome rates were achieved, namely 84.3% in the laparoscopic group and 82.5% in the open group (p = 0.629) (Table 5).

Survey concerning liver surgery in patients with benign liver lesions

The results of the survey conducted among the chief surgeons of the participating centers (n = 19) are reported in supplementary table 4. Concerning the indications for surgical resection of a HCA, all respondents deemed bleeding an indication for resection. More than three quarters of the respondents also labelled diagnostic uncertainty (84.2%), upper abdominal symptoms

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Table 3 Multivariable analyses

	Textbook outcome		Textbook outcome+		Severe morbidity		Prolonged length of stay	
Term	**aOR (95% CI)**	**P**	**aOR (95% CI)**	**P**	**aOR (95% CI)**	**P**	**aOR (95% CI)**	**P**
Time period								
First	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Second	0.776 (0.452–1.332)	0.358	1.451 (0.994–2.117)	0.053	1.309 (0.621–2.760)	0.479	**0.691 (0.477–1.001)**	**0.050**
Third	0.761 (0.433–1.337)	0.342	**1.680 (1.112–2.537)**	**0.014**	**2.159 (1.045–4.461)**	**0.038**	**0.596 (0.396–0.897)**	**0.013**
Gender, male								
Age at operation								
BMI			0.960 (0.911–1.013)	0.122				
Cirrhosis			**0.337 (0.118–0.960)**	**0.042**			**3.782 (1.529–9.350)**	**0.004**
ASA-score								
I/II	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
III/IV	0.587 (0.308–1.117)	0.105			1.912 (0.896–4.078)	0.094		
Previous hepatic surgery								
Size largest liver lesion	**0.994 (0.989–0.999)**	**0.036**			1.005 (0.999–1.011)	0.075		
Number of lesions								
Bilobar distribution								
Type of benign liver lesion								
Hemangioma	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Focal Nodular Hyperplasia							0.853 (0.574–1.267)	0.431
Hepatocellular adenoma							0.824 (0.565–1.201)	0.313
Other							2.081 (0.807–5.371)	0.130
Minimally invasive approach			**1.951 (1.377–2.763)**	**<0.001**	**0.382 (0.202–0.724)**	**0.003**	**0.331 (0.233–0.469)**	**<0.001**
Type of liver resection								
Minor	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Technically major	0.969 (0.527–1.782)	0.920	**0.619 (0.415–0.924)**	**0.019**	0.932 (0.430–2.021)	0.858	**1.713 (1.169–2.511)**	**0.006**
Major	**0.396 (0.233–0.671)**	**<0.001**	1.045 (0.683–1.599)	0.840	1.347 (0.664–2.729)	0.409	**0.371 (0.231–0.595)**	**<0.001**

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists.

which could be caused by the lesion (78.9%), male sex (78.9%), and persistent size ≥5 cm (78.9%, irrespective of an inflammatory status) indications for resection. Lesion growth (63.2%), pregnancy wish (26.3%) and a proven β-catenin mutation subtype (5.3%) were less often reported indications for resection. For FNH, a large proportion of the respondents deemed upper abdominal symptoms which could be caused by the lesion (78.9%) and diagnostic uncertainty (68.4%) indications for resection. Bleeding (36.8%), lesion growth (21.1%) and size (5.3%) were less often accepted indications. In case of a hemangioma, upper abdominal symptoms which could be caused by the lesion was again the most reported indication for resection (89.5%), followed by Kasabach-Merritt syndrome (73.7%) and diagnostic uncertainty (63.2%). A smaller proportion of the

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respondents also deemed bleeding (47.4%), lesion growth (26.3%), palpable mass (5.3%) and size (5.3%) indications for resection. In terms of absolute and relative contra-indications for MILS, respondents mainly stated patient (E.g., contraindication to pneumoperitoneum) and disease factors (large lesions, need for vascular or biliary reconstruction) as potential contra-indications for MILS. All respondents indicated that the management of FNH and hemangioma had not changed over the past 10 years in their center. However, seven respondents (36.8%) stated that the management of HCA did change and, among other things, declared that biopsies leading to a more precise histopathological diagnosis were more often performed and patients were more often treated conservatively.

