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The Safety and Efficacy of Approaches to Liver Resection: A Meta-Analysis

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ABSTRACT

Background: The aim of this study is to compare the safety and efficacy of conventional laparotomy with those of robotic and laparoscopic approaches to hepatectomy.

Database: Independent reviewers conducted a systematic review of publications in PubMed and Embase, with searches limited to comparative articles of laparoscopic hepatectomy with either conventional or robotic liver approaches. Outcomes included total operative time, estimated blood loss, length of hospitalization, resection margins, postoperative complications, perioperative mortality rates, and cost measures. Outcome comparisons were calculated using random-effects models to pool estimates of mean net differences or of the relative risk between group outcomes. Forty-nine articles, representing 3702 patients, comprise this analysis: 1901 (51.35%) underwent a laparoscopic approach, 1741 (47.03%) underwent an open approach, and 60 (1.62%) underwent a robotic approach. There was no difference in total operative times, surgical margins, or perioperative mortality rates among groups. Across all outcome measures, laparoscopic and robotic approaches showed no difference. As compared with the minimally invasive groups, patients undergoing laparotomy had a greater estimated blood loss (pooled mean net change, 152.0 mL; 95% confidence interval, 103.3–200.8 mL), a longer length of hospital stay (pooled mean difference, 2.22 days; 95% confidence interval, 1.78–2.66 days), and a higher total complication rate (odds ratio, 0.5; 95% confidence interval, 0.42–0.57).

Conclusion: Minimally invasive approaches to liver resection are as safe as conventional laparotomy, affording less estimated blood loss, shorter lengths of hospitalization, lower perioperative complication rates, and equitable oncologic integrity and postoperative mortality rates. There was no proven advantage of robotic approaches compared with laparoscopic approaches.

Key Words: Hepatectomy, Laparoscopy, Robotics, Meta-analysis, Minimally invasive surgery.

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INTRODUCTION

Historically, because of visibility issues and the complicated relationship between the liver and its vasculature, hepatectomy has presented a challenge to the surgeon. Laparoscopy for liver resection was first documented in the early 1990s, proving to be as safe as conventional open hepatectomy while retaining oncologic integrity.[1–7] However, laparoscopy has limitations in transection, mobilization, and the ability to control bleeding. To overcome some of these shortcomings, robot-assisted approaches have been devised and implemented that broaden visualization from 2 dimensions to 3 dimensions and increase range of motion to 360° via the EndoWrist (Intuitive Surgical Inc., Sunnyvale, California). Although minimally invasive approaches to surgery are known to decrease postoperative pain scores and length of hospitalization (LOH), with the rising costs of health care, controversy continues to surround discussions of these approaches.

The focus of this study is to evaluate the role of minimally invasive techniques in liver surgery as compared with a conventional open approach. We compared data related to operative time, perioperative complications, LOH, surgical margins, mortality rates, and cost analysis to assess differing approaches. This is the first systematic review to include analysis of the robotic approach, reflecting trends in modern surgery.

MATERIALS AND METHODS

Identification of Trials and Data Extraction

Two independent reviewers conducted a systematic search of PubMed and Embase on articles published until

August 2013. The following medical subject headings were used to locate articles: liver robotic, hepatic robotic, hepatic laparoscopic, hepatectomy laparoscopic, and hepatectomy open. The inclusion criteria for articles were as follows: (1) articles comparing conventional open liver resection with either a laparoscopic or robotic approach; (2) controlled clinical trials, multicenter studies, or randomized controlled trials; (3) studies that reported outcomes of intraoperative and postoperative outcomes, including total operative time, estimated blood loss (EBL), LOH, surgical margins, postoperative complications, and postoperative mortality rates; and (4) studies that reported a measure of variance (standard error, standard deviation, or confidence interval [CI]). The references of articles included in the analysis were manually searched for additional articles for inclusion. Excluded from analysis were articles on resection of colorectal cancer with synchronous liver metastasectomy and articles not published in English. In instances in which research groups reported findings using shared patient populations, the earliest publication by that research group was included for analysis. The results from the 2 independent reviews were compared for accuracy, with disagreement resolved by consensus. To achieve completeness and to assemble the most representative patient database, series with limited sample sizes were included so that their experience would find meaning in aggregate.

