



Laparoscopic liver resection in elderly patients: systematic review and meta-analysis

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Abstract

Laparoscopic liver resection (LLR) is becoming standard practice, replacing the open approach in terms of safety and feasibility. However, few data are available for the elderly. The objective of this study is to assess the feasibility of LLR in elderly patients, by making a comparison with open liver resection (OLR) and with non-elderly patients. Relevant studies found in the Cochrane Library, Embase, PubMed, and Web of Science were used in order to perform a systematic review and meta-analysis. Nine fully extracted comparative studies were included and two groups were identified: Group 1 with a comparison between OLR and LLR in the elderly and Group 2 with a focus on differences after LLR between elderly and non-elderly patients. A total number of 497 elderly patients who underwent LLR were analyzed. A random effect model was used for the meta-analysis. In Group 1, 1025 elderly patients were included: 640 underwent OLR and 385 underwent LLR. LLR was associated with minor blood loss (MD -240 mL, 95% CI -416.61 , -63.55 ; p 0.008; $I^2=96\%$), less transfusion (8% vs. 13.1%; RR 0.61, 95% CI 0.41, 0.91; $p=0.02$; $I^2=0\%$), fewer postoperative Clavien-Dindo III/IV complications (RR 0.48 in favor of LLR; 95% CI 0.29, 0.77; $p=0.003$; $I^2=0\%$). On the other hand, no significant difference was observed in terms of bile leakage, ascites, mortality, liver failure, or R0 resection. Group 2 included 112 elderly and 276 non-elderly patients who underwent LLR. The meta-analysis showed no significant difference in terms of blood loss, transfusions, liver failure, Clavien-Dindo III/IV complications, postoperative mortality, ascites, bile leak, hospital stay, R0 resection, and operative time. Laparoscopic liver resection is a safe and feasible procedure for elderly patients. However, further randomized studies are required to confirm this.

Keywords Liver resection · Elderly patients · Laparoscopic · Hepatectomy · Cancer

Abbreviations

LLR Laparoscopic liver resection
OLR Open liver resection
OS Overall survival

DFS Disease-free survival
ICC International consensus conference
MCCR Metastatic colorectal cancer
E Elderly patients

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NE	Non-elderly patients
MD	Mean deviation
SMD	Standard mean deviation
RE	Random effects

The minimally invasive approach has pervaded all fields of abdominal surgery since the first laparoscopic cholecystectomy performed by Philippe Mouret in Lyon, France. Reports about laparoscopic liver surgery were first made in 1994 [1], and over the last few years, laparoscopic surgery has become a gold standard treatment for many pathologies previously treated with open surgery [2–6]. The development of surgical technologies and instruments played a key role in the effectiveness of laparoscopic procedures, including hepatobiliary surgery, and, consequently, in increasing their safety and feasibility.

Due to the development of laparoscopic liver procedures, two consensus conferences were held to set limits to minimally invasive hepatic surgery. Of note, during the last international consensus conference (ICC), which took place in Morioka, Japan [7] in 2014, it was stated that minor laparoscopic liver resections (LLR) became standard practice. The reason for this is that, as opposed to open liver resection (OLR), LLR does not induce a higher rate of postoperative mortality, and is characterized by reduced postoperative complications, a shorter length of hospital stay, the same R0 percentage and overall survival (OS). On the other hand, major LLRs are still in the exploration phase. However, as mentioned above, its non-inferiority over OLR has not been analyzed yet.

One of the major problems of modern surgery is the population's increasing age. As a result, technologies should be adapted to this factor.

It was evidenced that aging does not represent a limiting factor for open liver resection. However, it is still unclear if more fragile elderly patients can benefit from minimally invasive surgery just as non-elderly ones. The most common concerns for surgeons and anaesthesiologists in this regard are as follows: longer operative times, pneumoperitoneum and its physiological consequences, diminished functional reserve, and postoperative co-morbidities [8, 9].

Over the past 5 years, some single-center retrospective studies have focused on the results of LLR in elderly patients [10–18]. Two different strategies were implemented: (1) comparison between the laparoscopic and open approaches in the elderly; and (2) comparison between the elderly and non-elderly population after laparoscopic liver resection. The objective of this study is to perform a review and a meta-analysis based on the state-of-the-art of laparoscopic liver resection in the elderly.

Materials and methods

Study design

The methodological algorithm for this review included different phases, namely selection criteria, definition of search strategies, assessment of study quality, and relevant data abstraction.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements checklist was used [19]. There was no need to obtain approval from the local Institutional Review Board or written consent from patients because no data of patients from our hospital were needed for the current review.

Study inclusion criteria

Selection criteria to identify eligible studies for this review and meta-analysis were stated above (is this what you meant?). Comparative studies on the effects of laparoscopic liver resection in elderly patients were analyzed. Two different groups of comparative studies were identified: Group 1, comparing open and laparoscopic liver resections in the elderly; and Group 2, focusing on differences after LLR between elderly and non-elderly patients.

Case reports, reviews, articles, non-comparative studies, commentaries, and studies with less than 10 patients were not considered, neither were series published before 2010. Only studies dealing with hepatic tumor resections were included (both benign and malignant, primitive and metastatic). No limitation for the extension of the surgical resection was applied.