Discussion

In this retrospective international multicenter cohort study, trends in the characteristics and perioperative outcomes of patients undergoing a liver resection for BLL over a 12-year time period were assessed. Although over time the proportion of patients undergoing a liver resection for benign or malignant disease did not change, more frail patients, in terms of patients with an ASA-score of 3 or 4, underwent surgery. The laparoscopic approach was increasingly employed, also for technically complex procedures (such as technically or anatomically major resections), in parallel with the expanding body of evidence and international consensus conferences on the topic.[8,18,25,26,38,39] During this implementation process, the textbook outcome rate remained stable above 80%, while the textbook outcome + rate considerably increased from 41.7% to 58.7%. After PSM, the textbook outcome rate was comparable for patients allocated to a laparoscopic or open approach (84.3% versus 82.5%, respectively, $p = 0.629$), but a significantly higher proportion of the patients allocated to laparoscopy achieved textbook outcome+ (55.4% versus 38.4%, respectively, $p < 0.001$).

To date, only a limited number of studies specifically assessing the indications for and perioperative outcomes of resections for BLL have been published, and none of these previous studies used textbook outcome as an outcome measure.[40–43] In agreement with the existing evidence on this topic, our study population mainly consisted of young, relatively fit (in terms of ASA-scores), female patients.[40] Therefore, the perioperative outcomes of this patient population can appropriately be seen as a benchmark for liver surgery in general. This is reflected in the relatively low transfusion, conversion, overall and severe morbidity rates of 4.4%, 5.7%, 18% and 6.2%, respectively, short median hospital stay of 4 days and high textbook outcome rate of 84.3%, when compared with recent studies assessing the perioperative outcomes of minimally invasive and open liver surgery for all indications.[8,22,44]

However, these results are in line with other studies solely assessing the perioperative outcomes of resections for benign liver lesions.[40,41] Importantly, several changes over time in the surgical indications and perioperative outcomes of these patients were observed. The number of patients undergoing a resection for HCA decreased substantially, especially following the first time period. In the absence of another explanation for this practice adjustment, it seems likely that this change was, at least partially, related to the improved understanding and detection of the HCA subtypes, and subsequent alteration of the American and European guidelines for the management of BLL.[1,4] This hypothesis is supported by the results of the conducted survey.

Over time, significant improvements in the perioperative outcomes occurred, while more patients with higher ASA-scores underwent surgery and the complexity of the procedures seemed to increase slightly, especially in the time period following the Southampton consensus guidelines.[26] These improvements seemed, at least in part, attributable to the adoption of the laparoscopic approach, since laparoscopic surgery was associated with several benefits over open liver surgery in both the multivariable and propensity score matched analyses. However, it seems that these benefits have not, as initially feared, led to a widening of the indications for surgery in patients with benign disease, as the proportion of patients undergoing liver surgery for malignant or benign disease remained stable, in line with the results of an earlier study.[18,45] In addition, a wider use of the laparoscopic approach was paralleled by a stability of the median size of the resected lesions. Importantly, patients with larger lesions were more often allocated to an open approach, irrespective of the time period, indicating that open surgery still plays an important role in the management of patients affected by more extensive disease and those requiring more technically challenging surgical procedures. In the survey, size was also often mentioned as a contra-indication for the use of MILS.

Besides these positive developments, the mortality rate in this cohort was unfortunately 1.3%, which is comparable to the reported mortality rates for all indications, but higher than in previous reports focusing on BLL.[24,40,41,44] While surgeons always strive for zero perioperative mortality, one could argue that achieving this is even more desirable in case of BLL, since the indications for surgery may be debatable and patients are often relatively young and fit.[1] Additional efforts should therefore be taken to enhance patient selection, preoperative optimization and perioperative care. With regards to minimally invasive liver surgical techniques, the increasingly employed robotic approach might facilitate a shorter learning curve and has been associated with improved intraoperative outcomes in the setting of technically complex resections for BLL.[46,47,48,49] Lessons might also be learned from living donor programs, since in this context a mortality rate of 0.02% has been reported in a large study of major liver resections.[50]

Additionally, further looking into the subcomponents of the current definition of textbook outcome+, technically major

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Table 4 Baseline, procedural and disease characteristics stratified by the used surgical approach, after propensity score matching

