The impact of mini-invasive right hepatectomy in the setting of living donation: a meta-analysis

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Abstract

Adult-to-adult living-donor liver transplantation (A2ALDLT) represents a challenging procedure, mainly when the right hepatic lobe is donated. Therefore, especially in Western countries, the medical community still considers it a “risky procedure”. The present meta-analysis investigated the postoperative results reported in donors undergoing right hepatectomy for A2ALDLT through a minimally invasive liver resection (MILR) vs. open liver resection (OLR) approach, with the intent to clarify the hypothesis that the MILR approach should minimize the risks for the donor. A systematic literature search was performed using MEDLINE-PubMed, Cochrane Library, and EMBASE electronic databases. The primary outcome investigated was the complication rate after transplant. Fifteen studies were included (n = 2094; MILR = 553 vs. OLR = 1541). The MILR group only merged the statistical relevance in terms of advantage in terms of a lower number of complications (OR = 0.771, 95% CI 0.578–1.028; P value = 0.077). Investigating the complications ≥ IIIa according to the Dindo-Clavien classification, the estimated blood loss, and the length of hospital stay, no statistical difference was reported between the two groups. MILR represents a novel and promising approach for improving the results in A2ALDLT. However, no benefits have been reported regarding blood loss, length of stay, and postoperative complications. More extensive experiences are needed to re-evaluate the impact of MILR in right lobe live donation.

Keywords Laparoscopic · Living donor right hepatectomy · Living donor liver transplantation · Minimally invasive · Robotic · Hand-assisted · Laparoscopic-assisted

Abbreviations

A2ALDLT Adult-to-adult living-donor liver transplantation
CI Confidence intervals
I2 Higgins statistic squared
LDLT Living-donor liver transplantation
MILR Minimally invasive liver resection
OLR Open liver resection
OR Odds Ratio
PRISMA Preferred Reporting Items for Systemic Reviews and Meta-Analysis
WMD Weighted mean difference

Introduction

The considerable progress made in conventional liver surgery and the experience gained from technical variants of whole liver transplantation consented to develop the first living-donor liver transplantation (LDLT) experiences [1, 2]. However, mainly in the specific setting of adult-to-adult (A2A)LDLT, several concerns were raised in terms of donor safety [3]. These obstacles were successfully overpassed in Asian countries, where the problem of deceased donation shortage was critical due to religious and cultural issues [4]. Therefore, the first series of A2ALDLT were performed using a left or a right hepatic lobe [5, 6]. However, A2ALDLT remains a challenging procedure, mainly when the right hepatic lobe is donated. This datum explains why, especially in Western countries, the medical community still considers the right hemi-liver donation as a “risky procedure” to be performed with caution and under certain conditions [7]. With the intent to minimize the risks of donation, the use of a minimally invasive liver resection (MILR) approach for liver donation has been postulated...
instead of a standard open liver resection (OLR). Increasing evidence has been reported on the safe use of MILR in several different liver diseases, as clearly stated in the Consensus Conferences of Louisville 2008, Morioka 2014, and Southampton 2017 [8–10]. Recently, International Expert Consensus Guidelines have been published explicitly investigating the impact of MILR in the setting of liver donation [11]. However, some questions still require a definitive answer, mainly in the right lobe MILR for A2ALDLT. With the intent to answer to these questions, we decided to perform a meta-analysis able to investigate the postoperative results reported in donors undergoing right hepatectomy for A2ALDLT through MILR vs. OLR approach. Our hypothesis, derived from the hepatic resection experiences, was that the MILR approach should decrease the risks of postoperative adverse course in the donors.

Materials and methods

Research strategy

Systematic research has been carried out on the role of MILR in A2ALDLT. The research strategy was carried out following the guidelines of the “Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA)” and the PRISMA for abstracts [12].

The specific research question formulated in this study includes the following components of PICO:

Patient: an individual undergoing right hepatectomy for A2ALDLT;

Intervention: right hepatectomy performed with MILR;

Comparison: right hepatectomy performed with OLR;

Outcome: duration of surgery/intraoperative blood loss/post-operative transaminases peak/any post-operative complication/post-operative Dindo-Clavien complication ≥ IIIa/duration of post-operative hospitalization.

A search was performed through MEDLINE-PubMed, Cochrane Library and EMBASE electronic databases, using the following keywords: “(liver OR hepat*) AND (transplant*) AND (laparosc* OR robot*) AND (donor OR donation)”. Studies published before September 01, 2020 have been evaluated.

Screening process

The qualitative systematic review included “a priori” research of scientific articles concerning adult patients (age > 18 years). Only articles in the English language were considered. All the studies with a comparative analysis between MILR and standard OLR for A2ALDLT donation were considered eligible. Exclusion criteria in the selection of the articles were: (a) insufficiently detailed articles; (b) reviews; (c) non-clinical studies; (d) expert opinions; (e) letters to the editor; (f) conference summaries; and (g) case reports. When studies coming from the same center were identified, a check for data overlapping was performed. In the case of overlapping, we considered only the study with the most considerable reported experience. Two independent authors (QL and FG) performed the screening process of the articles. During article selection, potential differences were resolved through consensus with a third reviewer (MR).

