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Laparoscopic Liver Resection: A Tool to Improve Outcomes in Obese Patients Requiring Liver Resection

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Abstract

Introduction: Obesity is associated with an increased risk of fatty liver disease, predisposing to liver fibrosis and cirrhosis, as well as increased occurrence of hepatocellular carcinoma. Obesity is intuitively considered a risk factor for increased post-hepatectomy morbidity and mortality. Nevertheless, peer-reviewed literature reveals significant heterogeneity between different cohorts contributing to varying conclusions. Outcomes in this cohort for Laparoscopic Liver Resection (LLR), especially in non-academic settings remain under-evaluated. The current study evaluated outcomes of LLR in obese patients, in a community health system. **Methods:** A retrospective analysis of all patients undergoing LLR at the flagship hospital in the community health system, between 2013 and 2020, was performed. Classified into two groups based on Body Mass Index (BMI): obese (BMI > 30 kg/m^2) vs non-obese (BMI < 30 kg/m^2). Variables between groups compared with univariate analysis (Fisher exact test, student t-test, or Mann Whitney U-test). Multivariate analysis using logistic regression, was performed to determine the association of obesity with composite complication score (including bile leak, infection, bleeding, and/or cardiorespiratory complication) (p-value < 0.05). **Results:** 90 patients underwent LLR during the 7-year period; obese = 38 and non-obese = 52. No statistically significant differences were noted between obese and non-obese cohorts, in baseline characteristics including age (53.1 ± 15.1 vs 56.8 ± 11.6 years), female gender (60.5% vs 53.8%), and ASA grade (3.13 ± 0.53 vs 3.02 ± 0.54) (all p > 0.05). Univariate analysis showed no statistically significant differences between obese and non-obese groups, comparing estimated blood loss [300 (100 - 500) vs. 200 (100 - 462.5) cc], operative time [177 (125 - 215) vs. 150.9 (111 - 207) minutes], bile leak (2.6% vs. 4.1%), post-operative bleeding (2.6% vs. 4.1%), infection (0% vs. 4.1%), cardiorespiratory complication (10.5% vs 12.2%), conversion rate (5.3% vs 5.8%), length of stay [4 (3 - 5) vs. 4 (2 - 5) days], 90-day reoperation (0% vs. 2%) and 90-day readmission (2.6% vs. 4.1%) ($p > 0.05$). Multivariate analysis showed no association between obesity and composite complication rate ($p = 0.97$), after adjusting for alcohol abuse, neoadjuvant therapy, and prior liver surgery. **Conclusion:** LLR is a key technique that can be replicated in the community setting to improve outcomes in obese patients requiring liver resection. Larger prospective multicenter studies are warranted to externally validate these findings.

Keywords

Liver Resection, Laparoscopic, Obesity, Surgical Outcomes, Minimally-Invasive

1. Introduction

Obesity is a pandemic, especially impacting the developing world, with a steeply increasing prevalence, currently estimated at approximately 42.4% in the United States [1]. It plays a major role in the pathogenesis of chronic diseases including metabolic syndrome, diabetes, cardiovascular, and respiratory illnesses, as well as liver diseases [2] [3] [4] [5]. In fact, liver disease secondary to obesity, is currently the most prevalent form of liver disease in the developed world [6]. An increase in BMI is directly associated with steatohepatitis, hepatic fibrosis, and Non-Alcoholic Fatty Liver Disease (NAFLD) [7] [8] [9]. Obesity is further associated with an increased risk of liver cirrhosis and hepatocellular carcinoma, especially in patients with NAFLD [10] [11]. Hepatocellular carcinoma has been noted to have an incidence of up to 2.6% in patients with NAFLD [12].

