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Comparative Study - Retrospective Cohort

# Indications, trends, and perioperative outcomes of minimally invasive and open liver surgery in non-obese and obese patients: An international multicentre propensity score matched retrospective cohort study of 9963 patients

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A R T I C L E I N F O

*Keywords:*
Overweight
Fatty liver
Open liver resection

A B S T R A C T

*Background:* Despite the worldwide increase of both obesity and the use of minimally invasive liver surgery (MILS), evidence regarding the safety and eventual benefits of MILS in obese patients is scarce. The aim of this study was therefore to compare the outcomes of non-obese and obese patients (BMI 18.5–29.9 and BMI≥30, respectively) undergoing MILS and OLS, and to assess trends in MILS use among obese patients.

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Laparoscopic liver resection
Minimally invasive liver resection

*Methods:* In this retrospective cohort study, patients operated at 20 hospitals in eight countries (2009–2019) were included and the characteristics and outcomes of non-obese and obese patients were compared. Thereafter, the outcomes of MILS and OLS were compared in both groups after propensity-score matching (PSM). Changes in the adoption of MILS during the study period were investigated.
*Results:* Overall, 9963 patients were included (MILS: n = 4687; OLS: n = 5276). Compared to non-obese patients (n = 7986), obese patients(n = 1977) were more often comorbid, less often received preoperative chemotherapy or had a history of previous hepatectomy, had longer operation durations and more intraoperative blood loss (IOBL), paralleling significantly higher rates of wound- and respiratory-related complications. After PSM, MILS, compared to OLS, was associated, among both non-obese and obese patients, with less IOBL (200 ml vs 320 ml, 200 ml vs 400 ml, respectively), lower rates of transfusions (6.6% vs 12.8%, 4.7% vs 14.7%), complications (26.1% vs 35%, 24.9% vs 34%), bile leaks(4% vs 7%, 1.8% vs 4.9%), liver failure (0.7% vs 2.3%, 0.2% vs 2.1%), and a shorter length of stay(5 vs 7 and 4 vs 7 days). A cautious implementation of MILS over time in obese patients (42.1%–53%, $p < .001$) was paralleled by stable severe morbidity ($p = .433$) and mortality ($p = .423$) rates, despite an accompanying gradual increase in surgical complexity.
*Conclusions:* MILS is increasingly adopted and associated with perioperative benefits in both non-obese and obese patients.

## 1. Introduction

The prevalence of obesity is increasing worldwide, and conditions that occur more frequently in the obese population (e.g., diabetes mellitus, cardiovascular and respiratory diseases) may worsen outcomes following abdominal surgery [1,2]. Furthermore, metabolic changes induced by obesity can lead to parenchymal liver injury, such as steatohepatitis or fatty liver disease, potentially increasing the perioperative risks of liver surgery [3,4]. Considering that obesity increases the technical difficulty of abdominal surgery in general, and liver surgery in particular, obese patients are a challenging surgical population from both a technical and clinical standpoint [5,6]. However, studies investigating the impact of obesity on outcomes after liver surgery have shown contrasting results, probably related to selection bias and variable body weight class comparisons.

Numerous observational and randomized controlled studies, including OSLO-COMET and LapOpHuva, have reported benefits of minimally invasive liver surgery (MILS) in selected patients [7–10]. Moreover, recent research indicates advantages of MILS over open liver surgery (OLS) among vulnerable patients [11,12]. In this context, obese patients may represent a frail group of patients especially benefitting from a surgical approach that aims to reduce surgical stress and enhance postoperative recovery. However, as previously stated in the Southampton consensus guidelines, there is currently limited evidence on the feasibility and safety of MILS in obese patients [13]. A limited number of comparative studies, often single centre with a relatively small sample size, have been published. Moreover, most of these studies have included non-matched cohorts, possibly leading to a substantial degree of selection bias [14].

The primary aims of this retrospective multicentre cohort study were therefore to assess differences in the characteristics and perioperative outcomes of non-obese and obese patients undergoing a liver resection, to compare the short-term outcomes of MILS and OLS in these two groups, and to investigate trends in the implementation and results of MILS in obese patients. Secondary aims were to compare the characteristics and perioperative outcomes of MILS and OLS in obese patients stratified by their obesity class and to assess liver surgeons' attitudes towards liver surgery in obese patients.

## 2. Methods

The prospectively maintained databases of patients who underwent MILS or OLS at 20 hepatobiliary referral centres were bundled in a multicentre database and retrospectively assessed. Adult patients who underwent an elective liver resection between January 2009 and December 2019 with a known body mass index (BMI) were included in this study. Patients who underwent hand-assisted or robotic-assisted liver resection, did not undergo a liver resection (for example cyst fenestration/deroofing, liver biopsies, or diagnostic laparoscopy) and those with a BMI lower than 18.5 were excluded. The report of this study was written following the guidelines outlined in the STROCSS statement [15].

## 3. Study design

Study patients were stratified in non-obese ($18.5 \leq BMI \leq 29.9$) and obese ($BMI \geq 30$) [16]. The characteristics and outcomes of non-obese and obese patients were compared. Thereafter, the characteristics and outcomes of patients undergoing MILS and OLS were compared in non-obese and obese patients, before and after propensity score matching (PSM) [17]. In addition, a subgroup analysis was performed in the obese patients: obese patients were stratified in three groups, according to the standard BMI classes (Class I ($30 \leq BMI \geq 34.9$), class II ($35\leq BMI \geq 39.9$), and class III ($BMI \geq 40$)), and the characteristics and outcomes of patients treated by MILS or OLS in each of these BMI classes were compared after PSM.

A trend analysis was performed by dividing the overall study population into three groups according to the time period during which the procedure was performed, thereafter comparing the characteristics and outcomes of patients in these three periods. These time periods were chosen based on the moments when the International Consensus Guidelines on MILS were developed (Louisville: 2008; Morioka: 2014; Southampton: 2017) [13,18,19]. All the analyses were conducted on an intention-to-treat basis: patients in which an attempt to perform MILS required a conversion to OLS were included in the MILS group.

## 4. Definitions

Preoperative portal vein occlusion (PVO) included portal vein embolization, ligation or resection. The resection margin was considered positive when <1 mm. Concerning the type of liver resection performed: a traditional major hepatectomy is the resection of three or more contiguous segments (e.g., trisegmentectomy, hemi-hepatectomy, extended hepatectomy) [20]. A minor hepatectomy is the resection of one or two Coinaud segments, located in areas of the liver which are "easy" to access (S2, S3, S4b, S5, and S6); finally, a technically major resection is a resection that would be considered anatomically minor (involving only one or two Couinaud segments) but is located in areas of the liver that are difficult to access (the so called postero-superior segments: S1, S4a, S7, and S8) [21].

Major concurrent procedures included biliary and vascular (portal, hepatic artery, hepatic vein) reconstructions, colorectal, pancreatic, diaphragm, bladder, spleen, gastric, ileal and lung resections. Wound-related complications included wound dehiscence, surgical site infection, bleeding and wound hematoma. Respiratory-related complications included pleural effusion, atelectasis, respiratory insufficiency, pneumonia, bronchitis, chronic obstructive pulmonary disease (COPD) exacerbation, pneumothorax and pulmonary embolism. The International Study Group of Liver Surgery (ISGLS) definitions for postoperative bile leak and liver failure were used [22,23]. Postoperative morbidity was assessed and graded up till 30-day postoperatively using the Clavien-Dindo classification, and complications grade 3 or higher were considered severe [24]. Postoperative length of stay (LOS) was defined as the time from the surgical procedure until the discharge date.

### 4.1. Preoperative assessment and surgical technique

Before undergoing liver resection, patients underwent routine blood tests and imaging with triphasic thoraco-abdominal Computed Tomography scans and Magnetic Resonance Imaging with liver specific contrast, when indicated. The indication for liver surgery was evaluated for each patient in a multidisciplinary meeting including surgeons, hepatologists, oncologists and radiologists. PVO was indicated when the future liver remnant would be less than 20–25% of liver volume in case of a healthy liver, less than 30% in case of a liver injured by chemotherapy or in obese patients, and less than 40% in case of patients receiving intensive (>6 cycles) preoperative chemotherapy or in case of a cirrhotic patient.

