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***Retrospective Study***

**Impact of body mass index in elderly patients treated by laparoscopic liver resection for hepatocellular carcinoma**

Conticchio M *et al*. Postoperative outcome in elderly obese patients

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**Abstract**

BACKGROUND

The impact of obesity on surgical outcomes in elderly patients candidate for liver surgery is still debated.

AIM

To evaluate the impact of high body mass index (BMI) on perioperative and oncological outcomes in elderly patients (> 70 years old) treated by laparoscopic liver resection for hepatocellular carcinoma (HCC).

METHODS

A retrospective multicenter study including 224 elderly patients (> 70 years old) operated by laparoscopy for HCC (196 with a BMI < 30 and 28 with a BMI ≥ 30) was performed from January 2009 to January 2019.

RESULTS

After propensity score matching, patients in the two groups presented comparable results, in terms of operative time (median range: 200 min *vs* 205 min in non-obese and obese patients, respectively, *P* = 0.7), complication rate (22% *vs* 26%, *P* = 1.0), length of hospital stay (median range: 4.5 d *vs* 6.0 d, *P* = 0.1). There were no significant differences in terms of short- and long-term postoperative results.

CONCLUSION

The present study showed that BMI does not impact perioperative and oncologic outcomes in elderly patients treated by laparoscopic resection for HCC.

**Key Words:** Hepatocellular carcinoma; Body mass index; Laparoscopy; Surgical resection; Elderly patients; Propensity score matching

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**Core Tip:** In order to evaluate the impact of high body mass index (BMI) in elderly patients who underwent laparoscopic resection for hepatocellular carcinoma (HCC), we compared perioperative data and long-term outcomes of patients from 10 European centers before and after propensity score matching. The present study showed that BMI does not impact perioperative and oncologic outcomes in elderly patients treated by laparoscopic resection for HCC.

**INTRODUCTION**

Obesity is a significant contributing factor for the development of liver disease, starting from the stage of non-alcoholic steatohepatitis up to cirrhosis and hepatocellular carcinoma (HCC)[1-4]. Due to the constant increase of population aging, the treatment of HCC in elderly obese patient has become a global clinical issue[5]. Laparoscopic liver resection (LLR) provides the benefits of minimally invasive approach in terms of short-term outcomes[6,7], guaranteeing oncological results comparable to the open surgical approach[8,9]. However, data about the impact of obesity in patients undergoing LLR remain controversial, with some studies reporting higher body mass index (BMI) as a predictor of an adverse postoperative outcome[10] and other studies not reporting an increased risk of postoperative morbidity linked to obesity[11]. The aim of this study was to evaluate the impact of BMI in elderly patients undergoing LLR for HCC, by comparing short- and long-term outcomes.

**MATERIALS AND METHODS**

This multicenter retrospective study included 224 patients treated between January 2009 and January 2019, at the following centers: Policlinico di Bari, Bari, Italy; Policlinico di Modena, Modena, Italy; Ospedale San Raffaele, Milan, Italy; Grande Ospedale Metropolitano Niguarda, Milan, Italy; Centre hépato-biliaire Paul Brousse, Villejuif, France; Hôpitaux Universitaires Henri Mondor, Créteil, France; Hospital Universitario Sofía, Córdoba, Spain; Hôpitaux Universitaires de Genève, Geneva, Switzerland; Nouvel Hôpital Civil, Strasbourg, France; Centre Hospitalier Universitaire, Reims, France.

This study investigated patients resected for HCC demonstrating the following inclusion criteria: Child-Pugh class A and B disease; age ≥ 70 years; no evidence of major vessel branch invasion and no distant metastases. Based on the World Health
Organization (WHO) definition of obesity (BMI > 30 kg/m2)[12], the patients were divided into the following two groups: BMI < 30 kg/m2 group and BMI > 30 kg/m2 group.

The diagnosis of HCC was done, according to the European Association for Study of Liver (EASL) consensus criteria[13], based on non-invasive findings or histopathology. The type of treatment was planned following multidisciplinary tumor board discussions.