Study selection criteria were defined according to the PICO framework. Elderly patients requiring hepatic surgical resection of a primary or metastatic tumor were included. Two different approaches, i.e., laparoscopy and the open approach were considered. Different resections were included (minor, major, wedge). We focused on two different comparisons. Group 1 aimed at comparing laparoscopic surgery versus open surgery in the elderly population. Group 2 aimed at comparing the elderly population versus the non-elderly population who underwent laparoscopic resection. Primary outcomes were intraoperative bleeding, postoperative complications, and mortality. Secondary outcomes included length of hospital stay, operative time, and complete tumor resection.

Literature search strategy

Online databases (MEDLINE, PubMed, EMBASE, and Scopus) were screened. Specific key words were entered

to identify all eligible studies: hepatic/liver laparoscopic resection, laparoscopic liver resection in the elderly/old. Additionally, the reference lists of eligible studies and other relevant review articles were cross-checked to identify additional relevant studies. Articles in English published before December 2017 were retrieved and reviewed if they met the selection criteria.

Study selection and quality assessment

The abstracts of the retrieved studies were independently and blindly screened for relevance by two reviewers (RM and MN). In order to achieve the highest sensitivity and specificity, records were selected for further analysis only if none of the reviewers rejected it. The selected studies were analyzed and data extraction was performed by both reviewers independently. Non-randomized studies were evaluated using the Newcastle–Ottawa Scale and the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. Any disagreement between the two reviewers during the process of selection and evaluation was discussed with the third and fourth reviewers (SR and PP).

Data extraction and analysis

Qualitative and quantitative analyses were performed with the data originating from the included studies. For dichotomous outcome data, the Mantel–Haenszel method was used

to estimate the risk ratio (RR, 95% CI). An RR of less than 1.00 was in favor of laparoscopy. Mean differences and 95% CI were used for continuous data. Outcome measures were extracted or calculated for each surgical approach (SD or median values). If SD was not reported, it was estimated according to the median rank and range. Heterogeneity was assessed with the I^2 statistic. Values of 25%, 50% and 75% were considered low, moderate, and high, respectively.

The pooled estimates of the mean differences were calculated using a random effect model to take into account potential inter-study heterogeneity and to adopt a more conservative approach. The robustness of the results and the potential sources of heterogeneity were then explored using sensitivity analyses. The pooled effect was considered significant with $p < 0.05$. The meta-analysis was performed using the RevMan software (version 5.3; Cochrane Collaboration).

Results

Literature search and selection

Figure 1 represents the PRISMA diagram followed by a selection of articles. Out of 740 studies initially identified, 700 were excluded after the screening of titles and abstracts because of irrelevance. A full-text evaluation of the remaining 40 articles was performed. In the end, nine studies were included in the meta-analysis, five of

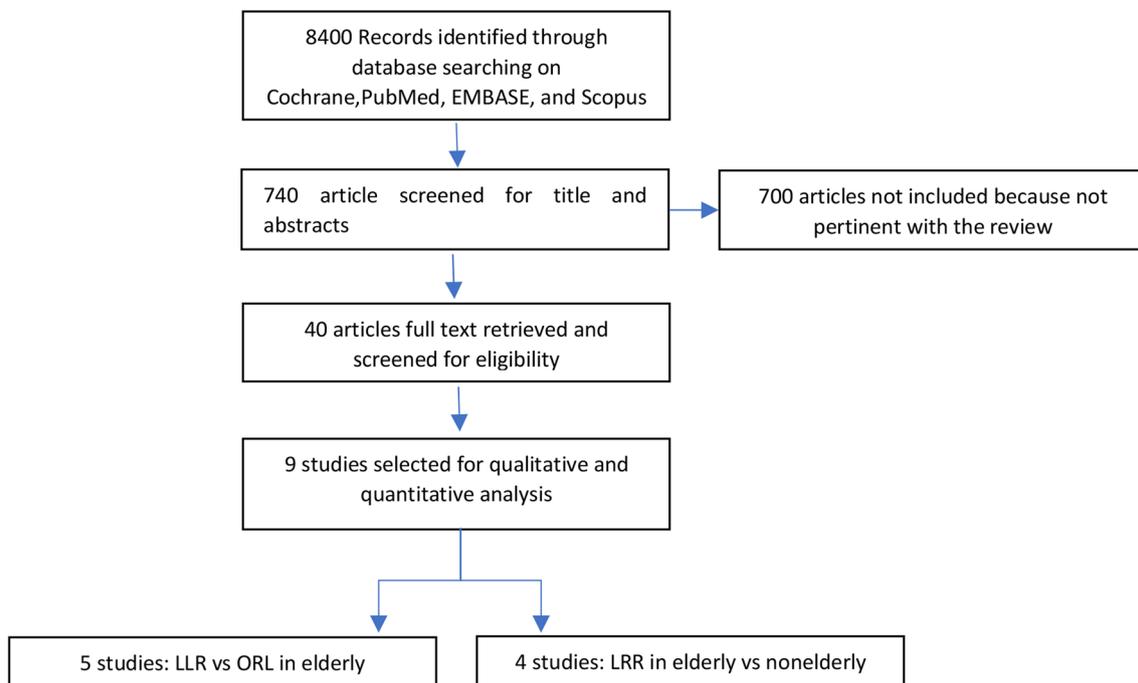


Fig. 1 PRISMA diagram

Table 1 Group 1 included studies in laparoscopic liver resection vs. open liver resection in the elderly population