Liver resections at the participating centres were performed according to similar techniques, independently from the chosen approach: at the beginning of the operation the number, location and size of hepatic lesions and their proximity to major vascular structures were investigated through intraoperative ultrasonography. In the majority of cases, parenchymal transection was performed with an ultrasonic dissector or a bipolar vessel sealer for the superficial part of the liver and an ultrasonic aspirator for the deep parenchyma. Vascular and biliary structures, based on their diameter, were sealed and divided with the used dissector device or were divided between metallic clips, Hem-o-Lok clips (Weck Closure Systems, Research Triangle Park, USA) or sutures or were closed and transected with mechanic staplers as required. A restriction in intravenous fluid administration was used during the parenchyma transection step in order to maintain a low central venous pressure. An intermittent Pringle manoeuvre was performed during liver transection at the discretion of the operating surgeon.

### 4.2. Survey on perception of liver surgery in obese patients

A survey was developed using Google Forms® (Google; Mountain View, CA, USA) by three of the authors (GZ, JS, and MAH), and subsequently submitted to the chief liver surgeons of the participating centres. The survey included 10 multiple choice questions investigating the surgeon's perception of obesity, different type of body fat distribution in obese patients, its impact on the difficulty of liver resections (MILS or OLS), and surgeons' attitudes in choosing the surgical approach (minimally invasive vs. open) when dealing with obese patients. All responses were handled anonymously. The survey is reported in the supplementary materials.

## 5. Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Mac OS X version 27.0 (SPSS Inc., Chicago, IL, USA) and R for Mac OS X version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Single imputation was used to impute missing baseline characteristics data. Categorical data was reported as percentages. When appropriate, comparisons of categorical data were performed using a Chi-square or Fisher's exact test. Continuous normally distributed variables were expressed as mean with the standard deviation and compared between groups using an unpaired T-test. Continuous not normally distributed variables were expressed as median with the interquartile range and compared between groups using a Kruskal-Wallis test. Normality was checked by visually inspecting histograms and Q-Q plots. A two-sided P-value $< .05$ was considered statistically significant.

PSM was performed in each BMI-category (non-obese, obese, class I, class II, and class III) with the MatchIt package to decrease the effect of selection bias in the comparison of MILS and OLS [25]. Covariates for PSM were chosen based on their potential influence on treatment allocation, these covariates were: age (<75 vs. ≥75 years old), sex, ASA-grade (I-II vs. III-IV), history of previous liver surgery, presence of Cirrhosis, treatment with neoadjuvant chemotherapy, type of disease (benign vs. malignant), preoperative PVO, size of the largest lesion (<50 vs. ≥50 mm), number of lesions (single vs. multiple), association of a major concurrent procedure, and type of liver resection performed (minor vs. technically major vs. traditional major). Based on these propensity scores, patients who underwent MILS were matched to patients who underwent OLS in a 1:1 ratio without replacement using a caliper width ranging from 0.001 to 0.1 [26]. Standardized differences (SD) were calculated to assess balance between both groups, with a SD ≤ 0.1 indicating optimal balance [27]. After PSM, categorical data were compared using McNemar's test or Marginal Homogeneity, when appropriate. Continuous data were compared using Wilcoxon Signed Rank test. A complete case sensitivity analysis was conducted to analyse the impact of the imputation of missing baseline data: patients with missing covariate data were excluded, after which PSM was performed in a similar fashion as described previously.

## 6. Results

Overall, 9963 patients were included and subsequently categorized into the two groups, non-obese and obese. Thereafter, patients were further classified according to the chosen surgical approach and their characteristics and outcomes were compared (See Fig. 1 for the study flowchart).

### 6.1. Comparison of the characteristics and outcomes of non-obese and obese patients

A comparison of the characteristics and outcomes of obese (n = 1977) versus non-obese (n = 7986) patients showed, among obese patients, significantly higher rates of ASA scores >2, an age higher than 75 years old (both $p < .001$), cirrhosis ($p = .039$), lower rates of preoperative chemotherapy ($p < .001$), a history of previous liver resection ($p = .011$), and use of MILS ($p = .001$), which paralleled longer operation durations ($p < .001$), more intraoperative blood loss (IOBL) ($p = .003$), and higher rates of wound- and respiratory related complications ($p < .001$ and $p = .031$, respectively). In contrast, among non-obese patients a significantly higher bile leak rate was observed, compared to obese patients ($p = .019$) (Table 1).

### 6.2. Comparison of the characteristics and perioperative outcomes of patients undergoing MILS versus OLS among non-obese and obese patients, before and after PSM

Among patients who underwent MILS, compared to OLS, significantly higher rates of liver cirrhosis and lower rates of previous extra-hepatic surgery and preoperative PVO were observed (all $p < .001$). Among OLS patients, higher rates of malignant disease (mainly related to higher rates of colorectal liver metastases, cholangiocarcinoma, and gallbladder cancer), larger maximum tumour diameters, and higher rates of multiple resected lesions were observed, compared to MILS (all $p < .001$). All these differences were observed both among non-obese and obese patients.

Such differences paralleled, among OLS patients, significantly higher rates of complex procedures, in terms of major liver resections and major concurrent procedures (all $p < .001$), longer operation duration, higher IOBL, and a more frequent need for intraoperative blood transfusion. These differences translated in higher rates of overall, liver related, and severe complications and mortality, as well as a longer LOS and higher

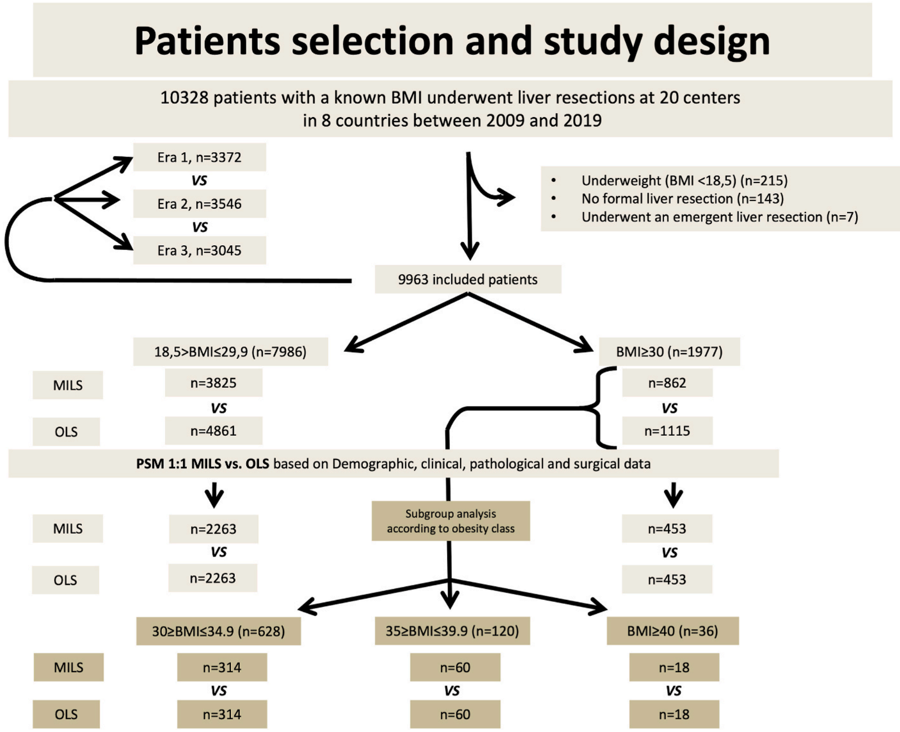


**Fig. 1.** Flow chart of patient selection and study design.

rates of positive surgical margins following OLS, compared to MILS, both among non-obese and obese patients (all $p < .001$) (Table 2).

After PSM, OLS remained associated, both among non-obese and obese patients, with a longer operation duration ($p < .001$ and $p = .002$, respectively), more IOBL ($p < .001$ for both), a more frequent need for intraoperative blood transfusion ($p < .001$ and $p = .009$, respectively), and higher rates of positive surgical margins ($p < .001$ and $p = .003$, respectively), overall postoperative complications ($p < .001$ and $p = .002$, respectively), bile leak ($p < .001$ and $p = .014$), liver failure ($p < .001$ and $p = .046$, respectively), and a longer LOS ($p < .001$ for both), compared to MILS (Table 3).