Statistical Analysis

The primary outcomes of interest in this study were total operative time, EBL, LOH, surgical margins, perioperative complications, and postoperative mortality rates. A cost analysis was included as a secondary outcome of interest. For continuous outcomes, mean net changes were calculated as primary outcomes, whereas for categorical outcomes, odds ratios (ORs) were calculated to examine the treatment effect. DerSimonian and Laird random-effects models were used to pool mean net changes or ORs across the studies.[8] The presence of heterogeneity was assessed with the Cochran Q test, and the extent of heterogeneity was quantified with the I^2 index. To assess publication bias, funnel plots were constructed for each outcome. The Begg rank correlation test was used to examine the asymmetry of the funnel plot, and the Egger weighted linear regression test was used to examine the association between the mean effect estimate and its variance. In addition, sensitivity analyses were conducted by excluding each study in turn to evaluate its relative influence on the pooled estimates. All analyses were conducted using Stata software, version 10 (StataCorp, College Station, Texas).

RESULTS

Search Results

Eight hundred seventy-three abstracts were identified, 867 of which were obtained via searches of 2 databases, with an additional 6 retrieved through manual searches of references. The final set of articles undergoing analysis was attained using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (**Figure 1**).[9] Of the 873 abstracts identified, 55 underwent full-text review and 49 articles are included in this meta-analysis, with 3 comparing laparoscopic liver resection with robotic hepatectomy[10–12] and 46 comparing laparoscopic liver resection with a conventional open approach (**Table 1**).[13–58]

Description of Included Trials and Demographic Data

The 49 articles analyzed represent a total of 3702 patients, with sample sizes ranging from 17 to 400 patients. The distribution of the patients was as follows: 60 in the robotic group, 1901 in the laparoscopic group, and 1741 in the open group. Baseline patient demographic data, including sex, age, and body mass index, were well matched among groups (**Table 2**) Distribution of resection type by the 40 articles mentioning this characteristic is listed in **Table 3**.[11–17,19–25,27–32,34,35,37–39,41–44,46–48,51–58]

Perioperative Outcomes

Forty-six publications reported total operative length, with similar results among groups[10–13,15–24,26–36,38–58] (**Figure 2a**). The mean total operative time was 203.6 minutes, 203.9 minutes, and 234.8 minutes for the laparoscopic, open, and robotic groups, respectively.

Regarding EBL, 44 studies reported this variable.[10–14,16–25,27–39,43,44,46–58] There was no difference between minimally invasive approaches, and there was a statistically significant increase in blood loss in laparotomy cases as compared with laparoscopy cases, with a pooled net mean change of 152.0 mL (95% CI, 103.3–200.8 mL) (**Figure 2b**).

The total number of conversions in the laparoscopic group was 106, which represents a 5.68% conversion rate to open surgery. In the robotic group, 9 cases