Source	Period of study	Type of study	Age of cut-off (ys)	Approach	N° pt	Median age (range)	Type of pathology n° (%)	Max median tumor size in mm (range)	
Badawy [11]	March 2009–July 2016	R	70	LLR	40	75 (72–79)	HCC 27 (67.5) ICC 1 (2.5) Mts 12 (30)	22 (4–45)	
				OLR	40	76 (73–79)	HCC 33 (82.5) ICC 1 (2.5) Mtsp 6 (15)	23.5 (5–48)	
Amato [10]	Jan 2010–Dec 2014	R	75	LLR	11	77 ± 1.6*	HCC	35.45 ± 5.27*	
				OLR	18	78 ± 1.9*	HCC	39.83 ± 6.8*	
Chan [13]	Jan 2002–Dec 2012	R	70	LLR	17	73 (70–94)	HCC 12 (70.5) ICC 1 (5.9) Mts 4 (23.6)	30 (8–95)	
				OLR	34	74 (70–83)	HCC 17 (50) ICC 2 (5.9) Mts 16 (44.1)	30 (10–100)	
Martinez-Cecilia [14]	Jan 2005–Dec 2012	P	70	LLR	287	75 (70–89)	Mts CRC	28 (4–152)	
				OLR	488	74 (70–93)	Mts CRC	34 (3–164)	
Wang [17]	Jan 2008–Oct 2014	R	70	LLR	30	71 (70–81)	HCC 25 (83.3) ICC 5 (16.7)	40.0 (10.5–100.0)	
				OLR	60	73 (70–84)	HCC 57 (95) ICC 3 (5)	50.0 (20.0–100.0)	
Source	Number of lesions median (range)	Single/multiple n° (%)	Major resection n° (%)	Liver failure (%)	n°	Conversion n° (%)	Postoperative mortality, n° (%)	5 years OS (%)	5 years DFS (%)
Badawy [11]	1 (1–3)	34/6 (85/15)	0	5 (12.5)	0	0	0	47	60
	1 (1–2)	34/6 (85/15)	0	11 (27.5)	0	0	0	48	19
Amato [10]	1	11/0 (100/0)	0	NA	0	0	0	NA	NA
	1	18/0 (100/0)	2	NA	0	0	0	NA	NA
Chan [13]		14/3 (82.4/16.6)	0	NA	0	0	0	NA	NA
		22/12 (64.7/35.3)	0	NA	0	0	0	NA	NA
Martinez-Cecilia [14]		195/92 (68/32)	49 (17)	1 (0.3)	18 (6)	1 (0.3)	43	31	
		183/306 (37/63)	180 (37)	4 (0.8)		9 (2)	46	29	
Wang [17]		27/3 (90/10)	0	NA	0	0	0	NA	NA
		53/7 (88.3/11.7)	0	NA		0	0	NA	NA

R: retrospective; P: prospective; LLR: laparoscopic liver resection; OLR: open liver resection; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; MTS: metastatic tumor; CRC: colorectal cancer, * mean ± SD, NA: not available

which compared laparoscopic and open approaches in elderly patients (Table 1), while the other four focused on the effects of laparoscopic surgery on younger and older patients (Table 2).

Study characteristics

A total number of 497 elderly patients who underwent LLR were analyzed. In order to define the elderly population, the cut-off age was 70 in six studies and 75 in the three remaining studies.

Group 1: LLR vs. ORL in the elderly

Out of five selected studies published between 2014 and 2017 [10, 11, 13, 14, 17], only one was prospective [14]. A total of 1025 patients were included: 640 underwent OLR and 385 underwent LLR. The cut-off age for elderly patients was 70 in four studies. In 2016, only Amato et al. [10] considered 75 instead. The median age ranged from 71 to 78 and the oldest patient was 94 years old. The most common pathology was colorectal cancer liver metastasis (303 LLR and 510 OLR). Seventy-seven patients underwent LLR for hepatocarcinoma, while 125 received OLR for the same

Table 2 Group 2 included studies in laparoscopic liver resection in elderly vs. non-elderly patients