### 6.3. *Comparison of the characteristics and outcomes of MILS versus OLS in different obesity classes*

After stratification of obese patients in class I (30≥BMI≤34.9, n = 1499), class II (35≥BMI≤39.9, n = 366), and class III obesity (BMI≥40, n = 112), patients in each BMI class were classified according to the surgical approach used (MILS or OLS) and PSM was performed to improve the comparability of MILS and OLS in each group of patients (Fig. 1). The comparison of MILS versus OLS after PSM showed that, despite a similarity in terms of demographic, clinical, pathological and operative characteristics, MILS was associated with significantly less IOBL among patients with class I and class II obesity ($p < .001$ and $p = .016$, respectively), with a shorter median operation duration among patients with class I and III obesity ($p < .001$ and $p = .006$) and with a shorter LOS in all three obesity classes ($p < .001$ for obesity class I and II, $p = .003$ for obesity class III) (Table 4). In addition, among MILS patients in obesity class I, significantly lower rates of overall complications, bile leak, positive surgical margins, and of postoperative mortality were observed, compared to OLS.

### 6.4. *Sensitivity analysis*

After exclusion of the patients with missing covariate data, 3622 and 822 patients could be matched in the non-obese and obese cohorts, respectively. Similar differences between patients that underwent MILS and OLS were observed. However, in obese patients, MILS was no longer associated with a significantly lower liver failure rate (Supplementary table 1). In non-obese patients, MILS was no longer associated with a significantly lower rate of liver failure and respiratory related complications. In the subgroups, 526, 94, and 32 patients could be matched in the respective obesity classes. The differences in the perioperative outcomes following MILS and OLS were similar to those observed in the imputed cohort (Supplementary table 2).

### 6.5. *Trend analysis of used surgical approaches and postoperative outcomes during the study period*

When assessing trends over the study period, the proportion of obese patients remained similar (19.5% vs. 20.2% vs. 19.9%, respectively, $p = .757$) (Fig. 2 and Table 5). The rate of patients who underwent MILS however increased among both non-obese (40.6%, 45%, and 59.4%, respectively; $p < .001$) and obese patients (42.1%, 37.1%, 53%, respectively; $p < .001$). Furthermore, the rate of complex liver resections, defined as anatomically and technically major hepatectomies, increased over time in both non-obese and obese patients undergoing MILS and OLS, although this increase was not statistically significant in the group of obese patients undergoing MILS [28]. Interestingly, the rate of complex liver resections performed by MILS mainly seemed to increase in the third time period.

These trends paralleled an increasing rate of overall complications (38.1%, 46.3%, and 41.8%, $p < .001$) and, although not-significant, mortality (3%, 4.5%, 4.2%, $p = .061$) among non-obese patients who underwent OLS. In contrast, the rates of overall morbidity (non-obese: 22%, 22.9%, 22.9%, $p = .839$; obese: 25%, 27.5%, 25%, $p = .733$), severe morbidity (non-obese: 7%, 8.1%, 8.7%, $p = .282$; obese: 6.9%, 9.4%, 6.8%, $p = .433$) and mortality (non-obese 1.8%, 1.1%, 1.4%, $p = .342$; obese 1.5%, 0.4%, 0.9%, $p = .423$) remained relatively stable over time among all patients who underwent MILS (Supplementary figure 1 and Table 5).

**Table 1**
Comparison of baseline characteristics and perioperative outcomes of non-obese and obese patients.

| *Characteristics* | Overall (n = 9963) | Non-obese (n = 7986) | Obese (n = 1977) | P |
|---|---|---|---|---|
| Sex, Male | 5829 (58.5) | 4638 (58.1) | 1191 (60.2) | 0.085 |
| Age, years | 64.5 [55.2, 72.1] | 64.7 [55, 72.6] | 64 [56, 71] | 0.136 |
| Age ≥75 years old | 1751 (17.6) | 1472 (18.4) | 279 (14.1) | <0.001 |
| ASA-score 3&4 | 3581 (35.9) | 2722 (34.1) | 859 (43.4) | <0.001 |
| Cirrhosis | 1473 (14.8) | 1151 (14.4) | 322 (16.3) | 0.039 |
| Non HBV/HCV related | 965 (9.7) | 730 (9.1) | 235 (11.9) | 0.001 |
| Previous extrahepatic surgery | 4359 (43.8) | 3480 (43.6) | 879 (44.5) | 0.493 |
| Previous hepatic surgery | 1052 (10.6) | 875 (11) | 177 (9) | 0.011 |
| Preoperative PVO | 896 (9) | 726 (9.1) | 170 (8.6) | 0.522 |
| Preoperative CHT | 2944 (29.5) | 2486 (31.1) | 458 (23.2) | <0.001 |
| *Pathologic characteristics* | | | | |
| Malignant disease | 8710 (87.4) | 6994 (87.6) | 1716 (86.8) | 0.369 |
| Disease | | | | 0.003 |
| CRLM | 4954 (49.7) | 4010 (50.2) | 944 (47.7) | |
| HCC | 1690 (17.0) | 1319 (16.5) | 371 (18.8) | |
| Cholangiocarcinoma | 857 (8.6) | 699 (8.8) | 158 (8) | |
| Gallbladder cancer | 248 (2.5) | 187 (2.3) | 61 (3.1) | |
| Benign | 1253 (12.6) | 992 (12.4) | 261 (13.2) | |
| Non-CRLM | 719 (7.2) | 597 (7.5) | 122 (6.2) | |
| Other | 242 (2.4) | 182 (2.3) | 60 (3) | |
| Size largest lesion, millimetres | 32 [20, 55] | 32.00 [20, 55] | 35 [20, 52.2] | 0.196 |
| Largest lesion ≥51 mm | 2635 (26.4) | 2138 (26.8) | 497 (25.1) | 0.148 |
| Multiple lesions | 3743 (37.6) | 3025 (37.9) | 718 (36.3) | 0.209 |
| *Operative characteristics* | | | | |
| Minimally invasive approach | 4687 (47) | 3825 (47.9) | 862 (43.6) | 0.001 |
| Type of resection | | | | 0.658 |
| Minor | 4073 (40.9) | 3248 (40.7) | 825 (41.7) | |
| Technically major | 2739 (27.5) | 2210 (27.7) | 529 (26.8) | |
| Traditional major | 3151 (31.6) | 2528 (31.7) | 623 (31.5) | |
| Major concurrent procedure(s) | 1490 (15) | 1207 (15.1) | 283 (14.3) | 0.391 |
| Median operation duration, minutes | 235.2 [165, 315] | **232 [160, 314.1]** | **241.4 [180, 325.5]** | **<0.001** |
| Median IOBL, ml | 270 [100, 550] | **260 [100, 510]** | **300 [100, 682.8]** | **0.003** |
| Perioperative PRBC transfusion | 789 (11.1) | 635 (10.8) | 154 (12.3) | 0.137 |
| Pedicle clamping | 3661 (39.9) | 2938 (39.9) | 723 (39.9) | 0.998 |
| Conversion to laparotomy (in case of MI approach) | 335 (7.3) | 267 (7.1) | 68 (8) | 0.397 |
| *Postoperative outcomes* | | | | |
| Overall complications | 3285 (33.1) | 2608 (32.8) | 677 (34.3) | 0.195 |
| Bile leak | 600 (6.1) | **504 (6.4)** | **96 (4.9)** | **0.019** |
| Ascites | 217 (2.3) | 185 (2.5) | 32 (1.7) | 0.070 |
| Liver failure | 202 (2.2) | 163 (2.2) | 39 (2.1) | 0.924 |
| Wound related | 158 (1.7) | **102 (1.4)** | **56 (3)** | **<0.001** |
| Respiratory related | 550 (5.9) | **421 (5.6)** | **129 (7)** | **0.031** |
| Major complications | 1162 (11.8) | 947 (12) | 215 (11) | 0.227 |
| 90-day mortality | 268 (2.7) | 213 (2.7) | 55 (2.8) | 0.821 |
| Positive surgical margin* | 1922 (23.5) | 1528 (23.2) | 394 (24.5) | 0.295 |
| Median LOS, days | 6 [4,9] | 6 [4,9] | 6 [4,9] | 0.667 |

Values are expressed in percentages or in median (IQR).
Abbreviations: ASA, American Society of Anaesthesiologists; HBV, Hepatitis B virus; HBC, Hepatitis C virus; PVO, portal vein occlusion; CHT, chemotherapy; CLRM, colorectal liver metastases; HCC, hepatocellular carcinoma; IOBL, intraoperative blood loss; PRBC, packed red blood cell; MI, minimally invasive; LOS, length of stay.
*Analysis only performed for patients operated for a malignant lesion.
Missing values in overall cohort before single imputation of baseline data (if ≥ 2%): age, 250; ASA, 354; cirrhosis, 225; previous extrahepatic surgery, 267; preoperative PVO, 762; surgical margin, 527; size largest lesion, 1398; uni/multiple lesions, 462; operation duration, 2428; IOBL, 3608; transfusion, 2826; pedicle clamping, 791; ascites, liver failure, wound related & respiratory related morbidity, 636; LOS, 251.