***LLR procedure***

The surgical procedure was planned based on tumor features and liver function. Minor and major liver resections were performed according to Brisbane classification[14]. The choice of position and the size of trocars depended on tumor location. Intraoperative ultrasonography represented a standardized initial step of surgical procedure. Liver parenchymal transection was performed with laparoscopic instruments using various energy devices such as the cavitation ultrasonic surgical aspirator and ultrasonic, monopolar and bipolar forceps. The extent of resection depended on the size and anatomical location of the tumor and it was defined as “minor” for the resection of two or fewer Couinaud’s liver segments, and ‘major’ for the resection ≥ 3 liver segments. The hepatic hilum was prepared for the Pringle’s maneuver. The specimen was placed in an endocatch bag and removed from one of the trocars’ incision sites.

***Follow-up***

Short-term outcomes after liver resection included the evaluation of the parameters in the perioperative period, including intraoperative variables such as operative time and blood transfusion rate, and postoperative variables such as complication rate (based on the Clavien-Dindo classification[15]) and length of hospitalization. Long-term outcomes included oncological results in terms of overall survival (OS) and disease-free survival (DFS). Liver blood tests were assessed on the first, third, and fifth postoperative days. Follow-up was performed once every 3 mo during the first year and every 4 mo thereafter with CT-scan and blood tests (including liver function and oncologic markers). Recurrence after treatment included repeat resection, locoregional treatment, liver transplantation, or supportive care based on the patient’s general status and liver disease according to the EASL-EORTC clinical practice guidelines[13].

***Statistical analysis***

Statistical analyses were carried out using the IBM SPSS Statistics 20 software. The *t*-test and Mann-Whitney *U* test were used to compare continuous variables. The chi-square test and Kruskal-Wallis test were performed to compare categorical variables. The Kaplan-Meier method was used to assess recurrence-free survival (RFS) and OS curves. The Cox proportional hazard model was used to analyse independent prognostic factors of long-term survival. A propensity score matching (PSM) analysis was performed to reduce selection bias, obtaining two more homogeneous matched groups of patients in the resection and ablation groups. Variables included in our propensity model included age, number of comorbidities ≥ 2, American Society of Anesthesiologists (ASA) score, Child-Pugh and model for end-stage liver disease (MELD) scores, extent of resection, and tumor number and size. A one-to-one PSM was performed with a caliper width of < 0.2 of the pooled standard deviation of estimated propensity scores, applying these variables to a logistic regression model and calculating C-statistics. A total of 27 out of the 196 patients in the BMI < 30 group and a total of 27 out of the 28 patients in the BMI > 30 group were matched for further analyses.

**RESULTS**

***Before PSM***

We included 224 patients treated by LLR for HCC and aged ≥ 70 years. One hundred and ninety-six patients presented a BMI < 30 kg/m2 and 28 presented a BMI > 30 kg/m2. Demographic data were similar between the two groups, except for a higher rate of males in the BMI ≥ 30 kg/m2 group than in the BMI < 30 kg/m2 group (69% *vs* 93%, *P* = 0.001). Associated comorbidities were not increased in obese patients, as ASA and MELD score (Table 1).

Perioperative and postoperative data are described in Table 2. There were no significant differences in surgical time (median range: 200 min *vs* 220 min in the BMI < 30 and BMI > 30 groups, respectively, *P* = 0.70), rate of blood transfusion (16% *vs* 3%, *P* = 0.09), and length of hospitalization (median range: 6.0 d *vs* 5.5 d, *P* = 0.20)

The global rate of postoperative complications was higher in the non-obese group (47% *vs* 25%, *P* = 0.02) compared to the obese group. Only the rate of wound infection was higher in the obese group (11% *vs* 2%, *P* = 0.04).

The 90-d mortality rate did not present a significant difference between the two groups (5% in BMI < 30 group and 0% in BMI > 30 group, *P* = 0.60). The estimated 1- and 3-year OS rates were 100% and 92.3% in the BMI > 30 group, and 96% and 91.4% in the BMI < 30 group (*P* = 0.004; Figure 1A), respectively. The estimated 1- and 3-year DFS rates were 96% and 67% in the BMI > 30 group, and 82% and 36% in the BMI < 30 group (*P* = 0.50; Figure 1B), respectively.