	Overall		SD	P	2008–2013		SD	P
	Laparoscopic	Open			Laparoscopic	Open		
	n = 250	n = 250			n = 126	n = 126		
Baseline characteristics								
Age (years)	46 [35, 58]	46.6 [39, 57]	0	0.913	45 [35, 56.4]	45.5 [38.1, 55]	0.05	0.690
Gender, male	70 (28)	75 (30)	0.02	0.655	34 (27)	31 (24.6)	0.02	0.737
BMI	26 [22.2, 28.4]	26 [22.9, 29.4]		0.385	27 [23.5, 28.9]	27 [24, 30.1]		0.568
ASA-score 3&4	37 (14.8)	32 (12.8)	0.02	0.607	14 (11.1)	13 (10.3)	0.01	0.833
Cirrhosis	8 (3.2)	6 (2.4)	0.01	0.634	4 (3.2)	3 (2.4)	0	0.991
Previous abdominal surgery								
Extrahepatic	41 (16.4)	35 (14)		0.548	17 (13.5)	14 (11.1)		0.578
Hepatic	6 (2.4)	8 (3.2)	0	0.754	2 (1.6)	2 (1.6)	0	0.982
Procedural characteristics								
Type of resection			0.05	0.112			0.04	0.528
Minor	127 (50.8)	114 (45.6)			78 (61.9)	73 (57.9)		
Wedge	65 (26)	55 (22)			38 (30.2)	28 (22.2)		
Segmentectomy	22 (8.8)	27 (10.8)			16 (12.7)	24 (19)		
Bisegmentectomy	40 (16)	32 (12.8)			24 (19)	21 (16.7)		
Technically major	58 (23.2)	66 (26.4)			26 (20.6)	29 (23)		
Wedge	34 (13.6)	34 (13.6)			16 (12.7)	13 (10.3)		
Segmentectomy	10 (4)	20 (8)			3 (2.4)	8 (6.3)		
Bisegmentectomy	14 (5.6)	12 (4.8)			7 (5.6)	8 (6.3)		
Major	63 (25.2)	69 (27.6)			22 (17.5)	24 (19)		
Trisegmentectomy	3 (1.2)	5 (2)			1 (0.8)	2 (1.6)		
Hemi hepatectomy	55 (22)	57 (22.8)			20 (15.9)	21 (16.7)		
Extended hemi hepatectomy	2 (0.8)	7 (2.8)			1 (0.8)	0		
Central hepatectomy	2 (0.8)	0			0	0		
Other anatomically major	1 (0.4)	0			0	0		
Disease characteristics								
Number of lesions	1 [1, 1]	1 [1, 1]	0.01	0.975	1 [1, 1]	1 [1, 1]	0	0.961
Bilobar distribution	31 (12.4)	34 (13.6)	0.01	0.662	10 (7.9)	12 (9.5)	0.01	0.713
Size largest lesion, millimeters	55 [55, 90]	60 [60, 100]	0.11	0.266	50 [27, 80]	60 [35, 89]	0.12	0.319
Type of benign liver lesion			0.04	0.497			0.04	0.488
Hemangioma	108 (43.2)	116 (46.4)			47 (37.3)	53 (42.1)		
Focal Nodular Hyperplasia	56 (22.4)	46 (18.4)			32 (25.4)	27 (21.4)		
Hepatocellular adenoma	78 (31.2)	79 (31.6)			46 (36.5)	46 (36.5)		
Other	6 (2.4)	7 (2.8)			1 (0.8)	1 (0.8)		

Values are expressed in percentages or in median (IQR).
Abbreviations: SD, standardized difference; BMI, body mass index; ASA, American Society of Anesthesiologists.

resections were independently associated with a higher odds ratio of a prolonged length of stay, while, conversely, major resections were associated with a lower odds ratio. Although the first result seems logical, a prolonged length of stay was previously not defined separately for minor and technically major resections.[22] Additionally, the latter result seems counterintuitive, since it is well known that major liver resections are associated with a higher postoperative morbidity risk, and postoperative morbidity often prolongs the length of stay.[51] Therefore, it seems worthwhile to revise the current definition of a prolonged length of stay for textbook outcome+, at least for this patient population. Of note, it is well known that length of stay is not only