### *6.6. Survey regarding liver surgery in obese patients*

Supplementary table 3 shows the results of the survey conducted among the chief surgeons of the participating centres (n = 18). Almost half of the surgeons (n = 8) mentioned that they were more inclined to perform MILS in obese patients due to the perception that this approach can have several advantages in this patient population. Nevertheless, all but one of the participating surgeons stated that they experienced obesity as a factor which increases the technical difficulty both during MILS and OLS. The majority of surgeons (n = 15) considered a different fat distribution pattern (predominantly subcutaneous or intraperitoneal) associated with different grades of technical difficulty. During MILS, a 'predominant intraperitoneal fat phenotype' was perceived as most challenging by a majority of the participating surgeons (n = 11). While during OLS most surgeons (n = 7) considered the two types of fat distribution equally responsible for increased surgical difficulty.

Half of the respondents (n = 9) believed that the benefits of MILS over OLS differed according to the body fat distribution of a patient. When queried about adaptations in surgical technique during MILS in obese patients, most surgeons (n = 11) reported modifications in the trocar position: a more cranial placement of the trocars was the most frequently mentioned change (n = 9). Only a quarter of the respondents (n = 5) used different instruments in obese patients (Supplementary table 3).

**Table 2**
Baseline characteristics and perioperative outcomes for non-obese and obese patients stratified by the used surgical approach, before PSM.

| | Non-obese (n = 7986) | | P | SD | Obese (n = 1977) | | P | SD |
|---|---|---|---|---|---|---|---|---|
| *Characteristics* | MILS (n = 3825) | OLS (n = 4161) | | | MILS (n = 862) | OLS (n = 1115) | | |
| Sex, Male | 2148 (56.2) | 2490 (59.8) | 0.001 | 0.075 | 522 (60.6) | 669 (60) | 0.838 | 0.011 |
| Age, years | 65 [55.2, 73] | 64.3 [55, 72] | 0.019 | 0.039 | 64 [55.8, 71] | 64 [56.4, 71.3] | 0.881 | 0.020 |
| Age >75 years old | 763 (19.9) | 709 (17) | 0.001 | 0.075 | 115 (13.3) | 164 (14.7) | 0.423 | 0.039 |
| ASA-score 3&4 | 1271 (33.2) | 1451 (34.9) | 0.128 | 0.035 | 403 (46.8) | 456 (40.9) | 0.011 | 0.118 |
| Cirrhosis | 665 (17.4) | 486 (11.7) | <0.001 | 0.162 | 204 (23.7) | 118 (10.6) | <0.001 | 0.353 |
| Previous extrahepatic surgery | 1567 (41) | 1913 (46) | <0.001 | 0.101 | 321 (37.2) | 558 (50) | <0.001 | 0.260 |
| Previous hepatic surgery | 370 (9.7) | 505 (12.1) | <0.001 | 0.079 | 79 (9.2) | 98 (8.8) | 0.833 | 0.013 |
| Preoperative PVO | 135 (3.5) | 591 (14.2) | <0.001 | 0.382 | 25 (2.9) | 145 (13) | <0.001 | 0.380 |
| Preop CHT | 1211 (31.7) | 1275 (30.6) | 0.338 | 0.022 | 196 (22.7) | 262 (23.5) | 0.731 | 0.018 |
| *Pathologic characteristics* | | | | | | | | |
| Malignant disease | 3263 (85.3) | 3731 (89.7) | <0.001 | 0.132 | 724 (84) | 992 (89) | 0.001 | 0.146 |
| Disease | | | <0.001 | 0.348 | | | <0.001 | 0.439 |
| CRLM | 1855 (48.5) | 2155 (51.8) | | | 353 (41) | 591 (53) | | |
| HCC | 752 (19.7) | 567 (13.6) | | | 226 (26.2) | 145 (13) | | |
| Cholangiocarcinoma | 200 (5.2) | 499 (12) | | | 48 (5.6) | 110 (9.9) | | |
| Gallbladder cancer | 45 (1.2) | 142 (3.4) | | | 15 (1.7) | 46 (4.1) | | |
| Benign | 562 (14.7) | 430 (10.3) | | | 138 (16) | 123 (11) | | |
| N-CRLM | 315 (8.2) | 282 (6.8) | | | 52 (6) | 70 (6.3) | | |
| Other | 96 (2.5) | 86 (2.1) | | | 30 (3.5) | 30 (2.7) | | |
| Size largest lesion, millimetres | 30 [18, 50] | 35 [20, 60] | <0.001 | 0.221 | 30 [20, 47.8] | 35 [22, 58] | <0.001 | 0.196 |
| Largest lesion ≥51 mm | 891 (23.3) | 1247 (30) | <0.001 | 0.151 | 179 (20.8) | 318 (28.5) | <0.001 | 0.181 |
| Multiple lesions | 1199 (31.3) | 1826 (43.9) | <0.001 | 0.261 | 245 (28.4) | 473 (42.4) | <0.001 | 0.296 |
| *Operative characteristics* | | | | | | | | |
| Type of liver resection | | | <0.001 | 0.751 | | | <0.001 | 0.798 |
| Minor | 2161 (56.5) | 1087 (26.1) | | | 505 (58.6) | 320 (28.7) | | |
| Technically major | 1030 (26.9) | 1180 (28.4) | | | 240 (27.8) | 289 (25.9) | | |
| Traditional major | 634 (16.6) | 1894 (45.5) | | | 117 (13.6) | 506 (45.4) | | |
| Major concurrent procedure(s) | 292 (7.6) | 915 (22) | <0.001 | 0.413 | 51 (5.9) | 232 (20.8) | <0.001 | 0.449 |
| *Intraoperative outcomes* | | | | | | | | |
| Median operation duration, min | **195 [128, 272]** | **265.7 [205.8, 353]** | **<0.001** | | **217 [150, 292.1]** | **270 [200.6, 350]** | **<0.001** | |
| Median IOBL, ml | **200 [100, 400]** | **380 [173.8, 723]** | **<0.001** | | **200 [100, 412.8]** | **490 [200, 864.5]** | **<0.001** | |
| Intraoperative PRBC transfusion | **183 (5.4)** | **452 (18.1)** | **<0.001** | | **44 (6.1)** | **110 (20.8)** | **<0.001** | |
| Pedicle clamping | **1385 (37.7)** | **1553 (42.1)** | **<0.001** | | 315 (38) | 408 (41.5) | 0.142 | |
| Conversion | 267 (7.1) | | | | 68 (8) | | | |
| *Postoperative outcomes* | | | | | | | | |
| Overall complications | **864 (22.7)** | **1744 (42.1)** | **<0.001** | | **222 (25.8)** | **455 (41)** | **<0.001** | |
| Bile leak | **129 (3.4)** | **375 (9.2)** | **<0.001** | | **17 (2)** | **79 (7.2)** | **<0.001** | |
| Ascites | **35 (1)** | **150 (3.9)** | **<0.001** | | **7 (0.9)** | **25 (2.4)** | **0.023** | |
| Liver failure | **28 (0.8)** | **135 (3.5)** | **<0.001** | | **6 (0.8)** | **33 (3.1)** | **0.001** | |
| Wound related | **25 (0.7)** | **77 (2)** | **<0.001** | | 17 (2.1) | 39 (3.7) | 0.066 | |
| Respiratory related | **141 (3.9)** | **280 (7.2)** | **<0.001** | | 49 (6.1) | 80 (7.6) | 0.253 | |
| Major complications | **305 (8)** | **642 (15.6)** | **<0.001** | | **66 (7.7)** | **149 (13.5)** | **<0.001** | |
| Positive surgical margin* | **546 (17.5)** | **982 (28.3)** | **<0.001** | | **134 (19.5)** | **260 (28.2)** | **<0.001** | |
| 90-day or in-hospital mortality | **54 (1.4)** | **159 (3.8)** | **<0.001** | | **8 (0.9)** | **47 (4.3)** | **<0.001** | |
| Median LOS, days | **4** [3,6] | **8** [6,12] | **<0.001** | | **4** [3,6] | **7** [6,11] | **<0.001** | |