Source	Period of study	Type of pathology	Nr of Pt	Age of cut-off	Mean age, years (range)	Type of pathology n° (%)	Max median tumor size in mm (range)	Median number of lesions (range)
Uchida [18]	2010–2014	R	21	≥75	NA	HCC 15 (71.5) ICC 2 (9.5) CRC mts 2 (9.5) Other 2 (9.5)	29.0±18.1*	NA
			40	<75	NA	HCC 30 (75) ICC 1 (2.5) CRC mts 7 (17.5) Other 2 (5)	28.7±18.1*	NA
Spampinato [16]	2008–2012	R	25	≥70	73 (70–83)	HCC 9 (36) ICC 0 CRC mts 14 (56) Other 2 (8)	30 (10–83)	1 (1–5)
			35	<70	62 (33–69)	HCC 7 (20) ICC 0 CRC mts 23 (65.7) Other 5 (14.3)	25 (10–80)	1 (1–6)
Nomi [15]	1998–2013	R	31	≥70	75 (70–85)	CRC mts	34 (10–100)	2 (1–8)
Cauchy [12]	2000–2013	R	62	<70	59 (32–69)	CRC mts	35 (7–140)	2 (1–6)
			35	≥75	77.0 (75.0–86.2)	HCC 10 (28.6) ICC 6 (17.1) CRC mts 17 (48.6) Other 2 (5.7)	NA	NA
			139	<75	63.9±1.45*	HCC 26 (18.7) ICC 19 (13.6) CRC mts 77 (55.4) Other 23 (12.3)	NA	NA
			Source	Single/multiple (%)	Major resection n° (%)	Conversion n° (%)	Liver failure n° (%)	Postoperative mortality, n° (%)
Uchida [18]	NA	NA	3 (14.2)	0	0	0	NA	NA
	NA	NA	7 (17.5)	0	0	0	NA	NA
Spampinato [16]	NA	5 (20)	1 (4)	NA	0	0	23 (18 m)	22 (18 m)
	NA	13 (37.1)	3 (8.5)	NA	1 (2.8)	1 (2.8)	30 (23 m)	26 (23 m)
Nomi [15]	NA	20 (64.5)	4 (12.9)	3 (9.6)	0	0	57.9	38.5
	NA	42 (67.7)	6 (9.6)	8 (12.9)	0	0	61.7	35.3
Cauchy [12]	24/9 (68.5/31.5)	2	9 (25.7)	0	1 (2.8)	1 (2.8)	NA	NA
	59/80 (42.4/57.6)	25	17 (12.2)	6 (4.3)	4 (2.8)	4 (2.8)	NA	NA

E: elderly; NE: non-elderly; R: retrospective; P: prospective; LLR: laparoscopic liver resection; OLR: open liver resection; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; MTS: metastatic tumor; CRC: colorectal cancer, *mean±SD., m: months

tumor. Cholangiocarcinoma accounted for 1.2% of pathologies. Conversion rate was 0% in four studies. Martínez-Cecilia et al. [14] reported a 6% conversion rate. Of note, this is the only study, which included major LLR (49, 17%). The postoperative mortality rate was very low both in LLR and OLR (Table 1; Fig. 2).

Group 2: LLR in elderly vs. non-elderly patients

These four studies, published between 2012 and 2016, included 388 cases (112 elderly and 276 non-elderly) [12,

15, 16, 18] with a retrospective design. The cut-off age was 70 in two studies. In 2016, Cauchy et al. [12] divided the non-elderly into two subgroups. However, they were considered together in the statistical analysis. In 2014, Nomi et al. focused on colorectal cancer liver metastasis, while the other papers included other pathologies (LMCRC: 56.4%, HCC: 24.7%, ICC: 7.2%, other: 9.2%). The conversion rate ranged from 4 to 25.7% and from 8.5 to 17.5% for the elderly and the non-elderly, respectively (Fig. 3).