***After PSM***

After matching, we obtained a more homogeneous population for both groups (Table 1). The variables included in the PSM were age, comorbidities, ASA and MELD scores, Child-Pugh score, tumor size, tumor number, and extent of resection. Perioperative and postoperative results are analytically described in Table 2. The postoperative follow up did not reveal any difference in the complication rate between the BMI > 30 and BMI < 30 groups (26% *vs* 22%, *P* = 1.0), nor in grade of severity (Clavien-Dindo grades III-IV) (4% *vs* 7%, *P* = 0.6). Moreover, operative time (median range: 205 min *vs* 200 min, *P* = 0.7) and rate of blood transfusion (3% *vs* 18%, *P* = 0.2) were similar. The estimated 1- and 3-year OS rates were 100% and 92.3% in the BMI > 30 group, and 88.4% and 83.5% in the BMI < 30 group (*P* = 0.2; Figure 1C), respectively.

The estimated 1- and 3-year DFS rates were 96.2% and 65.8% in the BMI > 30 group, and 87.5% and 86.2% in the BMI < 30 group (*P* = 0.5; Figure 1D), respectively.

**DISCUSSION**

The impact of obesity on surgical results in elderly patients who underwent liver resections remains a subject of vivid debate. An increased surgical risk has been expected because of comorbidities associated with obesity and old age, underlying liver disease, and technical difficulties[16-20]. Our multicenter study did not confirm this hypothesis and showed that LLR can be safely performed in treatment of HCC also in elderly patients with a BMI ≥ 30 kg/m2. The evaluation of the influence of BMI in elderly population is important because of the increasing prevalence of this condition associated with an higher average life expectancy[21,22].

The increasing BMI has been reported as a predisposition to develop various diseases, including diabetes mellitus, hypertension, respiratory disease, and certain types of cancer[23-25]. Our data did not show differences in term of rate of comorbidities or tumor characteristics, even after PMS analysis, according to various preoperative parameters (age, comorbidities, ASA and MELD scores, Child-Pugh score, tumor size, tumor number, and extent of resection), which resulted in a more homogeneous and therefore comparable population.

Even though the initial hypothesis that obesity negatively affected the outcomes of minimally invasive approach was not verified[26], data regarding LLR in obese patients were controversial. After the evaluation of surgical procedures ended with Second International Consensus Conference on LLR[27], a scoring system was built to stratify LLR into groups with increasing degree of difficulty[28]. This IWATE score aimed to preoperatively predict the technical difficulty of various LLR, but without including body habitus. So, the question whether anthropometric variables really have an impact on perioperative outcomes remains.

Using operative time, rate of blood transfusion, and rate of conversion as surrogates of surgical difficulty, Ome *et al*[29] reported significantly longer median operation time in obese compared to non-obese patients, while Uchida *et al*[30] found that BMI was an independent predictor of longer operative time > 200 min. Lee *et al*[31] reported a significant difference in operative time and incidence of blood transfusion in overweight compared to normal weight patients, but no difference for obese patients. In accordance to the abovementioned data, the results of this study also suggest similar rate of blood transfusion and operative time in patients with a BMI < 30 kg/m2 and those with a BMI ≥ 30 kg/m2.

The advantages of a minimally invasive approach in liver surgery, including lower abdominal wall morbidity and early postoperative rehabilitation[32,33], may be more beneficial for the subgroup of obese patients. A recent systematic review[34] reported similar rates of postoperative complications between obese and non-obese patients, although several issues including discrepancy in the obesity definition, limit the validity of these results. Nomi *et al*[35] reported that the postoperative course of obese patients was not negatively affected by a higher incidence of infectious complications nor liver specific complications. Yu *et al*[36] reported a higher rate of bile leak in obese compared to non-obese patients. The herein presented data demonstrate a similar postoperative outcome, with no significant differences in major complications (Clavien-Dindo III-IV) nor liver related complications in obese compared to non-obese patients.