Values are expressed in percentages or in median (IQR).
Abbreviations: MILS, minimally invasive liver surgery; OLS, open liver surgery; SD, standardized difference; PSM, propensity score matching; ASA, American Society of Anaesthesiologists; PVO, portal vein occlusion; CHT, chemotherapy; CLRM, colorectal liver metastases; HCC, hepatocellular carcinoma; IOBL, intraoperative blood loss; PRBC, packed red blood cell; LOS, length of stay.
*Analysis only performed for patients operated for a malignant lesion.

## 7. Discussion

This international study confirms an increasing trend in the use of MILS for the management of liver lesions in both non-obese and obese patients. It also shows a steady increase in the number of patients undergoing complex MILS (anatomically and technically major resections), especially following the Southampton consensus guidelines. These guidelines have specifically focused on the implementation and wider expansion of MILS in challenging clinical situations, of which obesity represents a good paradigm. Indeed, this was the first consensus meeting where the role of MILS in patients with a high BMI was specifically discussed and it was agreed that MILS may be feasible and safe for obese patients, but only in highly selected cases [13]. The observed increase in MILS use was however gradual and cautious, which may have led to the remarkably stable severe morbidity and mortality rates observed during this wide implementation phase. Notably, when comparing the perioperative outcomes of the minimally invasive approach with the traditional open approach, MILS offered advantages in both non-obese and obese patients.

Previous studies on the outcomes of liver resections in patients within different BMI-classes ranged between single centre experiences and large national databases analyses and have reported contrasting results. This may be due to differences in study populations, the used surgical approach, the baseline disease, and the utilization of different BMI cut-offs. These studies have alternatively associated an elevated BMI with higher rates of postoperative morbidity, wound-complications, need for blood transfusions, and a longer operation duration [29–33].

In our study, the incidence of obesity (20%) was similar to that observed among European adults (17%) and the rates of class II and III obesity (3.7% and 1.1%) mirrored those observed worldwide (3.1% and

**Table 3**
Baseline characteristics and perioperative outcomes for non-obese and obese patients stratified by the used surgical approach, after PSM.

| | Non-obese | | P | SD | Obese | | P | SD |
|---|---|---|---|---|---|---|---|---|
| | (n = 4526) | | | | (n = 906) | | | |
| *Characteristics* | MILS | OLS | | | MILS | OLS | | |
| | (n = 2263) | (n = 2263) | | | (n = 453) | (n = 453) | | |
| Sex, Male | 1364 (60.3) | 1347 (59.5) | 0.068 | 0.015 | 292 (64.5) | 289 (63.8) | 0.579 | 0.014 |
| Age, years | 67.7 [61, 73] | 66.9 [58, 73] | <0.001 | 0.112 | 66.5 [59, 71] | 66 [58.1, 71.4] | 0.278 | 0.060 |
| Age >75 years old | 373 (16.5) | 377 (16.7) | 0.775 | 0.005 | 43 (9.5) | 45 (9.9) | 0.683 | 0.015 |
| ASA-score 3&4 | 747 (33) | 758 (33.5) | 0.136 | 0.010 | 191 (42.2) | 190 (41.9) | 1 | 0.004 |
| Cirrhosis | 289 (12.8) | 285 (12.6) | 0.643 | 0.005 | 58 (12.8) | 63 (13.9) | 0.131 | 0.032 |
| Previous extrahepatic surgery | 991 (43.8) | 1111 (49.1) | <0.001 | 0.106 | 196 (43.3) | 225 (49.7) | 0.037 | 0.129 |
| Previous hepatic surgery | 233 (10.3) | 220 (9.7) | 0.801 | 0.019 | 29 (6.4) | 26 (5.7) | 0.505 | 0.028 |
| Preoperative PVO | 104 (4.6) | 104 (4.6) | 1 | <0.001 | 13 (2.9) | 10 (2.2) | 0.371 | 0.042 |
| Preop CHT | 753 (33.3) | 740 (32.7) | 0.208 | 0.012 | 112 (24.7) | 104 (23) | 0.080 | 0.041 |
| *Pathologic characteristics* | | | | | | | | |
| Malignant disease | 2022 (89.4) | 2001 (88.4) | 0.002 | 0.030 | 398 (87.9) | 397 (87.6) | 1 | 0.007 |
| Disease | | | 0.907 | 0.252 | | | 0.487 | 0.280 |
| CRLM | 1231 (54.4) | 1226 (54.2) | | | 222 (49) | 236 (52.1) | | |
| HCC | 392 (17.3) | 342 (15.1) | | | 93 (20.5) | 73 (16.1) | | |
| Cholangiocarcinoma | 134 (5.9) | 131 (5.8) | | | 26 (5.7) | 22 (4.9) | | |
| Gallbladder cancer | 26 (1.1) | 117 (5.2) | | | 9 (2) | 30 (6.6) | | |
| Benign | 241 (10.6) | 262 (11.6) | | | 55 (12.1) | 56 (12.4) | | |
| N-CRLM | 179 (7.9) | 148 (6.5) | | | 31 (6.8) | 19 (4.2) | | |
| Other | 60 (2.7) | 37 (1.6) | | | 17 (3.8) | 17 (3.8) | | |
| Size largest lesion, millimetres | 30 [19, 50] | 33 [20, 50] | <0.001 | 0.098 | 30 [20,45] | 33 [20, 50] | 0.145 | 0.080 |
| Largest lesion ≥51 mm | 544 (24) | 544 (24) | 1 | <0.001 | 89 (19.6) | 95 (21) | 0.149 | 0.033 |
| Multiple lesions | 919 (40.6) | 929 (41.1) | 0.332 | 0.009 | 152 (33.6) | 150 (33.1) | 0.773 | 0.009 |
| *Operative characteristics* | | | | | | | | |
| Type of resection | | | 0.004 | 0.027 | | | 0.008 | 0.082 |
| Minor | 926 (40.9) | 912 (40.3) | | | 228 (50.3) | 222 (49) | | |
| Technically major | 791 (35) | 779 (34.4) | | | 152 (33.6) | 144 (31.8) | | |
| Traditional major | 546 (24.1) | 572 (25.3) | | | 73 (16.1) | 87 (19.2) | | |
| Major concurrent procedure(s) | 227 (10) | 227 (10) | 1 | <0.001 | 30 (6.6) | 33 (7.3) | 0.628 | 0.026 |
| *Intraoperative outcomes* | | | | | | | | |
| Median operation duration, min | **210 [139.8, 300]** | **240.3 [189.5, 310]** | **<0.001** | | **215 [150, 296]** | **240 [180, 320.4]** | **0.002** | |
| Median IOBL, ml | **200 [100, 450]** | **320 [150, 610.8]** | **<0.001** | | **200 [100, 400]** | **400 [180, 800]** | **<0.001** | |
| Intraoperative PRBC transfusion | **133 (6.6)** | **170 (12.8)** | **<0.001** | | **18 (4.7)** | **33 (14.7)** | **0.009** | |
| Pedicle clamping | 847 (38.9) | 801 (40.1) | 0.258 | | 154 (35.2) | 165 (41.2) | 0.073 | |
| Conversion | 175 (7.9) | | | | 39 (8.7) | | | |
| *Postoperative outcomes* | | | | | | | | |
| Overall complications | **589 (26.1)** | **789 (35)** | **<0.001** | | **113 (24.9)** | **156 (34.5)** | **0.002** | |
| Bile leak | **91 (4)** | **155 (7)** | **<0.001** | | **8 (1.8)** | **22 (4.9)** | **0.014** | |
| Ascites | **23 (1.1)** | **51 (2.4)** | **0.001** | | 1 (0.2) | 7 (1.6) | 0.131 | |
| Liver failure | **15 (0.7)** | **49 (2.3)** | **<0.001** | | **1 (0.2)** | **9 (2.1)** | **0.046** | |
| Wound related | 18 (0.9) | 29 (1.4) | 0.155 | | 10 (2.4) | 9 (2.1) | 0.814 | |
| Respiratory related | **98 (4.6)** | **134 (6.3)** | **0.018** | | 25 (6) | 35 (8.2) | 0.488 | |
| Major complications | 212 (9.4) | 239 (10.7) | 0.159 | | 30 (6.6) | 47 (10.4) | 0.058 | |
| Positive surgical margin* | **358 (18.4)** | **460 (24.6)** | **<0.001** | | **67 (17.9)** | **96 (26.2)** | **0.003** | |
| 90-day or in-hospital mortality | 39 (1.7) | 53 (2.4) | 0.175 | | **2 (0.4)** | **15 (3.4)** | **0.003** | |
| Median LOS, days | **5** [3,7] | **7** [5,10] | **<0.001** | | **4** [3,6] | **7** [5,10] | **<0.001** | |