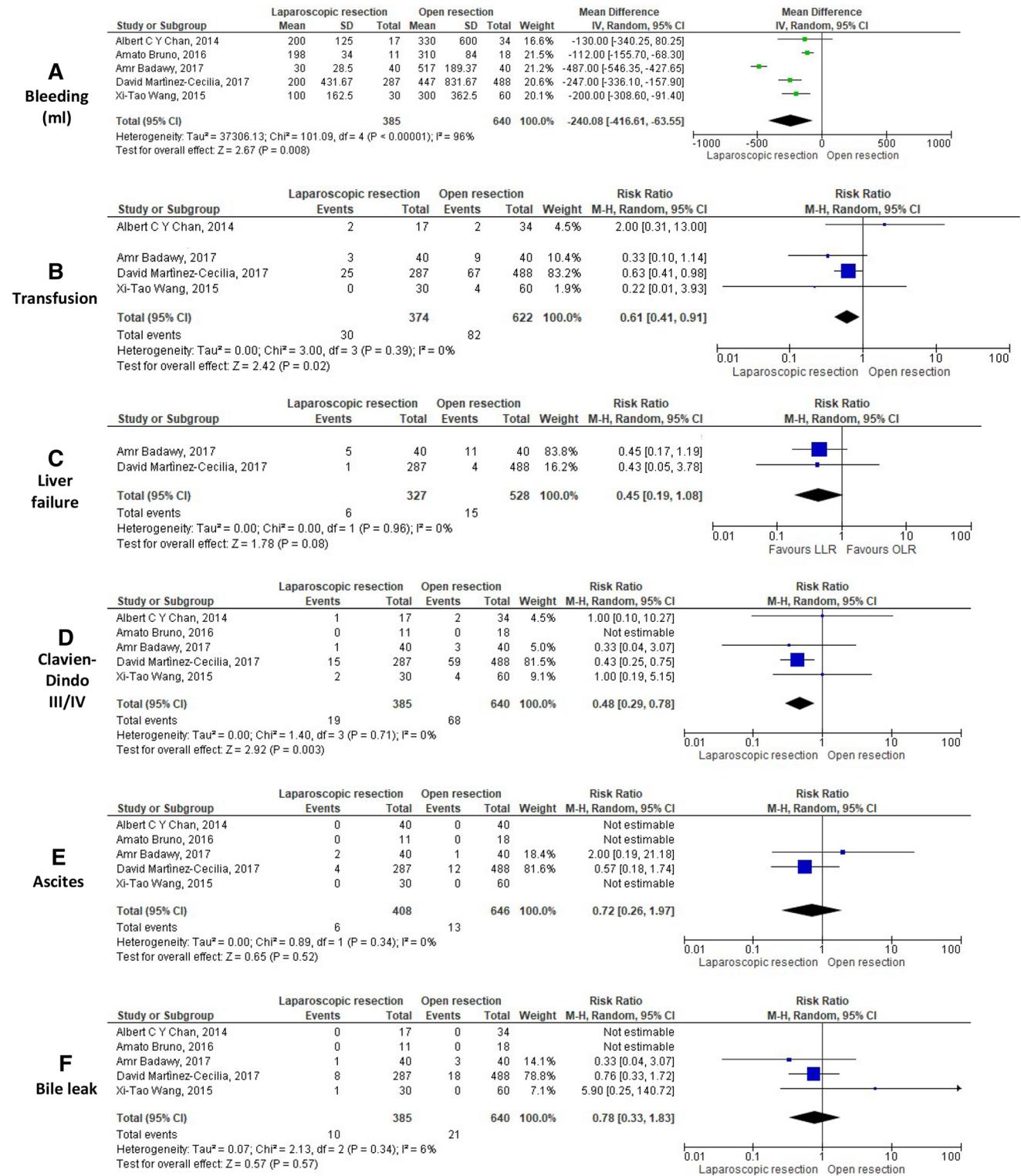


Fig. 2 Primary outcomes Group 1. Laparoscopic liver resection vs. open liver resection in elderly patients. **A** Intraoperative bleeding. **B** Transfusion. **C** Postoperative liver failure. **D** Clavien-Dindo III–IV complications. **E** Postoperative ascites. **F** Postoperative bile leak

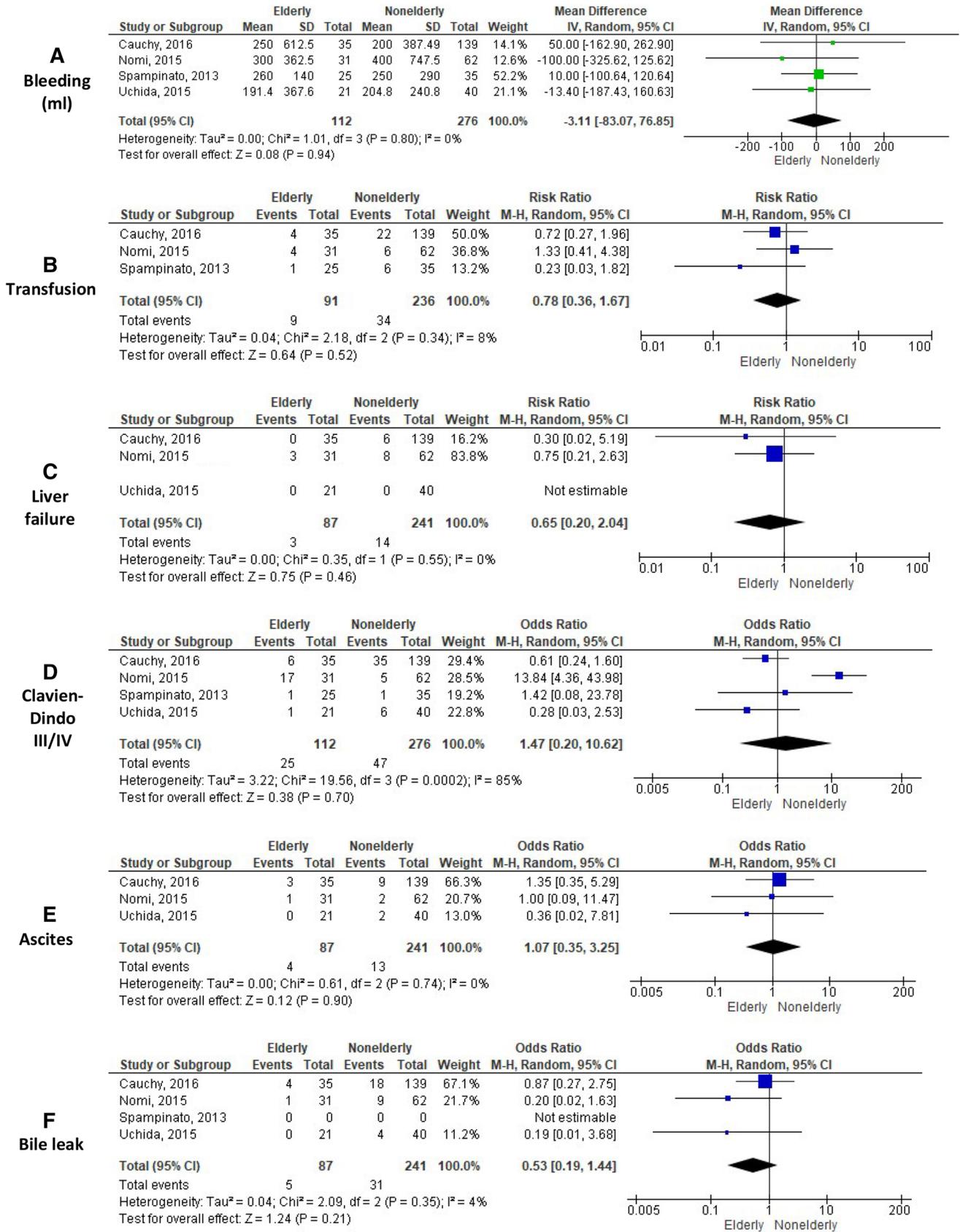


Fig. 3 Primary outcomes Group 2. Laparoscopic liver resection in elderly vs. non-elderly patients. **A** Intraoperative bleeding. **B** Transfusion. **C** Postoperative liver failure. **D** Clavien-Dindo III–IV complications. **E** Postoperative ascites. **F** Postoperative bile leak