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2014–2016		SD	P	2017–2019		SD	P
Laparoscopic	Open			Laparoscopic	Open		
n = 53	n = 53			n = 38	n = 38		
Baseline characteristics							
51 [39.5, 66]	48 [43.3, 65]	0.03	0.901	50 [37, 61.3]	49.6 [37, 57]	0.03	0.874
15 (28.3)	19 (35.8)	0.06	0.502	12 (31.6)	12 (31.6)	0.01	0.952
26 [22, 28]	24.7 [22.7, 28.8]		0.975	25 [21.3, 29]	24.5 [21, 29]		0.832
5 (9.4)	6 (11.3)	0.02	0.795	7 (18.4)	9 (23.7)	0.05	0.647
1 (1.9)	1 (1.9)	0	0.706	2 (5.3)	1 (2.6)	0.02	0.763
Previous abdominal surgery							
12 (22.6)	7 (13.2)		0.240	4 (10.5)	10 (26.3)		0.357
1 (1.9)	0	0.04	NA	1 (2.6)	1 (2.6)	0	0.720
Procedural characteristics							
		0.08	0.433			0.01	0.933
27 (50.9)	23 (43.4)			11 (28.9)	11 (28.9)		
13 (10.3)	16 (12.7)			5 (13.2)	7 (18.4)		
8 (6.3)	1 (0.8)			1 (2.6)	1 (2.6)		
6 (4.8)	6 (4.8)			5 (13.2)	3 (7.9)		
14 (26.4)	16 (30.2)			11 (28.9)	11 (28.9)		
7 (5.6)	10 (7.9)			8 (21.1)	7 (18.4)		
6 (4.8)	5 (4)			0	3 (7.9)		
1 (0.8)	1 (0.8)			3 (7.9)	2 (5.3)		
13 (24.5)	15 (28.3)			17 (44.7)	16 (42.1)		
0	1 (0.8)			1 (2.6)	1 (2.6)		
12 (9.5)	12 (9.5)			14 (36.8)	12 (31.6)		
0	2 (1.6)			1 (2.6)	3 (7.9)		
0	0			1 (2.6)	0		
1 (0.8)	0			0	0		
Disease characteristics							
1 [1, 1]	1 [1, 1]	0.12	0.677	1 [1, 1]	1 [1, 2]	0.06	0.777
9 (7.1)	9 (7.1)	0	0.951	6 (15.8)	6 (15.8)	0.01	0.944
60 [35, 85]	60 [32, 97.5]	0	0.999	65 [25, 70.1]	62.5 [30, 90]	0.01	0.963
		0.06	0.491			0.09	0.860
27 (21.4)	30 (23.8)			19 (50)	18 (47.4)		
5 (4)	4 (3.2)			9 (23.7)	12 (31.6)		
18 (14.3)	16 (12.7)			9 (23.7)	7 (18.4)		
3 2.4)	2 (1.6)			1 (2.6)	1 (2.6)		

dependent on surgical quality but also on factors such as transfer of care and patients' willingness to go home.[52] Nevertheless, it is seen as a relevant outcome measure, and embedded in many textbook outcome definitions in hepato-pancreato-biliary surgery.[53] Thus, we believe it adds value to report textbook outcome and textbook outcome + alongside each other.

Evidently, patients should always be well informed about these associated risks by their physician, and the decision to pursue surgical treatment should only be taken after a diligent shared decision-making process. In case of symptomatic lesions, patients should also be aware that their symptoms may not disappear after surgical treatment.[40] In this regard, it is also a limitation that patient-reported outcomes are not included in the current definition of textbook outcome, as these surgical treatments can only be a real 'success' if the intended treatment goals are achieved.

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Table 5 Intra- and postoperative outcomes stratified by the used surgical approach, after propensity score matching

	Overall		P	2008–2013		P
	Laparoscopic	Open		Laparoscopic	Open	
	n = 250	n = 250		n = 126	n = 126	
Intraoperative outcomes						
Operative time, minute	178 [111.5, 263.1]	197 [150, 260.5]	0.310	170 [103, 233.8]	173 [140, 231]	0.767
Blood loss, milliliters	150 [50, 300]	300 [100, 750]	0.081	150 [50, 350]	300 [100, 750]	0.180
Perioperative blood transfusion	**6 (2.4)**	**24 (9.6)**	**0.006**	4 (3.2)	9 (7.1)	0.479
Pringle maneuver	98 (39.2)	108 (43.2)	0.364	43 (34.1)	48 (38.1)	0.573
Intraoperative incidents			**0.014**			0.682
Grade 1	**6 (2.4)**	**14 (5.6)**		5 (4)	5 (4)	
Grade 2	**12 (4.8)**	**20 (8)**		9 (9.1)	9 (9.1)	
Grade 3	**1 (0.4)**	**4 (1.6)**		1 (0.8)	3 (2.4)	
Conversion	15 (6.3)			7 (5.8)		
Postoperative outcomes						
Overall morbidity	**35 (14)**	**65 (26)**	**0.002**	18 (14.3)	27 (21.4)	0.163
Severe morbidity	**11 (4.4)**	**25 (10)**	**0.048**	3 (2.4)	9 (7.1)	0.222
Length of stay, days	**4 [3, 5]**	**6 [5, 8]**	**<0.001**	**4 [3, 5]**	**6 [5, 7.8]**	**<0.001**
Prolonged length of stay[a]	**62 (26.3)**	**120 (50.6)**	**<0.001**	**34 (29.3)**	**68 (57.1)**	**<0.001**
90-day or in-hospital mortality	5 (2)	2 (0.8)	0.340	1 (0.8)	1 (0.8)	0.367
Readmission	14 (5.6)	22 (8.8)	0.290	4 (3.2)	7 (5.6)	0.556
Textbook outcome	134 (84.3)	175 (82.5)	0.629	63 (88.7)	87 (86.1)	0.726
Textbook outcome+	**102 (55.4)**	**88 (38.4)**	**<0.001**	41 (49.4)	39 (34.2)	0.058

Values are expressed in percentages or in median (IQR).