Values are expressed in percentages or in median (IQR).
Abbreviations: MILS, minimally invasive liver surgery; OLS, open liver surgery; SD, standardized difference; PSM, propensity score matching; ASA, American Society of Anaesthesiologists; PVO, portal vein occlusion; CHT, chemotherapy; CLRM, colorectal liver metastases; HCC, hepatocellular carcinoma; IOBL, intraoperative blood loss; PRBC, packed red blood cell; LOS, length of stay.
*Analysis only performed for patients operated for a malignant lesion.

1.1%), suggesting a similarity in the distribution of BMI values in the overall population and the patients undergoing a liver resection in our study population [34,35]. The comparison of study patients according to BMI showed a certain grade of heterogeneity in patients' demographical and clinical characteristics, reflecting differences in operative technique and perioperative outcomes. An increasing BMI was associated with a worsening of patients' clinical conditions, independently from the used surgical approach (MILS or OLS), as suggested by higher rates of ASA-score >2 and cirrhosis among obese patients, compared to non-obese. In particular, this association, probably in addition to a perceived increase in surgical difficulty and risks related to operating obese patients, accounted for a less frequent use of MILS in these patients. The sum of these differences may account for the better intra- and postoperative outcomes observed among non-obese patients, compared to those with obesity, in line with previously published results.

Concerning the impact of the used surgical approach on the perioperative outcomes of obese patients, previously published studies have indicated that MILS is feasible, safe, and associated with non-inferior or even superior results in terms of a shorter LOS, lower IOBL, and need for perioperative blood transfusions [36–43]. These findings are in line with the findings in our study: when taking into account the whole study population, before PSM, MILS displayed superior perioperative outcomes both among non-obese and obese patients. However, this was the result of an evident unbalance in favour of MILS in terms of patients' pathological and surgical characteristics, reflecting a selection bias, with MILS preferentially being used in patients affected by benign disease or by less extensive disease and needing less technically challenging surgeries. Indeed, when specifically focusing on tumor type (malignant versus benign), it should be highlighted that one of the aims during the surgical treatment for malignant liver disease is to obtain a negative

**Table 4**
Baseline characteristics and perioperative outcomes per obesity-class stratified by the used surgical approach, after PSM.

| | 30 ≥ BMI ≤34.9 | | P | SD | 35 ≥ BMI ≤39.9 | | P | SD | BMI ≥40 | | P | SD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (n = 628) | | | | (n = 120) | | | | (n = 56) | | | |
| *Characteristics* | MILS | OLS | | | MILS | OLS | | | MILS | OLS | | |
| | (n = 314) | (n = 314) | | | (n = 60) | (n = 60) | | | (n = 18) | (n = 18) | | |
| Sex, Male | 220 (70.1) | 220 (70.1) | 1 | <0.001 | 29 (48.3) | 32 (53.3) | 0.371 | 0.100 | 5 (27.8) | 7 (38.9) | 1 | 0.237 |
| Age, years | 67 [59.6, 71.2] | 65.2 [58, 71] | 0.035 | 0.106 | 62.7 [54, 69] | 62.3 [54.7, 68.7] | 0.520 | 0.116 | 60.5 [55.5, 66.8] | 64.2 [59.3, 70.6] | 0.130 | 0.487 |
| Age >75 years old | 28 (8.9) | 30 (9.6) | 0.480 | 0.022 | 3 (5) | 5 (8.3) | 0.683 | 0.134 | 1 (5.6) | 2 (11.1) | 1 | 0.202 |
| ASA score 3&4 | 123 (39.2) | 122 (38.9) | 1 | 0.007 | 21 (35) | 23 (38.3) | 0.683 | 0.069 | 13 (72.2) | 14 (77.8) | 1 | 0.129 |
| Cirrhosis | 46 (14.6) | 46 (14.6) | 1 | <0.001 | 7 (11.7) | 7 (11.7) | 1 | <0.001 | 3 (16.7) | 2 (11.1) | 1 | 0.161 |
| Previous extrahepatic surgery | 150 (47.8) | 162 (51.6) | 0.311 | 0.076 | 21 (35) | 28 (46.7) | 0.248 | 0.239 | 6 (33.3) | 6 (33.3) | 1 | <0.001 |
| Previous hepatic surgery | 19 (6.1) | 20 (6.4) | 1 | 0.013 | 0 | 0 | 1 | <0.001 | 1 (5.6) | 1 (5.6) | 1 | <0.001 |
| Preoperative PVO | 8 (2.5) | 8 (2.5) | 1 | <0.001 | 1 (1.7) | 0 | 1 | 0.184 | 0 | 1 (5.6) | | 0.343 |
| Preop CHT | 79 (25.2) | 82 (26.1) | 0.371 | 0.022 | 11 (18.3) | 11 (18.3) | 1 | <0.001 | 1 (5.6) | 2 (11.1) | | 0.202 |
| *Pathologic characteristics* | | | | | | | | | | | | |
| Malignant disease | 281 (89.5) | 282 (89.8) | 1 | 0.010 | 50 (83.3) | 50 (83.3) | 1 | <0.001 | 15 (83.3) | 15 (83.3) | 1 | <0.001 |
| Disease | | | 0.364 | 0.276 | | | 0.459 | 0.526 | | | 0.872 | 0.660 |
| CRLM | 162 (51.6) | 178 (56.7) | | | 22 (36.7) | 28 (46.7) | | | 7 (38.9) | 5 (27.8) | | |
| HCC | 70 (22.3) | 52 (16.6) | | | 14 (23.3) | 7 (11.7) | | | 3 (16.7) | 3 (16.7) | | |
| Cholangiocarcinoma | 19 (6.1) | 13 (4.1) | | | 3 (5) | 4 (6.7) | | | 0 | 2 (11.1) | | |
| Gallbladder cancer | 6 (1.9) | 19 (6.1) | | | 2 (3.3) | 5 (8.3) | | | 2 (11.1) | 3 (16.7) | | |
| Benign | 33 (10.5) | 32 (10.2) | | | 10 (16.7) | 10 (16.7) | | | 3 (16.7) | 3 (16.7) | | |
| N-CRLM | 15 (4.8) | 13 (4.1) | | | 8 (13.3) | 3 (5) | | | 2 (11.1) | 2 (11.1) | | |
| Other | 9 (2.9) | 7 (2.2) | | | 1 (1.7) | 3 (5) | | | 1 (5.6) | 0 | | |
| Size largest lesion, millimetres | 30 [20, 45] | 30 [20, 45] | 0.702 | 0.004 | 35 [20, 59] | 39 [24.9, 56.3] | 0.824 | 0.034 | 23.5 [15, 43.8] | 31 [15, 43.8] | 0.459 | 0.275 |
| Largest lesion ≥51 mm | 55 (17.5) | 54 (17.2) | 1 | 0.008 | 18 (30) | 18 (30) | 1 | <0.001 | 2 (11.1) | 1 (5.6) | 1 | 0.202 |
| Multiple lesions | 111 (35.4) | 107 (34.1) | 0.221 | 0.027 | 18 (30) | 15 (25) | 0.248 | 0.112 | 1 (5.6) | 3 (16.7) | 0.480 | 0.359 |
| *Operative characteristics* | | | | | | | | | | | | |
| Type of resection | | | 0.149 | 0.041 | | | 0.392 | 0.090 | | | 0.317 | 0.133 |
| Minor | 162 (51.6) | 159 (50.6) | | | 29 (48.3) | 28 (46.7) | | | 10 (55.6) | 11 (61.1) | | |
| Technically major | 97 (30.9) | 95 (30.3) | | | 22 (36.7) | 21 (35) | | | 5 (27.8) | 4 (22.2) | | |
| Traditional major | 55 (17.5) | 60 (19.1) | | | 9 (15) | 11 (18.3) | | | 3 (16.7) | 3 (16.7) | | |
| Major concurrent procedure(s) | 15 (4.8) | 17 (5.4) | 0.480 | 0.029 | 3 (5) | 4 (6.7) | 1 | 0.071 | 0 | 0 | 1 | <0.001 |
| *Intraoperative outcomes* | | | | | | | | | | | | |
| Median operation duration, min | **215 [149, 289.1]** | **240 [180, 319.7]** | **<0.001** | | 190 [152, 255] | 262.3 [169.3, 312.4] | 0.107 | | **159 [114, 214.4]** | **264 [222, 330.6]** | **0.006** | |
| Estimated blood loss | **200 [100, 400]** | **400 [180, 800]** | **<0.001** | | **150 [100, 350]** | **700 [220, 800]** | **0.016** | | 400 [75, 550] | 450 [277.5, 2075] | 0.461 | |
| Intraoperative PRBC transfusion | **16 (5.9)** | **24 (15.5)** | **0.019** | | 3 (5.8) | 3 (11.1) | 0.617 | | 0 | 3 (23.1) | 0.250 | |
| Pedicle clamping | 105 (34.7) | 115 (43.1) | 0.063 | | 16 (27.6) | 21 (40.4) | 0.118 | | 3 (16.7) | 7 (38.9) | 0.450 | |
| Conversion | 27 (8.7) | | | | 6 (10.3) | | | | 0 | | | |
| *Postoperative outcomes* | | | | | | | | | | | | |
| Overall complications | **86 (27.4)** | **114 (36.3)** | **0.019** | | 13 (21.7) | 15 (25.4) | 0.823 | | 2 (11.1) | 6 (33.3) | 0.289 | |
| Bile leak | **4 (1.3)** | **17 (5.5)** | **0.009** | | 0 | 2 (3.4) | 0.500 | | 0 | 1 (5.6) | 1 | |
| Ascites | 0 | 4 (1.3) | 0.250 | | 0 | 1 (1.8) | 1 | | 0 | 1 (5.9) | 1 | |
| Liver failure | 1 (0.4) | 8 (2.7) | 0.221 | | 1 (1.8) | 1 (1.8) | 1 | | 0 | 0 | 1 | |
| Wound related | 4 (1.4) | 8 (2.7) | 0.387 | | 2 (3.5) | 0 | 0.500 | | 0 | 1 (5.9) | 1 | |
| Respiratory related | 17 (6.0) | 23 (7.7) | 0.596 | | 4 (7) | 3 (5.3) | 1 | | 1 (5.6) | 0 | 1 | |
| Major complications | 24 (7.6) | 36 (11.5) | 0.127 | | 5 (8.3) | 5 (8.5) | 1 | | 0 | 2 (11.1) | 0.500 | |
| Positive surgical margin* | **46 (17.4)** | **76 (28.9)** | **0.002** | | 5 (11.1) | 11 (25) | 0.450 | | 2 (15.4) | 2 (13.3) | 1 | |
| 90-day or in-hospital mortality | **2 (0.6)** | **10 (3.3)** | **0.043** | | 2 (3.3) | 1 (1.7) | 1 | | 0 | 1 (5.6) | 1 | |
| Median LOS, days | **4 [3,6]** | **7 [5,10]** | **<0.001** | | **4 [3,6]** | **7 [5,8]** | **<0.001** | | **4 [3,5]** | **7 [6, 10.5]** | **0.003** | |