View magnification of and optimal exposure with liver mobilization, as well as the increase of dedicated tools, allow a clearer visualization of deep structures, small vessels, and biliary ducts[7,36,37]. The authors speculate that this “power” of laparoscopy can justify a lower rate of postoperative complications not only in terms of preservation of abdominal wall integrity, linked with prevention of respiratory diseases and reduction of postoperative pain, but also with a greater accuracy in resection technique, especially in the hands of experienced surgeons.

Oncological outcomes following PSM were also similar, as no differences were noted in DFS and OS in obese *vs* non-obese patients undergoing LLR for HCC. This is also in accordance with the majority of published data[34]. These results suggest that elderly obese patients can also benefit from surgical treatment in terms of long-term outcomes, mainly driven by the excellent short-term outcome of laparoscopy.

**CONCLUSION**

In conclusion, according to the present study, BMI does not impact surgical outcomes of LLR in elderly patients treated for HCC. Thorough patient selection, based on liver volume and function evaluation, as well as patient habitus and comorbidities, could result in safe and feasible LLR in elderly obese patients.

**ARTICLE HIGHLIGHTS**

***Research background***

A high body mass index (BMI) could represent a factor which impacts perioperative outcomes in elderly patients who underwent laparoscopic liver resection (LLR).

***Research motivation***

To evaluate postoperative outcomes between elderly (age > 70 years) patients with a BMI ≥ 30 and BMI < 30 who underwent a LLR for hepatocellular carcinoma (HCC).

***Research objectives***

To analyse short- (perioperative) and long-term (oncological results) outcomes.

***Research methods***

The analysis of data was performed before and after propensity score matching.

***Research results***

After propensity score matching, patients in the two groups presented comparable results, in terms of operative time, complication rate, and length of hospital stay. There were no significant differences in terms of short- and long-term postoperative results.

***Research conclusions***

The present study showed that BMI does not impact perioperative and oncologic outcomes in elderly patients treated by laparoscopic resection for HCC.

***Research perspectives***

Randomized controlled studies are needed to better explore these results.

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**Footnotes**

**Institutional review board statement:** This study did not require the approval by the Ethics Committee of the Azienda Ospedaliera Universitaria Policlinico of Bari, General Regional Hospital “F. Miulli”, Acquaviva delle Fonti (BA), San Raffaele Hospital of Milan, Gustave Roussy Cancer Campus Grand Paris of Paris, Hospital University Reina Sofía of Córdoba, Centre Hospitalier Universitaire Henri Mondor of Paris, Geneva University Hospitals and Medical School of Geneva, University of Modena and Reggio Emilia of Modena, Institut de Recherche Contre les Cancers de l’Appareil Digestif (IRCAD) of Strasbourg, Hôpital Robert Debré of Reims, Niguarda Hospital of Milan, and Centre Hepatobiliaire, Hopital Paul Brousse of Paris.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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**Data sharing statement:** No additional data are available.

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**Figure Legends**



**Figure 1 Survival curves and tumor recurrence curves (Kaplan-Meier method) of elderly patients with hepatocellular carcinoma with a body mass index < 30 or ≥ 30 who underwent laparoscopic liver resection before propensity score matching.** A: Overall survival (OS) curves were constructed using the Kaplan-Meier method and compared using the log-rank test. OS significantly did not differ between the two groups; B: Recurrence-free survival (RFS) curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Hepatocellular carcinoma recurrence significantly differed between the two groups; C: OS curves were constructed using the Kaplan-Meier method and compared using the log-rank test. After propensity score matching, survival remained significantly different; D: RFS curves were constructed using the Kaplan-Meier method and compared using the log-rank test. After propensity score matching, recurrence remained significantly different. BMI: Body mass index.