Primary outcomes

Group 1: LLR vs. ORL in the elderly

Intraoperative blood loss was reported in all five selected studies. The overall MD between LLR and ORL was -240 mL (95% CI -416.61, -63.55; $p=0.008$), in favor of LLR, although a high heterogeneity index was noted between studies ($I^2=96%$). The need for blood transfusion (reported in four studies) was 8% in LLR and 13.1% in ORL, and the overall RR was 0.61 (95% CI 0.41, 0.91; $p=0.02$) with no heterogeneity ($I^2=0%$). The mortality rate was 0% in 4 out of 5 studies, and was consequently not suitable for a meta-analysis evaluation. The postoperative liver failure rate was reported in two studies. It occurred in 18.3% of LLR and in 28.4% of OLR, with a slight and insignificant overall difference (RR 0.45; 95% CI 0.19, 1.08; $p=0.08$; $I^2=0%$). The RR for Clavien-Dindo III/IV complications was 0.48 in favor of LLR (95% CI 0.29, 0.77; $p=0.003$) with an optimal heterogeneity index ($I^2=0%$). The analysis of surgical complications showed a similar incidence of postoperative ascites in LLR (RR 0.72; 95% CI 0.26, 1.97; $p=0.52$; $I^2=0%$). The postoperative bile leak rate was 2.5% in LLR and 3.2% in OLR with no significant difference (RR 0.78, 95% CI 0.33, 1.83; $p=0.57$, low heterogeneity $I^2=6%$) (Fig. 4).

Group 2: LLR in the elderly vs. the non-elderly

Intraoperative blood loss was reported in four studies, with little MD (-3.11) in favor of the elderly with no heterogeneity (95% CI -83.07, 76.85; $p=0.94$, $I^2=0%$). The blood transfusion rate was 9.8% in the elderly and 14.4% in the non-elderly, with an overall RR of 0.78 slightly in favor of the elderly (95% CI 0.36, 1.67; $p=0.52$, $I^2=8%$). Postoperative mortality RR was 0.78, in favor of the elderly, with no significant difference (95% CI 0.13, 4.63; $p=0.78$, $I^2=0%$). Postoperative liver failure was reported in 3 out of 4 studies, RR was 0.65 in favor of the elderly (95% CI 0.20, 2.04; $p=0.46$, $I^2=0%$). Clavien-Dindo III/IV complications were less frequent in non-elderly patients (RR 1.47; 95% CI 0.20, 10.62) with no significant results and a high heterogeneity ($p=0.7$, $I^2=85%$). Postoperative ascites and bile leak were reported equally in the elderly and the non-elderly (ascites RR 1.07; 95% CI 0.35, 3.25, $p=0.9$, $I^2=0%$; bile leak RR 0.53, 95% CI 0.19, 1.44, $p=0.21$, $I^2=4%$) (Fig. 5).

Secondary outcomes

Group 1: LLR vs. ORL in the elderly

LLR was associated with a shorter duration of hospital stay (MD -4.93 days). However, a high heterogeneity