Obesity is suggested to increase the risk of surgical morbidity, including cardiovascular complications, surgical site infections and thrombotic events [13]. However, a more recent concept of the "obesity paradox" notes improved surgical outcomes in overweight and moderately obese patients [14]. A retrospective analysis comparing laparoscopic and open hepatectomy for obese patients showed no differences in surgical outcomes between the two groups [15] [16]. Additionally, while studies acknowledge technical difficulties, they report equivalent oncological outcomes with the improved length of stay, lower estimated blood loss, and reduced post-operative pain, in patients undergoing laparoscopic hepatectomy [17]. The primary aim of this study was to ascertain the safety of minimally invasive liver resection in obese patients, compared to non-obese patients, in a community health setting. The secondary aim was to evaluate any differences in intra-operative and post-operative morbidity and mortality between the two groups.

2. Materials and Methods

2.1. Study Population

This was a retrospective analysis of a prospectively collected database of all adult patients who underwent liver resection by a minimally invasive method, between September 2013 and November 2020 at ProMedica Toledo Hospital, Toledo, Ohio, and the flagship hospital of the ProMedica Health System. Minimally invasive liver resections included pure laparoscopic and hand-assisted techniques.

2.2. Patient Data

Data collection included demographics, disease variables and operative data as well as postoperative outcomes. Patients were divided into 2 groups, obese, defined as a BMI of more than 30 kg/m^2, and non-obese, BMI less than 30 kg/m^2. This determination was made per the CDC definition of obesity, which defines overweight as BMI > 25 kg/m^2 and obesity as BMI > 30 kg/m^2 [1]. The two groups were compared for baseline difference in demographics and disease characteristics. Comparison of intra-operative and post-operative outcomes between the two groups, to evaluate the safety of minimally invasive surgery in the obese cohort compared to the non-obese, was then performed. Finally, obesity as a risk factor for post-operative morbidity in patients undergoing minimally invasive liver resection, was analyzed. The study was approved by the local institutional review board.

2.3. Surgical Procedures

Surgical technique and safety of laparoscopic liver resection has been well described [18] [19]. Major hepatectomy defined as resection of three or more contiguous segments and type of hepatectomy classified according to Brisbane 2000 terminology [20]. All of the procedures were performed by a single AHPBA fellowship trained HPB (hepato-pancreato-biliary) surgeon (KAS). Intraoperative ultrasound was utilized routinely to confirm number, size and location of lesions in relationship to major vascular and biliary structures. Liver parenchymal transection was performed by ultrasonic dissector, Harmonic® (Ethicon Endo-Surgery, Inc., Cincinnati, OH) and laparoscopic endo GIA stapler (Coviden LP, Mansfield, MA). Barbed suture, V-Loc® suture (Coviden LP, Mansfield, MA) and heme-o-lok polymer clips, Weck® clips (Teleflex Morrisville, NC) utilized as necessary for additional hemostasis or reinforcement in area of concern for bile leak. Pringle maneuver was not routinely utilized.

2.4. Postoperative Outcomes

Operative variables included operative time, estimated blood loss, vascular resection, and additional procedures performed at time of initial liver resection. Post-operative outcomes included presence of surgical site infection, bile leak, bleeding, and cardiopulmonary complications. Liver specific complications included liver failure as per the International Study Group for Liver Surgery (ISGLS) definitions [21]; hemorrhage defined as any postoperative transfusion of packed red blood cells for falling hemoglobin and or need for invasive intervention or return to the operating room; and bile leak defined as per the ISGLS definitions

[22]. Clavien-Dindo classification was utilized to grade all complications and a major complication was considered a grade ≥ 3 [23]. Readmission, reoperation and 90 day mortality were also noted.

2.5. Statistical Analysis

Categorical variables were recorded as frequency and percentage with continuous variables recorded as mean and standard deviation or median with inter-quartile range. The categorical variables were compared using Fisher's exact tests. Continuous variables were tested for normality using Shapiro-Wilk test and compared using independent student t test or Mann Whitney U tests as appropriate. Survival curve constructed using the Kaplan-Meier method where date of surgery and date of last contact or death date were used to determine follow up period; log-rank test was used to compare survival based on obesity category. Cox proportional hazard regression models were created to investigate factors associated with mortality in this cohort with stepwise backward/forward regression based on AIC (Akaike's Information Criterion) to determine variables to be included in an optimal model. All analyses were performed using statistical software R version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) and $p < 0.05$ was utilized to determine statistical significance.