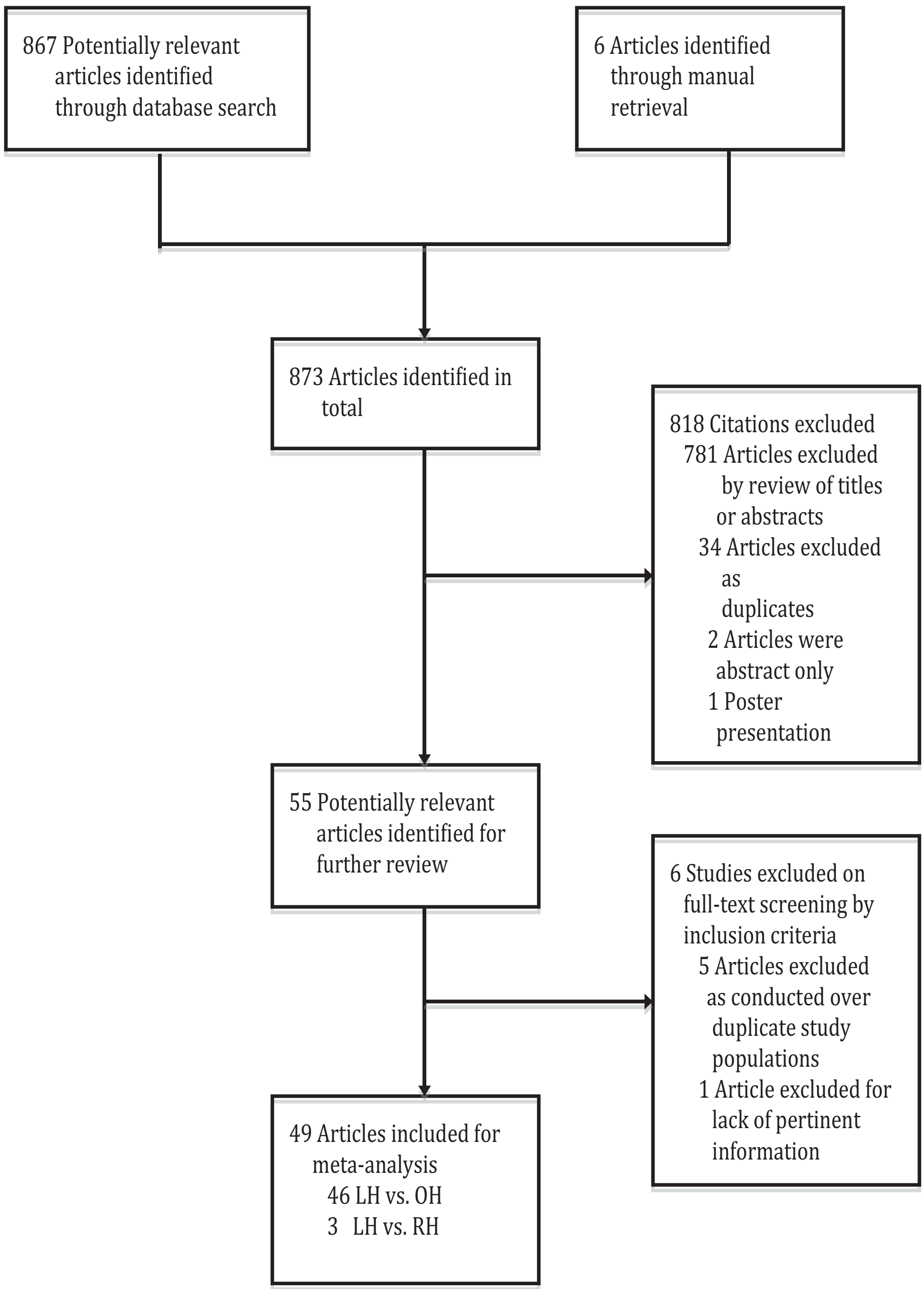

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing literature search and study selection.[9] LH = laparoscopic hepatectomy; OH = open hepatectomy; RH = robotic hepatectomy.

required conversion to open surgery, representing a 15% conversion rate.

Twenty-nine studies included results of pathologic resection margin status in their analyses.[13–16,19–21,23–25,28,29,31–33,38,41–43,45–49,51,53,56,57] Laparoscopy showed a significantly higher rate of negative surgical margins (pooled OR 1.06) as compared with laparotomy (pooled OR 1.01).