[a] Defined as > 4 days for minor and >7 days for major laparoscopic liver resections, >5 days for minor and >9 days for major open liver resections.

The results of this study have to be interpreted in the context of various other limitations. First, the well-known risk of confounding inherent to its multicenter and retrospective design. While multivariable analyses were used to mitigate the influence of confounding, unknown confounders might still influence the outcomes of interest. Second, geographical differences, center and surgeon volumes might also have an influence on the investigated outcomes. However, the used multicenter database only contains data from Western centers with extensive experience in both minimally invasive and open liver surgery. Additionally, in a previously performed study there was no correlation between annual center volume and postoperative outcomes in this setting.[41] Third, data regarding the adoption of enhanced recovery after surgery (ERAS) protocols for liver surgery in the participating centers were unfortunately not available. Although this is a factor which has probably had an impact on the perioperative outcomes, as previously demonstrated, the ERAS guidelines for liver surgery have been introduced at the end of 2016.[54,55] Therefore, it is likely that this development has only had an influence on the results of the third time period in our study, while the biggest improvement in the textbook outcome + rate occurred during the second time period.

In light of the aforementioned, it is our opinion that future research should focus on the development of a novel composite outcome measure for the surgical treatment of benign liver disease, encompassing patient-reported outcome measures. Textbook outcome may not be the ideal concept to use in this setting, as laparoscopy was associated with several advantages over open surgery in this study, but achieved comparable textbook outcome rates. This may suggest that textbook outcome as an all-or-nothing principle can provide an overall assessment of surgical quality, but may lack the granularity to enable, for example, an adequate assessment of the superiority of one surgical approach over the other. In this regard, a more holistic approach seems desirable.[56] Lastly, efforts must be undertaken to develop shared decision-making aids for BLL using up to date outcome information, in order to assist physicians and patients in the shared decision-making process. Prospective studies are also required to study the natural course of BLL and the impact of surgical interventions on patient reported symptoms.[57]

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2014–2016		P	2017–2019		P
Laparoscopic	Open		Laparoscopic	Open	
n = 53	n = 53		n = 38	n = 38	
Intraoperative outcomes					
172.9 [110, 259.4]	214 [164.5, 260.5]	0.339	210 [159.2, 275]	225 [170, 267.8]	0.849
150 [50, 300]	300 [300, 500]	0.098	110 [50, 360]	250 [100, 600]	0.214
2 (3.8)	5 (9.4)	0.196	2 (5.3)	3 (7.9)	0.712
23 (43.4)	23 (43.4)	0.997	23 (60.5)	23 (60.5)	0.929
		0.518			0.336
0	4 (7.5)		1 (2.6)	2 (5.3)	
4 (7.5)	3 (5.7)		2 (5.3)	3 (7.9)	
0	1 (1.9)		0	1 (2.6)	
5 (9.8)			3 (8.8)		
8 (15.1)	14 (26.4)	0.263	**6 (15.8)**	**15 (39.5)**	**0.035**
3 (5.7)	6 (11.3)	0.406	2 (5.3)	7 (18.4)	0.214
4 [3, 6]	6 [5, 7]	0.098	4 [3, 5]	6 [5, 8]	0.111
13 (26)	25 (49)	0.066			0.131
1 (1.9)	0	0.178	1 (2.6)	1 (2.6)	0.543
4 (7.5)	7 (13.2)	0.391	2 (5.3)	4 (10.5)	0.664
31 (81.6)	37 (80.4)	0.999	19 (82.6)	29 (80.6)	0.696
23 (56.1)	18 (36)	0.132	17 (65.4)	18 (51.4)	0.379

Conclusion

From 2008 to 2019, the surgical treatment of BLL has evolved with, among other things, a strong implementation of the laparoscopic approach. This evolution was paralleled by stable textbook outcome rates above 80%, while the textbook outcome + rate increased from 41.7% to 58.7%. The laparoscopic approach was independently associated with higher textbook outcome + rates. Nevertheless, approximately one-fifth of the patients did not achieve textbook outcome, emphasizing that BLL should not be resected when there is no clear indication for surgery.

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Author contributions

Study conception and design: Sijberden, Abu Hilal.
Acquisition of data: All authors.
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Drafting of manuscript: Sijberden, Abu Hilal.
Critical revision: All authors.

Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.10.016.

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