3. Results

Ninety patients met inclusion criteria and were included in this analysis, among which 38 patients were obese with BMI > 30 kg/m^2 and 52 were non-obese. Average age of patients in the cohort was 55.3 ± 13.2 years and 56.7% were female. Patients included in analysis underwent resection for benign conditions including hepatic adenoma, hepatic cysts, hemangioma, and focal nodular hyperplasia, as well as for malignant conditions including Hepatocellular Carcinoma (HCC) and liver metastasis, mainly from colon and neuroendocrine primaries.

Demographic characteristics comparison between patients in obese and non-obese cohorts revealed no statistically significant differences in patient age (53.1 ± 15.1 vs 56.8 ± 11.6 years; p = 0.21), female gender (60.5% vs. 53.8%, p = 0.53), ASA (American Society of Anesthesiologists) grade (p = 0.78), ECOG (Eastern Cooperative Oncology Group) functional status (p = 0.69), history of smoking (p = 0.17) or history of alcohol intake (p = 0.52) (**Table 1**). Among disease variables, patients in the obese cohort had significantly lower rates of malignant diagnosis (42.1% vs. 73.1%, p = 0.003). Patient factors noted lower rates of previous abdominal surgery (26.3% vs. 53.8%, p = 0.01) in obese patients compared to non-obese patients, with no significant differences noted in rates of cirrhosis or previous liver resection, pre-operative albumin levels, pre-operative bilirubin levels, rate of vascular involvement and percentage of patients whom received neoadjuvant therapy (all p > 0.05) (**Table 1**).

On univariate analysis, no statistically significant differences were noted in intra-operative and post-operative outcomes between obese and non-obese

Table 1. Demographics and disease variables.

Variables		Obese (n = 38)	Non-obese (n = 52)	P-value
Age		53.1 ± 15.1	56.8 ± 11.6	0.21
Female gender		23 (60.5%)	28 (53.8%)	0.53
ASA grade	2	3 (8.6%)	7 (13.5%)	0.78
	3	25 (71.4%)	37 (71.2%)	
	4	7 (20%)	8 (15.4%)	
BMI		34.5 (31.6 - 39.7)	25.3 (22.7 - 27.9)	<0.01
ECOG scale	0	19	28	0.69
	1	17	18	
	2	2	5	
	3	0	1	
Previous abdominal surgery		10 (26.3%)	28 (53.8%)	0.01
Previous liver resection		2 (5.3%)	6 (11.5%)	0.46
Smoking	Current/former	17 (44.7%)	32 (61.5%)	0.17
	Never	21 (55.3%)	20 (38.5%)	
Alcohol		22 (57.9%)	26 (50%)	0.52
Cirrhosis		3 (7.9%)	11 (21.2%)	0.09
Albumin (pre-operative)		4.0 (3.8 - 4.2)	4.1 (3.75 - 4.2)	0.66
T.Bilirubin (pre-operative)		0.6 (0.325 - 0.70)	0.6 (0.4 - 0.9)	0.08
Vascular involvement		1 (3.3%)	1 (2.0%)	1.00
Neoadjuvant therapy		7 (18.4%)	13 (25%)	0.61
Malignant diagnosis		16 (42.1%)	38 (73.1%)	<0.01

Abbreviations: ASA, American Society of Anesthesiology; BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group. Values are denoted as mean ± standard deviation, median (Interquartile range) or occurrence (percentage). P-value < 0.05 considered significant.