Table 1.
Studies Selected for Meta-Analysis

Authors	Year	Country	Journal	Comparison	n
Packiam et al[10]	2012	USA	*J Gastrointest Surg*	LH[a] vs RH[a]	29
Berber et al[11]	2010	USA	*HPB*	LH vs RH	32
Troisi et al[12]	2013	Belgium	*Int J Med Robot*	LH vs RH	263
Inoue et al[13]	2013	Japan	*Am Surg*	LH vs OH[a]	47
Slakey et al[14]	2013	USA	*JSLS*	LH vs OH	62
Kim et al[15]	2011	South Korea	*J Korean Surg Soc*	LH vs OH	55
Abu Hilal et al[16]	2008	UK	*Eur J Surg Oncol*	LH vs OH	44
Endo et al[17]	2009	USA	*Surg Laparosc Endosc Percutan Tech*	LH vs OH	21
Cai et al[18]	2009	Germany	*Surg Endosc*	LH vs OH	38
Ito et al[19]	2009	USA	*J Gastrointest Surg*	LH vs OH	130
Morino et al[20]	2003	USA	*Surg Endosc*	LH vs OH	60
Belli et al[21]	2007	Italy	*Surg Endosc*	LH vs OH	46
Aldrighetti et al[22]	2008	USA	*J Gastrointest Surg*	LH vs OH	40
Topal et al[23]	2008	USA	*Surg Endosc*	LH vs OH	152
Kandil et al[24]	2012	USA	*Surgery*	LH vs OH	36
Cannon et al[25]	2012	USA	*Surgery*	LH vs OH	175
Polat[26]	2012	Turkey	*Surg Laparosc Endosc Percutan Tech*	LH vs OH	19
Johnson et al[27]	2012	USA	*J Am Coll Surg*	LH vs OH	212
Bhojani et al[28]	2012	Canada	*J Am Coll Surg*	LH vs OH	171
Tranchart et al[29]	2010	France	*Surg Endosc*	LH vs OH	84
Tang et al[30]	2005	Hong Kong	*Surg Endosc*	LH vs OH	17
Lesurtel et al[31]	2003	France	*J Am Coll Surg*	LH vs OH	38
Cheung et al[32]	2013	Hong Kong	*Ann Surg*	LH vs OH	60
Kobayashi et al[33]	2013	Japan	*Surg Endosc*	LH vs OH	83
Slim et al[34]	2012	Italy	*Langenbecks Arch Surg*	LH vs OH	92
Hu et al[35]	2012	China	*Surg Laparosc Endosc Percutan Tech*	LH vs OH	26
Hu et al[36]	2011	China	*World J Gastroenterol*	LH vs OH	60
Gustafson et al[37]	2012	USA	*Surg Endosc*	LH vs OH	76
Nguyen et al[38]	2011	USA	*Arch Surg*	LH vs OH	86
Tu et al[39]	2011	China	*World J Gastroenterol*	LH vs OH	31
Vanounou et al[40]	2010	Canada	*Ann Surg Oncol*	LH vs OH	73
Castaing et al[41]	2009	France	*Ann Surg*	LH vs OH	120
Carswell et al[42]	2009	UK	*BMC Surg*	LH vs OH	20
Dagher et al[43]	2009	France	*Am J Surg*	LH vs OH	72
Rowe et al[44]	2009	Canada	*Surg Endosc*	LH vs OH	30
Sarpel et al[45]	2009	USA	*Ann Surg Oncol*	LH vs OH	76
Tsinberg et al[46]	2009	USA	*Surg Endosc*	LH vs OH	74
Cai et al[47]	2008	China	*Surg Endosc*	LH vs OH	62

Table 1 continued on next page.

Table 1. (continued)
Studies Selected for Meta-Analysis

Authors	Year	Country	Journal	Comparison	n
Lee et al[48]	2007	Hong Kong	*Hong Kong Med J*	LH vs OH	50
Mala et al[49]	2002	Norway	*Surg Endosc*	LH vs OH	27
Rau et al[50]	1998	Germany	*Hepatogastroenterology*	LH vs OH	34
Shimada et al[51]	2001	Japan	*Surg Endosc*	LH vs OH	55
Farges et al[52]	2002	France	*J Hepatobiliary Pancreat Surg*	LH vs OH	42
Laurent et al[53]	2003	France	*Arch Surg*	LH vs OH	27
Kaneko et al[54]	2005	Japan	*Am J Surg*	LH vs OH	58
Polignano et al[55]	2008	UK	*Surg Endosc*	LH vs OH	50
Lai et al[56]	2009	China	*Arch Surg*	LH vs OH	58
Truant et al[57]	2011	France	*Surg Endosc*	LH vs OH	89
Koffron et al[58]	2007	USA	*Ann Surg*	LH vs OH	400

[a]LH = laparoscopic hepatectomy; OH = open hepatectomy; RH = robotic hepatectomy.

Table 2.
Demographic Characteristics

Characteristic	Total (%)	LH[a]	OH[a]	RH[a]
Sex				
Male	1535 (48.7)	712	786	37
Female	1329 (42.1)	705	601	23
Age, y	58.95	58.79	58.87	62.73
BMI[a]	26.67	26.46	26.31	31.00
Lesions				
Mean number	3.26	4.35	2.72	1.49
Mean size, cm	5.11	4.86	4.06	27.50
Surgical indication				
CRC[a] metastases	836	396	412	28
Adenoma	117	110	7	0
FNH[a]	127	109	18	0
Hemangioma	114	85	23	6
HCC[a]	951	436	509	6
Hydatid cyst	108	86	18	4
Living donor	52	32	20	0
Cholangiocarcinoma	15	8	6	1

[a]BMI = body mass index; CRC = colorectal cancer; FNH = focal nodular hyperplasia; HCC = hepatocellular carcinoma; LH = laparoscopic hepatectomy; OH = open hepatectomy; RH = robotic hepatectomy.