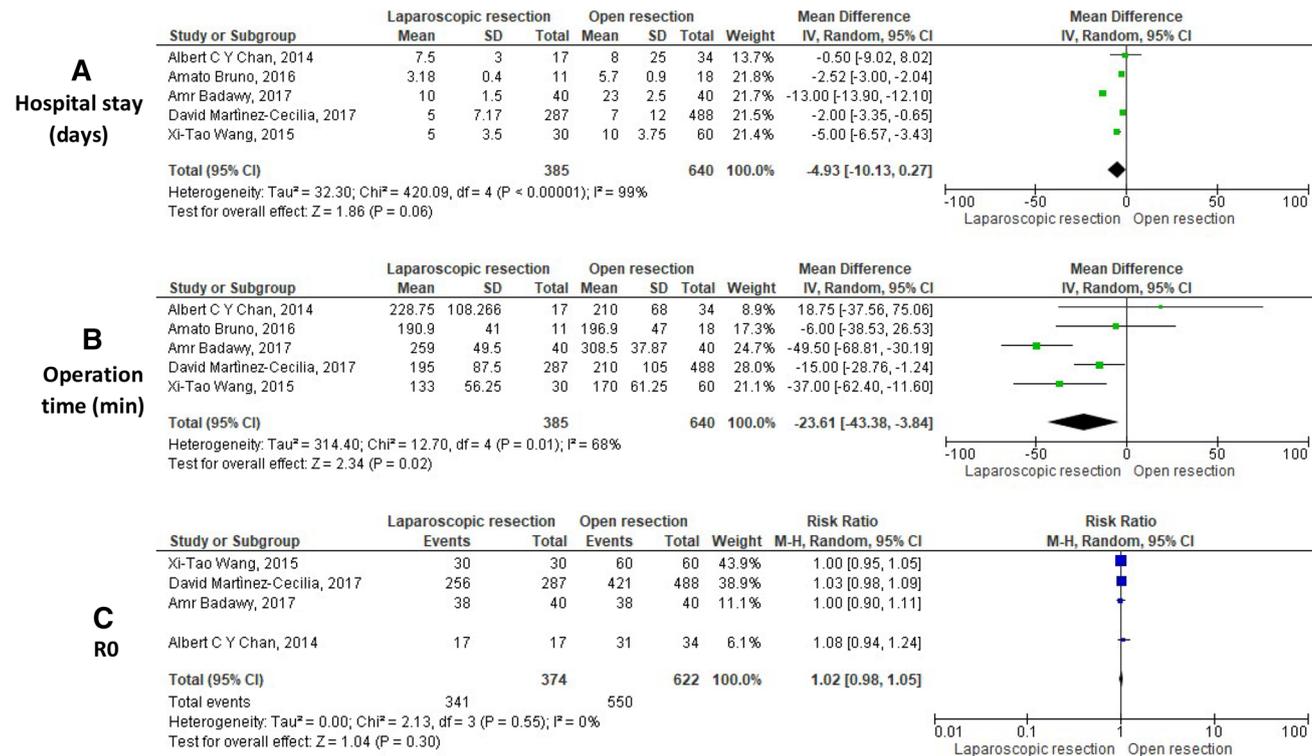


Fig. 4 Secondary outcomes Group 1. Laparoscopic liver resection vs. open liver resection in elderly patients. **A** Length of hospital stay. **B** Operation time. **C** Complete tumor resection R0

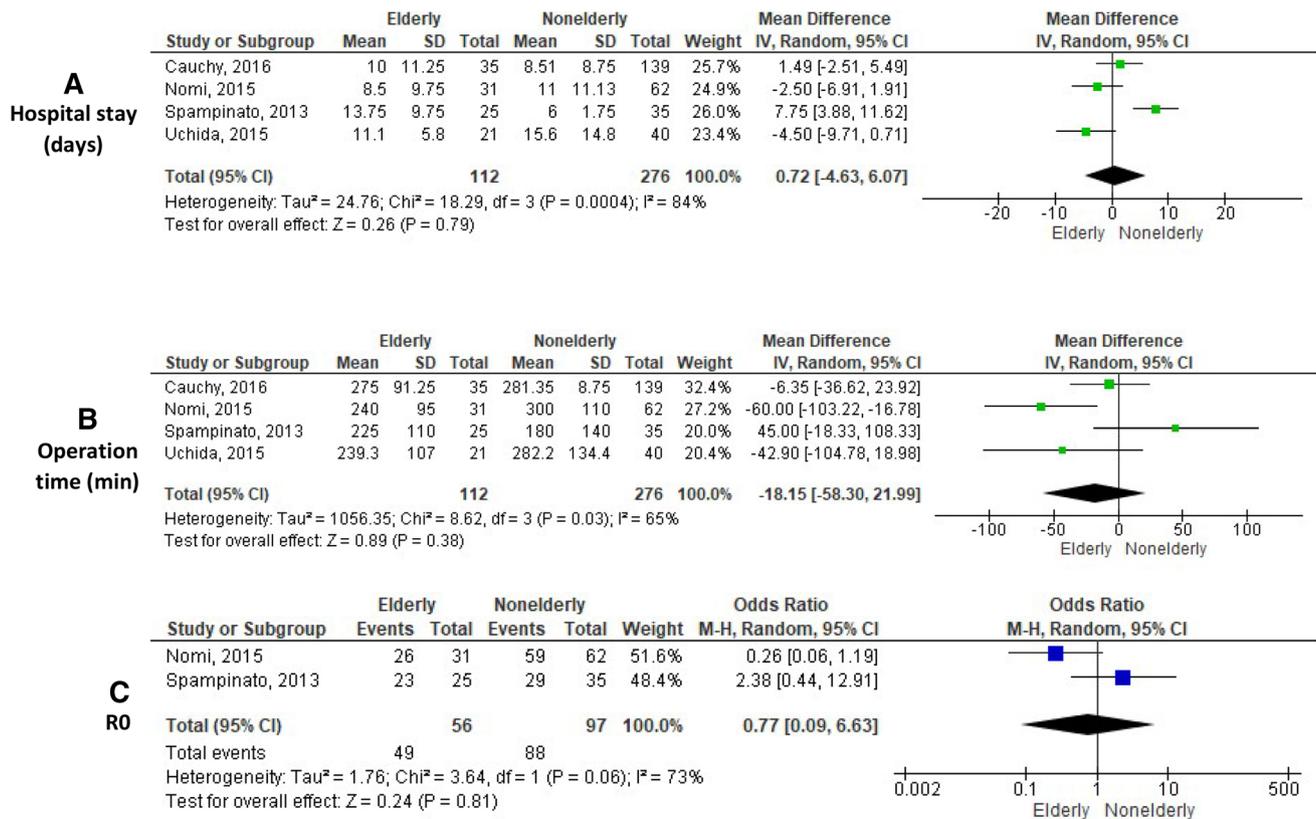


Fig. 5 Secondary outcomes Group 2. Laparoscopic liver resection in elderly vs. non-elderly patients **A** Length of hospital stay. **B** Operation time. **C** Complete tumor resection R0

index affected the overall statistical analysis (95% CI – 10.13, 0.27; $p = 0.06$; $I^2 = 99\%$). Operative time was shorter in LLR than in ORL (MD – 23.61 min; 95% CI – 43.38, – 3.84; $p = 0.02$) even if heterogeneity was moderate ($I^2 = 68\%$). Complete resection (R0) was reported in 4 out of 5 studies, and it was achieved in 91.1% and 88.4% in LLR and OLR, respectively. Any significant difference was identified (RR 1.06; 95% CI 0.88, 1.27; $p = 0.3$; $I^2 = 0\%$).