**Table 1 Preoperative and clinical characteristics of elderly patients with hepatocellular carcinoma with a body mass index < 30 or ≥ 30 who underwent laparoscopic liver resection**

|  |  |  |
| --- | --- | --- |
|  | **LLR before PSM (224)** | **After PSM (54)** |
|  | **BMI < 30 (196)** | **BMI ≥ 30 (28)** | ***P*** | **BMI < 30 (27)** | **BMI ≥ 30 (27)** | ***P*** |
| MALE | 135 (69) | 26 (93) | 0.00 | 17 | 25 | 0.02 |
| Age (yr), median (range) | 75.2 (69.5-90.0) | 75.3 (69.7-86.6) | 0.70 | 76.3 (70.6-81.2) | 73.1 (70-82.3) | 0.70 |
| BMI (kg/cm²), median (range) | 26.7 (19.0-29.0) | 32.5 (30.0-52.0) | 0.00 | 26.7 (25.0-267.0) | 33 (30-37) |  |
| Co-morbidities > 2, *n* (%) | 77 (80) | 9 (32) | 0.50 | 14 | 9 | 0.27 |
| Cause of Cirrhosis, *n* (%) |  |  |  |  |  |  |
| Hepatitis C virus | 102 (52) | 12 (43) | 0.40 | 16 | 11 | 0.27 |
| Hepatitis B virus | 39 (20) | 4 (14) | 0.60 | 7 | 4 | 0.50 |
| Alcohol | 23 (12) | 7 (25) | 0.07 | 1 | 7 | 0.05 |
| Others | 32 (16) | 5 (18) | 0.80 | 3 | 5 | 0.70 |
| ASA score, *n* (%) |  |  | 0.80 |  |  | 1.00 |
| I-II | 84 (43) | 11 (39) |  | 10 | 10 |  |
| III-IV | 112 (57) | 17 (61) |  | 17 | 17 |  |
| Blood tests median (range) |  |  |  |  |  |  |
| Bilirubin (mg/dL) | 0.9 (0.2-4.2) | 0.9 (0.2-2.1) | 0.8 | 0.9 (0.3-1.1) | 0.5 (0.2-1.1) | 0.70 |
| Creatinine (mg/dL) | 0.9 (0.2-2.5) | 0.9 (0.4-1.9) | 1.00 | 0.9 (0.8-1.5) | 0.9 (0.7-2) | 0.80 |
| Platelet count, × 109/L | 176 (45-421) | 187 (72-468) | 0.3 | 144 (47-337) | 168 (117-396) | 0.80 |
| INR | 1.1 (0.6-2.0) | 1.08 (0.7-1.67) | 0.3 | 1.1 (1-1.5) | 1 (1-1.3) | 0.50 |
| CHILD-PUGH, *n* (%) |  |  | 0.2 |  |  | 1.00 |
| A | 177 (90) | 23 (82) |  | 23 | 22 |  |
| B | 19 (68) | 5 (18) |  | 4 | 5 |  |
| MELD median (range) | 6 (6-16) | 6 (6-13) | 0.6 | 8 (6-12.5) | 8 (6-13) | 0.40 |
| Tumors number n (%) |  |  | 0.06 |  |  | 1.00 |
| Single nodule | 191 (97) | 25 (89) |  | 24 | 24 |  |
| Multi nodules | 5 (3) | 3 (11) |  | 3 | 3 |  |
| Tumors size (mm), median (range) | 30 (9-50) | 30 (18-50) | 0.6 | 30 (9-50) | 27 (24-35) | 0.30 |
| Bilobar tumor, *n* (%) | 1 (0.5) | 1 (3) | 0.2 | 1 | 1 | 1.00 |
| Tumor in PS segment, *n* (%) | 41 (21) | 6 (21) | 1.00 | 5 | 5 | 1.00 |
| Histologically proven n (%) | 31 (16) | 8 (29) | 0.11 |  |  |  |
| Previous treatment, *n* (%) | 12 (6) | 3 (10) | 0.4 |  |  |  |
| Major hepatectomy, *n* (%) | 22 (11) | 2 (7) | 0.7 | 1 | 2 | 1.00 |
| Operative time > 240 min | 73 (37) | 12 (43) | 0.7 | 150 (80-210) | 150 (65-155) | 0.70 |

Continuous variables were compared using an independent sample *t*-test and Mann-Whitney *U* test. Categorical variables were compared using the chi-square test and Kruskal-Wallis test respectively. LLR: Laparoscopic liver resection; PSM: Propensity score matching; HCC: Hepatocellular carcinoma; BMI: Body mass index; ASA: American Society of Anesthesiologists; MELD: Model for End Stage Liver Disease; LLR: Laparoscopic liver resection.