Table 3.
Resection Type

Resection Type	LH[a]	OH[a]	RH[a]
Monosegmentectomy	304	250	7
Subsegmentectomy/wedge	270	249	15
Bisegmentectomy	173	141	8
Left lateral sectionectomy	323	231	2
Right trisegmentectomy	7	6	0
Mixed segments	26	0	8
Right hepatectomy	173	169	0
Left hepatectomy	113	72	0
R extended hepatectomy	12	22	0
Major hepatectomy	110	119	0
Nonanatomical/atypical	105	88	0
P-S segment	110	37	22

[a]LH = laparoscopic hepatectomy; OH = open hepatectomy; RH = robotic hepatectomy.

Postoperative Considerations

Forty-four studies reported LOH.[10,12,13,15–32,34–40,42–44,46–58] As compared with patients undergoing the laparoscopic approach, those undergoing a conventional open approach had a significantly longer LOH (pooled mean difference, 2.22 days; 95% CI, 1.78–2.66 days) (**Figure 2c**).

Postoperative morbidity, including wound infection, biliary leakage, pleural effusion, bleeding, fluid collection, incisional hernia formation, renal failure, and ascites or cirrhotic decompensation, was reported by 47 articles.[10–32,34–41,43–58] For total postoperative complications, minimally invasive approaches showed similar results with a rate significantly lower than that of the open group (OR, 0.49; 95% CI, 0.42–0.57) (**Figure 2d**). Specifically, minimally invasive approaches had lower rates of wound infections (OR, 0.39; 95% CI, 0.22–0.68), incisional hernias (OR, 0.20; 95% CI, 0.06–0.67), and ascites and cirrhotic decompensation events (OR, 0.50; 95% CI, 0.29–0.87) than the open group.

Forty studies reported data on postoperative mortality rates.[10–20,22–37,39–43,45–49,53,54,56,57] There were no statistically significant differences between laparotomy and minimally invasive approaches for rates of both in-hospital mortality (OR, 1.01; 95% CI, 0.67–1.54) and postoperative mortality within 30 days of discharge (OR, 0.88; 95% CI, 0.41–1.88).

Cost Analysis

Eight studies included cost analyses and discussion on this outcome.[10,28,38,40,44,46,55,58] Of these, one was excluded because it was out of scope.[58] Four studies reported cost differences between minimally invasive approaches and conventional approaches, with three comparing laparotomy with laparoscopy and one comparing a robotic approach with an open approach.[10,28,46,55] These studies showed a nonsignificant trend of higher total operative costs of $334.10 (95% CI, –$753.50–$1421.60) for minimally invasive approaches. Four studies reported total hospital cost differences, with all comparing laparotomy with laparoscopy.[28,40,46,55] These researchers found a trend of higher total hospital costs in patients undergoing the conventional open approach of $3223 (95% CI, –$474–$692). Of note, one additional article normalized cost values for both total operative costs and total hospital costs and was subsequently not included in the statistical analysis.[38]

DISCUSSION

This meta-analysis of 3702 patients over a 14-year period yielded 49 pertinent studies showing minimally invasive approaches for hepatectomy to be as safe and efficacious as conventional laparotomy, with similar total operative times. Minimally invasive approaches afford shorter LOH, decreased EBL, and decreased postoperative morbidity. Specifically, these approaches resulted in fewer incisional hernias, wound infections, and ascites or cirrhotic decompensation events and retained oncologic integrity. All approaches to liver resection resulted in similar mortality rates. In terms of cost, minimally invasive approaches required nearly the same amount of money in the operating room as the conventional approach but saved money over the entire LOH.