groups: EBL [300 (100 - 500) vs. 200 (100 - 462.5) cc; p = 0.6], operative time [177 (125 - 215) vs. 150.9 (111 - 207) minutes; p = 0.34], bile leak (2.6% vs. 4.1%; p = 0.1), post-operative bleeding (2.6% vs. 4.1%; p = 0.1), infection (0% vs. 4.1%; p = 0.5), cardiorespiratory complication (10.5% vs. 12.2%; p = 1.0), liver failure (5.2% vs. 5.7%; p = 0.92), complication Clavien grade (p = 0.87) or conversion to open surgery (5.3% vs. 5.8%; p = 1.0). No statistically significant differences were noted in length of stay [4 (3 - 5) vs. 4 (2 - 5) days, p = 0.54], 90-day reoperation (0% vs. 2%; p = 1.0) or 90-day readmission rate (2.6% vs. 4.1%; p = 1.0) of obese versus non-obese groups (Table 2).

A composite complication score was then created (by analyzing if a patient had any of the following complications: bile leak, bleeding, infection, or cardiorespiratory complication) and aimed to determine an association with obesity. On univariate analysis, incidence of composite complication score was similar

Table 2. Univariate comparisons of intra-operative and post-operative complications.

Variables	Obese (n = 38)	Non-obese (n = 52)	P-value
EBL (ml)	300 (100 - 500)	200 (100 - 462.5)	0.60
Operative time (minutes)	177 (125 - 215)	150.9 (111 - 207)	0.34
LOS	4 (3 - 5)	4 (2 - 5)	0.54
Bile leak	1 (2.6%)	2 (4.1%)	1.00
Bleeding	1 (2.6%)	2 (4.1%)	1.00
Infection	0 (0.0%)	2 (4.1%)	0.50
Cardiorespiratory complication	4 (10.5%)	6 (12.2%)	1.00
Liver failure	2 (5.2%)	3 (5.7%)	0.92
Serious complication (Clavien ≥ 3)	4 (10.5%)	7 (13.5)%	0.75
Composite complication	6 (15.8%)	8 (15.4%)	1.00
Clavien score			
Zero	24 (63.2)	28 (58.3)	
One	5 (13.2)	4 (8.3)	
Two	5 (13.2)	9 (18.8)	0.87
Three	2 (5.3)	3 (6.3)	
Four	2 (5.3)	4 (8.3)	
Conversion to open	2 (5.3%)	3 (5.8%)	1.00
Reoperation within 90 days	0 (0%)	1 (2.1%)	1.00
Readmission within 90 days	1 (2.6)%	2 (4.1)%	1.00
Death within 90 days	0 (0%)	0 (0%)	1.00

Abbreviations: EBL, Estimated Blood Loss; LOS, Length of Stay. Values are denoted as median (Interquartile range) or occurrence (percentage). All p-values < 0.05 were considered significant.

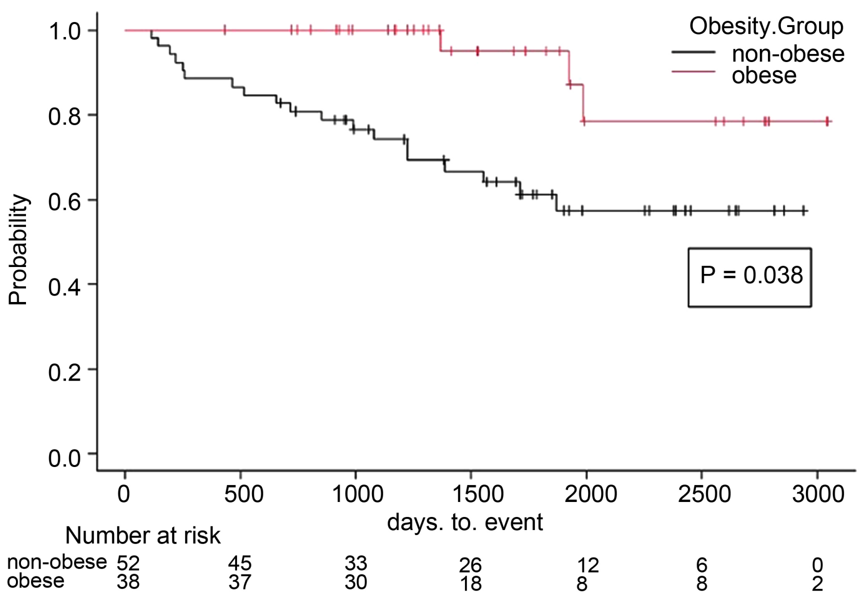

Figure 1. Kaplan-Meier survival estimates for obese versus non-obese patients.