**Table 2 Preoperative and clinical characteristics of elderly patients with hepatocellular carcinoma with a 30 > body mass index ≥ 30 who underwent laparoscopic liver resection**

|  |  |  |
| --- | --- | --- |
|  | **LLR Before PSM (224)** | **After PSM (54)** |
|  | **BMI < 30 (196)** | **BMI ≥ 30 (28)** | ***P*** | **BMI < 30 (27)** | **BMI ≥ 30 (27)** | ***P*** |
| Operative time (min), median (range) | 200 (70-600) | 220 (65-337) | 0.70 | 200 (80-320) | 205 (65-337) | 0.7 |
| Blood transfusion, *n* (%) | 32 (16) | 1 (3) | 0.09 | 5 (18) | 1 (3) | 0.2 |
| Dindo-Clavien classification, *n* (%) |  |  | 0.23 |  |  | 0.6 |
| I-II | 18 (92) | 27 (97) |  | 23 (93) | 26 (96) |  |
| III-IV | 16 (8) | 1 (3) |  | 2 (7) | 1 (4) |  |
| Postoperative complications, *n* (%) |  |  | 0.02 |  |  | 1.0 |
| Yes | 93 (47) | 7 (25) |  | 6 (22) | 7 (26) |  |
| No | 103 (53) | 21 (75) |  | 21 (78) | 20 (74) |  |
| Type of complication, *n* (%) |  |  |  |  |  |  |
| Liver failure | 15 (8) | 1 (3) | 0.70 | 2 (7) | 1 (4) | 1.0 |
| Ascites | 24 (12) | 2 (7) | 0.70 | 3 (11) | 2 (7) | 1.0 |
| Biliary leakage | 2 (1) | 1 (3) | 0.30 | 0 | 1 (4) | 1.0 |
| Hemorrhage | 8 (4) | 0 | 0.60 | 2 (7) | 0 | 0.5 |
| Systemic infection | 14 (7) | 1 (3) | 0.70 | 2 (7) | 1 (4) | 1.0 |
| Intra-abdominal abscess | 7 (3) | 0 | 0.60 | 2 (7) | 1 (4) | 1.0 |
| Wound infection | 4 (2) | 3 (11) | 0.04 | 0 | 3 (11) | 0.2 |
| Portal thrombosis | 2 (1) | 0 | 1.00 | 1 (4) | 0 | 1.0 |
| Pulmonary | 15 (7) | 0 | 0.20 | 2 (7) | 0 | 0.5 |
| Cardiac | 11 (5) | 1 (3) | 1.00 | 2 (7) | 1 (4) | 1.0 |
| Renal | 8 (4) | 0 | 0.60 | 2 (7) | 0 | 0.5 |
| Reoperation, *n* (%) | 6 (6) | 1 (3) | 1.00 | 0 | 1 (4) | 1.0 |
| Postoperative death, *n* (%) | 7 (3) | 0 | 0.60 | 2 (7) | 0 | 0.5 |
| Postoperative treatment, *n* (%) | 6 (3) | 1 (3) | 1.00 | 0 | 1 (4) | 1.0 |
| Length of hospital stay, median (range) | 6 (2-40) | 5.5 (3-21) | 0.20 | 4.5 (2-40) | 6 (3-21) | 0.1 |
| Mortality at 90 d, *n* (%) | 9 (5) | 0 | 0.60 | 2 (7) | 0 | 0.5 |

Continuous variables were compared using an independent sample *t*-test and Mann-Whitney *U* test. Categorical variables were compared using the chi-square test and Kruskal-Wallis test.