Values are expressed in percentages or in median (IQR).
Abbreviations: MILS, minimally invasive liver surgery; OLS, open liver surgery; SD, standardized difference; PSM, propensity score matching; ASA, American Society of Anaesthesiologists; PVO, portal vein occlusion; CHT, chemotherapy; CLRM, colorectal liver metastases; HCC, hepatocellular carcinoma; IOBL, intraoperative blood loss; PRBC, packed red blood cell; LOS, length of stay.

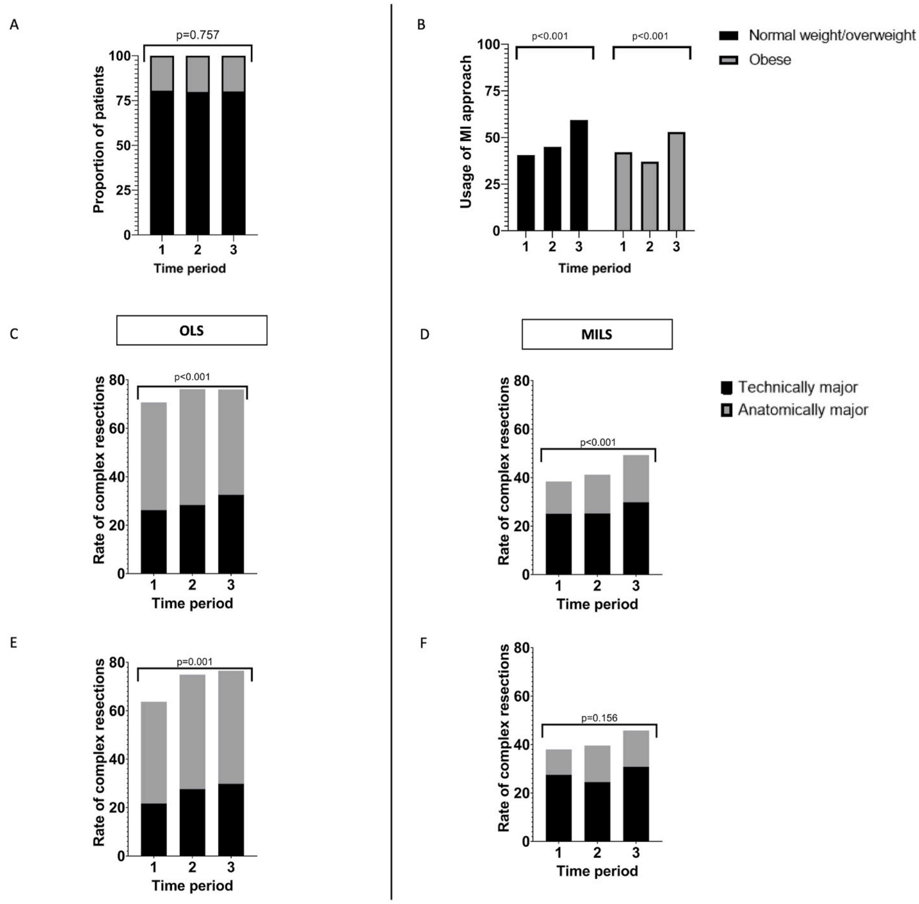


**Fig. 2.** Trend analysis of patients characteristics during the three chosen time periods: A) proportion of non-obese and obese patients; B) proportion of patients operated by a MI approach; C) rate of complex resections performed in non-obese patients by OLS; D) rate of complex resections performed in non-obese patients by MILS; E) rate of complex resections performed in obese patients by OLS; F) rate of complex resections.