between the obese and non-obese cohorts (15.8% vs 15.4%, p = 1.0). On multivariate analysis, using logistic regression, no significant association was noted between obesity and composite complication score (OR = 0.98; 95% CI = 0.29 - 3.28; p = 0.97), after adjusting for previous alcohol use, history of neoadjuvant therapy, and prior liver surgery (**Table S1**).

On analyzing the association between obesity and survival, utilizing Kaplan-Meier estimates, median survival in obese patients was 66.1 months compared to 51.7 months in non-obese patients (p = 0.038) (**Figure 1**). However on Cox regression analysis, obesity was not significantly associated with overall survival in these patients (HR = 0.288, 95% CI = 0.08 - 1.09; p = 0.067), after adjusting for age, smoking status, previous abdominal surgery, cirrhosis, malignant diagnosis and pre-operative total bilirubin (**Table S2**).

4. Discussion

The incidence of obesity, defined as a BMI more than 30 kg/m^2, has significantly increased from 30.5% to 42.4%, in the United States, in less than two decades [1]. Along with this increase, strong associations between obesity and various chronic diseases, including cardio-respiratory, metabolic and hepatocellular diseases have been reported [2] [4] [5]. An increased risk of solid organ malignancies including hepatocellular carcinoma, breast carcinoma and colon cancer with obesity has also been established [11] [24].

Obesity has long being described as a risk factor for surgical morbidity [13]. It was also considered a relative contraindication to minimally invasive surgery about 3 decades ago, however many large cohort studies and meta-analysis looking at outcomes of minimally invasive surgery in this cohort, have shown improved outcomes with laparoscopic surgery, with the expected preponderance of focus on bariatric surgery [25] [26]. After the Louisville statement, the international consensus on the safety and efficacy of laparoscopic liver resection in 2008, rates of laparoscopic hepatectomies increased significantly. Still there continued to be concerns expressed by some surgeons regarding technical challenges and oncological adequacy of margins, while others reported reduction in length of stay and no changes in oncological survival with laparoscopic liver resection [27] [28]. Subequent recommendations from the second international consensus conference held in Morioka in 2015 as well as the Southampton consensus guidelines for laparoscopic liver surgery in 2018 continued to support the advantages and increased utilization of laparoscopic liver surgery [18] [29]. As a result, interest in the utilization of minimally invasive surgery for hepatectomy in all patients, including overweight and obese patients has increased at a more rapid rate.

However, some trepidation remained regarding potential technical challenges of minimally invasive liver surgery in obese patients with malignancy [30] [31]. Several recent studies addressing this concern reported safety of laparoscopic hepatectomy in obese patients compared to non-obese patients, improved surgical outcomes in obese patients with laparoscopic hepatectomy compared to an open approach, and no differences in oncological outcomes with minimally invasive surgery, when completed successfully [32] [33] [34]. Thus, further emphasizing the need to increase utilization of minimally invasive approach in this cohort of patients [35] [36] [37].

No negative impact of obesity was observed in the current study, on intra-operative outcomes (operative time and EBL), post-operative morbidity (including composite complication rates) or mortality. This is in concordance with these previous analyses which have similarly shown no impact of obesity and increased BMI on the intra-operative and post-operative outcomes of patients undergoing laparoscopic hepatectomy [35] [36] [38] [39].

Additionally, no difference in liver failure rates and no mortalities were observed in this study between the obese and non-obese patients. Given higher risk of liver failure due to underlying comorbidities associated with obesity supports the dictum that with appropriate patient selection in terms of liver function, liver volume and associated comorbidities good outcomes can be achieved in the obese population [28] [37] [38]. Again, increased rates of post-operative morbidity including liver failure in obese patients undergoing open hepatectomy compared to the non-obese patients are observed, and the associated risks appears to be mitigated when both groups are treated with the laparoscopic approach [40].