Group 2: LLR in elderly vs. non-elderly patients

Length of hospital stay between the elderly and the non-elderly had the MD of 0.72 days, with a high level of heterogeneity (95% CI – 4.63, 6.07, $p = 0.79$, $I^2 = 84\%$). MD of operation time was – 18.15 min in favor of the elderly (95% CI – 58.3, 21.99; $p = 0.38$, moderate heterogeneity level $I^2 = 65\%$). Total tumor resection was reported in 2 out of 4 studies and was 87.5% in elderly and 90.7% in non-elderly patients, with no significant difference (95% CI 0.09, 6.63; $p = 0.38$, high heterogeneity level $I^2 = 73\%$).

Discussion

After the 2014 International Consensus Conference, the OSLO-COMET trial represented a big step forward. Indeed, it was the first randomized controlled trial, which assessed the superiority of the laparoscopic approach for the treatment of colon cancer liver metastasis [20], in terms of postoperative complications, reduced intraoperative bleeding, and shorter hospital stay. The same advantages were observed for hepatocellular carcinoma laparoscopic treatment according to the retrospective propensity score analysis [21–24].

This review and meta-analysis focused on the elderly population aiming to demonstrate that laparoscopic liver resection is safe and feasible in this group of fragile patients. Concerning the rarity of paper on this subject, we included in our analysis studies in which cut-off of “elderly” was set at 70 years old or 75 years.

Our analysis showed that the laparoscopic approach significantly limited intraoperative blood loss, transfusions,

and postoperative Clavien–Dindo complications III/IV as compared to the open approach.

Complications usually associated with hepatic surgery, namely ascites, bile leak, and liver failure, had a similar rate in LLR and OLR. Oncological results in terms of R0 resection rate were similar for LLR and OLR.

The laparoscopic approach is usually associated with a shorter hospital stay due to lower abdominal pain, precocious bowel transit, and patient mobilization. Surprisingly, our meta-analysis did not evidence any significant difference between LLR and OLR, although there was a clear tendency towards a shorter hospital stay for LLR. This result can be explained by the fragility of the elderly population. The overall recovery period was indeed shorter but it was affected by the age of the considered population.

Operation time for LLR was shorter than for OLR. This can be explained by the fact that more difficult resections had been addressed using OLR in these studies.

Additionally, no significant difference was detected in terms of complications, blood transfusion or hospital stay after LLR among patients of different ages, which means that elderly patients can also benefit from laparoscopic liver resection, especially in terms of postoperative complications and need for transfusions.

Of note, laparoscopic surgery in elderly patients for other tumors, such as for colorectal cancer, has also been discussed. Randomized trials [25], multicentric trials [26], systematic reviews, and meta-analyses [27, 28] stated that elderly patients undergoing laparoscopic colorectal resection can benefit from a lower risk of blood transfusion, a lower rate of postoperative complications, a shorter postoperative ileus, fewer wound infections, with the same oncological accuracy. Longer operative time and pneumoperitoneum did not affect short-term pulmonary or cardiac complications. OS and DFS did not depend on the choice of the surgical approach. Additionally, the incidence of postoperative cognitive dysfunction in the elderly undergoing a longer laparoscopic colorectal surgery did not differ from the open approach, while the rate of stress-induced serum proteins (IL-6) was higher in case of open surgery [29].

These results have an important impact on the choice of the surgical approach. Indeed, age should not be considered as a limiting factor for laparoscopy because a minimal access is beneficial for higher-risk patients such as elderly people. However, our study is limited, due to the lack of analysis regarding comparable populations and the absence of randomized perspective studies, except for Martinez-Cecilia et al. in 2017. In addition, in the selected articles, long-term OS and DFS were not systematically reported (only by Spampinato in 2012 [16] and Nomi, 2014 [15] in Group 2, and by Badawy in 2017 [11], and by Martinez-Cecilia in 2017 [14], in Group 1). Another point to consider is the extensive period of time during which data were

collected, i.e., from the introduction to the latest experience in LLR. It also included a learning curve for laparoscopy. New randomized prospective comparative studies must be performed in order to better evaluate LLR vs. OLR in the elderly population.

In conclusion, in the era of increasing parenchymal sparing hepatectomies [30], enhanced recovery protocol, and increasing age of surgical patient [31], LLR is feasible and safe in selected elderly patient, with a better postoperative course and comparable oncological outcome.

Compliance with ethical standards

Disclosure Margherita Notarnicola, Emanuele Felli, Stefania Roselli, Donato Francesco Altomare, Michele De Fazio, Nicola de'Angelis, Tullio Piardi, Silvana Acquafredda, Michele Ammendola, Alessandro Verbo, Patrick Pessaux, and Riccardo Memeo have no conflicts of interest or financial ties to disclose.

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