Favorable operative outcomes, such as decreased EBL and lower rates of postoperative morbidity, lend credence to increased implementation of minimally invasive approaches. Bile leaks and massive hemorrhages are two important perioperative considerations in hepatic surgery owing to the unique anatomic structure of the liver, with minimally invasive approaches showing decreased intraoperative blood loss and equitable postoperative bile leak rates. The observed lower EBL is likely multifactorial, owing to both hepatic vein tamponade from pneumoperitoneum and improved dissection via field magnification. Furthermore, higher EBL and consequent blood transfusions are associated with increased postoperative morbid-

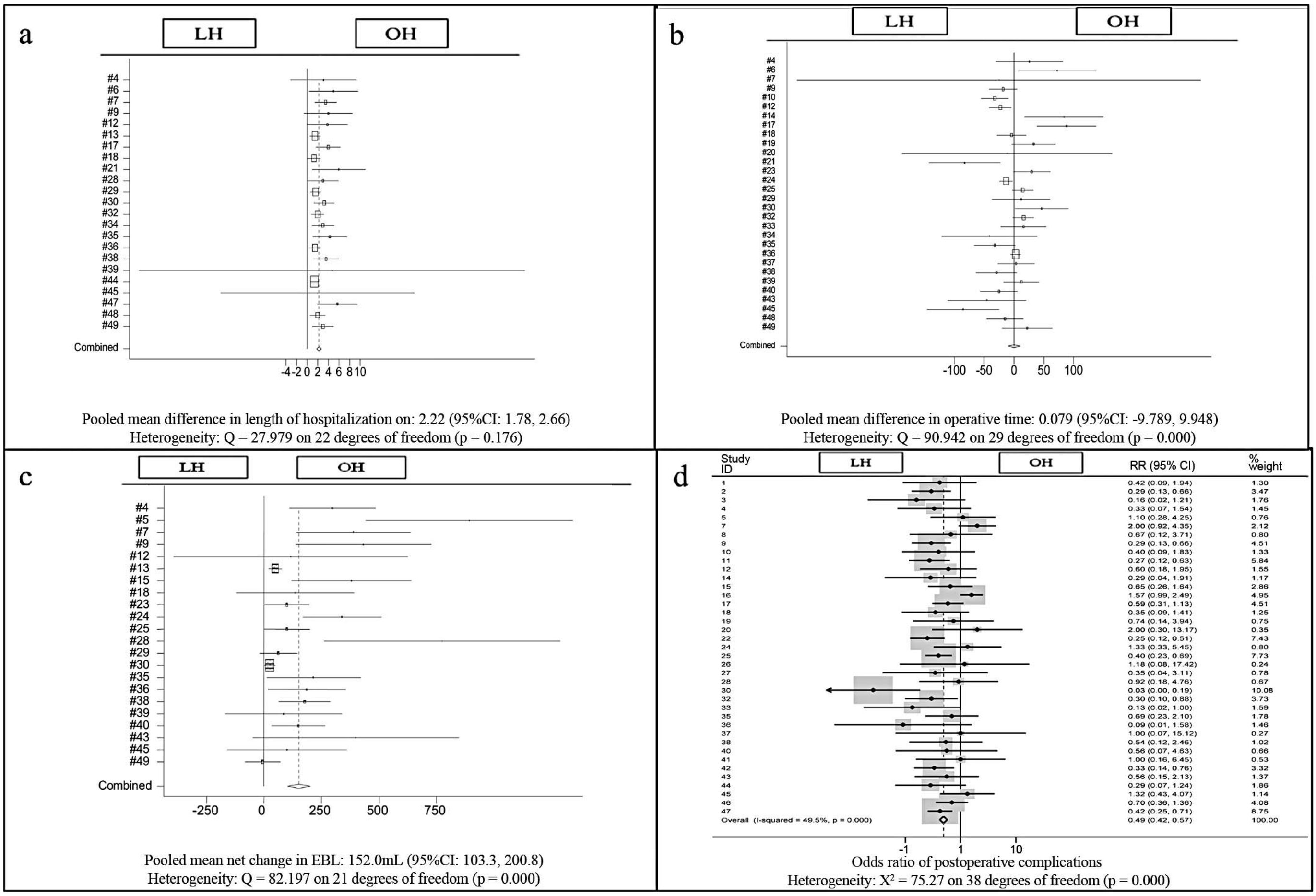

Figure 2. Forest plots and pooled analyses of mean difference in length of hospitalization (a), operative time (b), estimated blood loss (c), and odds ratio of postoperative complications (d). The mean difference is reported for each study (black boxes). LH = laparoscopic hepatectomy; OH = open hepatectomy.