Survival analysis of obese versus non-obese patients in the current study revealed improved survival in the obese cohort. However, on multivariate analysis, after stepwise regression, no significant difference was noted in the survival rates of the two cohorts. This is supported by previously reported literature in other laparoscopic abdominal surgeries as well as by the concept of "obesity paradox" [41] [42]. Obesity paradox in surgical procedure suggests that patients with extremes of BMI have worse post-operative outcomes than those with overweight or moderate obesity [14] [43] [44].

Limitations

Despite the promising results of this study, laparoscopic liver resection has its limitations. These limitations include those known to laparoscopic surgery especially in patients with comorbidities who would be unable to tolerate pneumoperitoneum. Further limitations include the learning curve for laparoscopic liver resection, as the feasibility and safety of this surgery correlates with specialized surgeons in high volume centers. Additionally, laparoscopic liver resection may be limited anatomically by lesions in the superior and posterior aspect of the liver and larger lesions, specifically those more than 5 cm in size.

The current study does have some limitations. As a retrospective analysis, it does have the potential for unconscious selection bias, as evidenced by differences in the baseline characteristics of the cohorts (lower rates of previous abdominal surgery and rates of malignant disease in the obese cohort). Adjustments were made in the multivariate analysis in an attempt to compensate for the baseline differences. Secondly, with a sample size of 90 patients, this is not a large study. Further, while this data is from a single surgeon at a single institute, and is thus homogenous in management practices, a larger multicenter cohort will allow further subgroup analysis and the ability to draw stronger conclusions. However, a prospective randomized study of LLR would be rather difficult to perform as LLR has already become widespread as a standard procedure by HPB surgeons and instead more collaborative efforts such as the Americas Minimally Invasive Liver Resection (AMILES) Database to provide more insight and stronger conclusions are encouraged.

5. Conclusion

Minimally invasive surgery has previously been reported to improve operative outcomes including intra-operative blood loss, post-operative pain, and post-operative length of stay. Laparoscopic liver resection is beneficial in small, solitary liver lesions in the inferior, and anterior segments of the liver. The current study reports laparoscopic liver resection is a safe and feasible operation in obese patients, with outcomes comparable to non-obese patients. We additionally also report that these outcomes can be replicated in a community health system with no increased risk of morbidity and mortality in obese patients undergoing laparoscopic liver resection. These findings support large and multi-center studies to further analyze and tailor the application of laparoscopic liver surgery in this very unique and growing cohort of patients.

Authors' Contribution

Research idea formulation by AC and KAS. Data collection by AC, MD, and RM. Statistical analysis by RR. Manuscript writing by AC and KAS. Critical edits of the manuscript by all co-authors. Project coordination and supervision by KAS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplement

Table S1. Logistic regression analysis for composite complication score.

Variables	Odds ratio	95% confidence interval	P-value
Obesity	**0.980**	**0.29 - 3.28**	**0.973**
Past liver surgery	<0.001	0.00 - inf	0.994
Alcohol	0.302	0.88 - 1.03	0.055
Neoadjuvant therapy	0.204	0.024 - 1.74	0.147

All p-values < 0.05 were considered significant.

Table S2. Cox-regression analysis for association of obesity with survival.

Variables	Hazard ratio	95% confidence interval	P-value
Obesity	**0.288**	**0.08 - 1.09**	**0.067**
Age	1.006	0.96 - 1.05	0.792
Non-smoker	0.256	0.08 - 0.80	0.019
Previous abdominal surgery	1.222	0.36 - 4.18	0.749
Cirrhosis	0.813	0.17 - 3.83	0.794
Diagnosis-malignant	9.985	1.24 - 80.24	0.030
Bilirubin	1.817	0.43 - 7.77	0.421

All p-values < 0.05 were considered significant.