(more or less extended, according to the tumor characteristics) surgical margin. To achieve this, an anatomical liver resection may be required, translating in a more extensive and challenging operation compared to liver resections performed for benign disease, which usually do not require an extended surgical margin and for which, except than for cases with an undetermined diagnosis, a narrow margin is usually acceptable. Nevertheless, even after selection bias mitigation through PSM, MILS remained associated with several benefits, namely with less IOBL, a less frequent need for intraoperative blood transfusions, lower rates of overall morbidity and bile leak, and a shorter LOS. Notably, these benefits were evident among both non-obese and obese patients. In this context, our results strengthen the hypothesis that the benefits of reduced wall trauma in MILS may translate into an earlier postoperative rehabilitation and may facilitate cardiopulmonary recovery in obese patients. The additional subgroup analysis aiming at investigating and comparing the characteristics and outcomes of MILS and OLS among obese patients stratified in three different obesity classes allowed us to overcome the limitations of including obese patients in a single study group and to expand on MILS benefits in different obesity classes. The results of this subgroup analysis showed, despite a significant sample size reduction limiting the statistical power, a persisting benefit of MILS over OLS in terms of a shorter LOS, supporting the idea that MILS may also be of benefit in severely obese patients.

The increasing experience in and confidence with MILS when operating on obese patients is deducible from the earlier mentioned trends and from the results of the conducted survey, wherein it was clear that the majority of surgeons have increased their adoption of MILS in obese patients during their own clinical practice. This widening of indications was based on a strong belief that obese patients may benefit from a minimally invasive approach when undergoing liver surgery. However, all surgeons recognized that obesity is an important challenging factor that increases the difficulty of both MILS and OLS.

Our study has several limitations that need to be acknowledged and discussed. The first is the study's observational and retrospective nature, with its associated loss of data. However, the imputation methods strengthened by the sensitivity analysis allowed us to include all patients in the PSM analysis. Second, the low number of patients included in the subgroup analysis of obesity class 3 accounted in the statistical power reduction for the comparison between MILS and OLS, possibly leading to type 2 errors. Nevertheless, we believe that the stratification of obese patients in three obesity classes allows for a more precise and in-depth assessment of the characteristics and outcomes of obese patients. In particular, this methodology and the large available cohort in this study made it possible to present an interesting overview of the characteristics and results of patients in obesity classes II and III, which are frequently not specifically assessed. Third, the retrospective nature of the study did not allow for the collection of data which may have affected the choice of the used surgical approach. Specifically, the lack of data concerning the tumor deepness and proximity to intrahepatic major vessels may have determined a selection bias in the choice of performing a MILS or OLS and may have contributed to an unbalance between the two groups of patients, both among normal weight and obese patients. The lack of data concerning the ethnicity of the patients may also represent a potential study limitation. The impact of patient ethnicity on the characteristics and outcomes of patients affected by a liver tumor, mainly for HCC, has been widely assessed by research groups in the United States.

**Table 5**
Trend analysis.

| *Characteristics* | Jan. 2009 Dec. 2013 (n = 3372) % | Jan. 2014 Dec. 2016 (n = 3546) % | Jan. 2017 Dec. 2019 (n = 3045) % | P |
|---|---|---|---|---|
| Proportion of obese patients | 19.5 | 20.2 | 19.9 | 0.757 |
| Usage of MI approach | | | | |
| Non-obese | 40.6 | 45 | 59.4 | <0.001 |
| Obese | 42.1 | 37.1 | 53 | <0.001 |
| *Surgical complexity* | | | | |
| **Laparoscopic liver surgery** | | | | |
| Non-obese | | | | <0.001 |
| Minor | 61.6 | 58.8 | 50.6 | |
| Technically major | 25.1 | 25.2 | 29.8 | |
| Traditional major | 13.3 | 16 | 19.5 | |
| Obese | | | | 0.156 |
| Minor | 62 | 60.4 | 54.2 | |
| Technically major | 27.5 | 24.5 | 30.8 | |
| Traditional major | 10.5 | 15.1 | 15 | |
| **Open liver surgery** | | | | |
| Non-obese | | | | <0.001 |
| Minor | 29.2 | 23.8 | 23.7 | |
| Technically major | 26.2 | 28.3 | 32.5 | |
| Major | 44.5 | 47.8 | 43.5 | |
| Obese | | | | 0.001 |
| Minor | 36.1 | 25 | 23 | |
| Technically major | 21.6 | 27.6 | 29.8 | |
| Major | 42.1 | 47.3 | 46.7 | |
| *Postoperative outcomes* | | | | |
| **Laparoscopic liver surgery** | | | | |
| Overall morbidity rate | | | | |
| Non-obese | 22 | 22.9 | 22.9 | 0.839 |
| Obese | 25 | 27.5 | 25 | 0.733 |
| **Open liver surgery** | | | | |
| Overall morbidity rate | | | | |
| Non-obese | 38.1 | 46.3 | 41.8 | <0.001 |
| Obese | 38.1 | 40.4 | 45.6 | 0.147 |
| **Laparoscopic liver surgery** | | | | |
| Severe morbidity rate | | | | |
| Non-obese | 7 | 8.1 | 8.7 | 0.282 |
| Obese | 6.9 | 9.4 | 6.9 | 0.433 |
| **Open liver surgery** | | | | |
| Severe morbidity rate | | | | |
| Non-obese | 15.1 | 16.5 | 15.2 | 0.482 |
| Obese | 12.5 | 12.5 | 16.5 | 0.242 |
| **Laparoscopic liver surgery** | | | | |
| Mortality rate | | | | |
| Non-obese | 1.8 | 1.1 | 1.4 | 0.342 |
| Obese | 1.5 | 0.4 | 0.9 | 0.423 |
| **Open liver surgery** | | | | |
| Mortality rate | | | | |
| Non-obese | 3 | 4.5 | 4.2 | 0.061 |
| Obese | 3.9 | 4.1 | 4.9 | 0.806 |

These research groups have suggested that patients belonging to an ethnic minority (African, Asian, or Hispanic) have poorer outcomes, compared to caucasian patients, probably due to social-economic disparities (affecting the healthcare access) among different ethnicities [44, 45]. However, we believe that the low rates of people belonging to ethnic minorities in European countries, which represented the majority of countries participating to the current study, in association with the regulations for healthcare access in place for European citizens, may make an analysis of ethnicity impact on characteristics and outcomes of operated patients clinically unrelevant in the current study. Similarly, the lack of laboratory, imaging, and histologic tests needed for diagnosing non-alcoholic fatty liver disease (NAFLD) prevented us from investigating eventual associations between NAFLD and cirrhosis among patients included in the current study. However, the statistically significant higher rates of cirrhosis among obese patients, compared to non-obese, and the persistence of such difference even after the exclusion of patients with chronic hepatitis B or C related cirrhosis (Table 1), suggests a possible association between NAFLD and cirrhosis among obese patients. Additionally, the lack of specific intraoperative data, as well as of in-depth histologic data in patients resected for malignancies, prevented us from assessing the feasibility and safety of techniques for selective vascular inflow occlusion among obese patients and from comparing its outcomes with Pringle maneuver, as well as from assessing eventual association of tumor histologic characteristics, like lymphovascular invasion, with obesity. We strongly believe that this is an interesting area for future research. Finally, data concerning the pattern of fat distribution was not available for the patients included in this study, precluding the investigation of its impact on perioperative outcomes. The prevalence of a visceral fat distribution may be associated with sarcopenia and can negatively affect the postoperative outcomes of patients undergoing a liver resection [46]. In this context, further studies are needed to investigate this association and its impact. However, the results of our survey conducted among the chief surgeons of the participating centres may partially fill this knowledge gap.

## 8. Conclusion

This large international multicentre study has found a gradual and cautious adoption of MILS in the surgical management of liver lesions in both non-obese and obese patients. Additionally, it has confirmed the safety, feasibility, and perioperative benefits of this approach in patients within different BMI classes, despite the fact that obesity remains a factor that may increase the technical difficulty of liver surgery, as objectified by longer operative times, more IOBL and the results of our survey.


## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Conflicts of interest and source of funding

No conflicts of interest or funding.


## Data statement

The data that support the findings of this study are available from the corresponding author, MAH, upon reasonable request. The data are not publicly available since this could compromise the privacy of research participants.

## CRediT authorship contribution statement

**Giuseppe Zimmitti:** Formal analysis, Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Jasper P. Sijberden:** Formal analysis, Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Mohammed Abu Hilal:** Formal analysis, Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2022.106957.

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