ity, helping explain the lower rates of postoperative morbidity observed in this study.[59]

Long-term mortality rates were reported for 22 of the included study samples.[11,15,17,19,24,25,29,32,33,35,36,38,41,45,47,48,51,53,54,56,57] When immediate postoperative deaths were excluded, nonsignificant differences were found between laparoscopic hepatectomy and open hepatectomy for overall survival and for disease-free survival by all research groups except one. Kandil et al[24] found no difference in overall survival (P = .818) but found a significant difference in disease-free survival, with 100% 3-year survival in laparoscopic hepatectomy patients versus 71.4% survival in open hepatectomy patients (P = .03). Of note, the operative indication for this research group was neuroendocrine metastasis, whereas the indications for the remaining groups were primarily hepatocellular carcinoma or colorectal cancer metastases (**Table 2**). Perhaps a survival advantage exists in this population of patients; however, further studies are needed to establish the potential validity of this relationship.

A focus of debate regarding implementation of minimally invasive surgery centers on cost. In comparing total operative costs and total hospital costs among groups, studies found that although operative costs were higher for laparoscopic groups, their hospitalization costs were lower because of shorter LOH, which is intimately tied to postoperative morbidity, as well as decreased intensive care unit admission rates.[38,40,60] Only 1 article assessed comparative costs between robotic and conventional open approaches, finding increased operating room costs with the robotic approach.[10] However, without discussion of total hospital costs, no conclusions can be drawn from that study regarding the potential financial tradeoff gained by implementing robotic intervention. Further studies including the economic impact of minimally invasive surgery are needed to advance this discussion.

Minimally invasive approaches to surgery afford the surgeon increased visibility and the patient decreased LOH, improved cosmesis, and decreased postoperative pain. Colorectal metastases are a leading indication for hepatectomy, for which a majority of patients need repeat hepatectomy. Minimally invasive approaches not only better facilitate reoperations in this patient population but also allow for simultaneous operations in colorectal cancer patients with synchronous hepatic metastases.[61–64]

Although this study is comprehensive and is the most current evaluation of approaches to liver resection, there are several limitations and shortcomings to our study. First, the included studies are nonrandomized, retrospective studies, making them of moderate quality with increased selection bias. Also contributing to selection bias was patient selection by the surgeon, wherein healthier patients more fit for surgery were more likely to undergo minimally invasive options, leading to more favorable postoperative outcomes. Furthermore, patients selected for laparoscopic surgery may have had more easily resectable tumors, possibly contributing to their relative increase in negative margins. Intimately linked to minimally invasive surgical outcomes is both the surgeon's experience with the procedure and the volume of cases to which each care center is accustomed, neither of which was included in these studies, thereby prohibiting subanalysis. These studies exhibited moderate heterogeneity, with varying surgical techniques and differing outcome measures. Specifically, significant heterogeneity in reporting of resection outcomes, positive and negative versus R0–R1, prevents subanalysis of this outcome.

Although 873 citations were initially identified, an overwhelming majority of these were out of scope, focusing on tangential topics relating to liver donations, radiofrequency ablation, and tumor staging. Moreover, although these articles may have marginally touched on some of our primary outcomes, they neglected to contain data pertinent to this study. Furthermore, patient overlap by research groups led to the exclusion of 5 articles from analysis, totaling 488 patient experiences that are not represented.

The only statistically significant difference noted between minimally invasive approaches was a roughly 10% lower conversion rate to open surgery in the laparoscopic group as compared with the robotic group. With only 3 comparative studies including a robotic group, the ability to accurately ascertain any relationship to the robotic group is limited by its underpowering and the subsequent inability to perform subgroup analysis. Further comparative studies that include robotic approaches are needed. At present, the limited volume is likely because of the financial investment and operative training required to implement robots into common surgical practice.

CONCLUSION

To our knowledge, this review represents the largest, most current analysis of outcomes related to minimally invasive approaches to hepatectomy, with minimally invasive approaches showing improved postoperative morbidity, retained oncologic integrity, and potentially decreased economic burden to the health care system. Furthermore, future research comparing the robotic approach with the laparoscopic approach, as well as assessing the cost associated with each approach, is warranted.

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