Data extraction

After the screening process, the selected articles’ full text was analyzed in detail for data extraction. Two independent authors (QL and FG) performed data extraction and compared the results. During data extraction, potential differences were resolved through consensus with a third reviewer (MR).

The characteristics derived from each study were collected in Tables 1, 2 and 3. The following characteristics were collected: author, year, type of surgical approach, type of incision, conversion in case of minimally invasive approach, age, sex, BMI, duration of surgery, estimated blood loss, complications, rate of complication ≥ IIIa according to Dindo-Clavien classification, postoperative AST peak, postoperative ALT peak, and duration of hospitalization.

Quality assessment

The selected studies have been systematically reviewed to identify potential sources of error. The work quality was defined using the Risk of Bias In Non-randomized Studies of Interventions (Robins-I) tool [13].

Statistical analysis

The meta-analyses were performed using the OpenMetaAnalyst [14]. The continuous variables were expressed as average ± standard deviations. Continuous variables reported as medians in the included studies were transformed into means and standard deviations (https://smcrath.shinyapps.io/estmeansd/) [15]. In continuous data, the Weighted Mean difference (WMD) was used as a summary measure between the groups. For dichotomous data, the Odds Ratio (OR) was used. In both the measurements, 95% confidence intervals (95% CI) were also reported. The statistical heterogeneity was evaluated with the Higgins statistic squared ($I^2$). $I^2$ values were considered indicative of heterogeneity among the studies: low = 0–25%; 26–50% = moderate; ≥ 51% = high. The fixed-effects model was used when low-to-moderate (0–50%) heterogeneity was detected among the studies. The random-effects model was used when high heterogeneity
was reported. A P value < 0.05 was considered indicative of statistical significance.

Results

Characteristics of selected articles

The article selection process is explained in Fig. 1. A total of 333 articles was initially identified for screening. A further article was added after a manual search. Two hundred and sixty-eight articles were removed according to their title or abstract evaluation. Of the 66 remaining papers, 21 were excluded after the entire text evaluation. Fifteen articles were excluded from the analysis as reviews, letters to the editor, and commentaries. Nine articles were removed because exclusively dedicated to pediatric LDLT or reporting a mixed adult/pediatric activity. Six articles were further removed because they reported overlapping data. Lastly, 15 studies were selected for a total of 2094 cases investigated. The MILR cases were 553 (26.4%), and the OLR 1,541 (73.6%) [16–30].

Regarding the quality of the studies reported, all the articles investigated were retrospective cohort studies with a low risk of bias according to the criteria proposed by Robins-I. No randomized controlled trials were present among the selected studies. Figure 2 shows the overall high quality of the studies identified.

Surgical techniques

As reported in Table 1, a laparoscopic-assisted approach was reported in nine articles (n = 302/553; 54.6%). A hand-assisted technique was performed in two studies (n = 45/553; 8.1%). These procedures were classified in the “hybrid” subgroup (n = 347/553; 62.7%).

Pure laparoscopy (n = 158/553; 28.6%) and robotic (n = 48/553; 8.7%) surgery were documented in two articles each. Both these procedures were classified in the “pure laparoscopy” subgroup (n = 206/553; 37.3%).

A progressive numerical increment of the MILR cases was reported across the years (Fig. 3A). Contextually, a change in the different MILR techniques adopted was observed during the years (Fig. 3B). During the period 2009–2015, only laparoscopic-assisted and hand-assisted cases were reported. Contrarily, the pure laparoscopy and robotic cases were observed only during the period 2016–2020.

Data on conversion from minimally invasive to open approach were reported in 12 articles (n = 454). A total of

| Author [References] | Center | Year | MILR | Type | Conversion | Incision in MILR | OLR | Incision in OLR |
|---------------------|--------|------|------|------|------------|-----------------|-----|---------------|
| Baker [16]          | Chicago, US | 2009 | 33   | LA   | 2          | 5-cm upper midline | 33  | J-shaped      |
| Choi [17]           | Catholic University Seoul, Korea | 2012 | 20   | LA   | NA         | 15-cm right subcostal + 3 ports | 90  | Right subcostal |
| Nagai [18]          | Detroit, US | 2012 | 28   | LA   | 0          | 10-cm UML         | 30  | J-shaped      |
| Ha [19]             | Asan Medical Center Seoul, Korea | 2013 | 20   | Hand-assisted | 0 | 8-cm right subcostal + 3 ports | 20  | 10- or 12-cm right subcostal |
10/454 (2.2%) conversions were observed. Most of the conversions (7/10 cases) occurred during a pure laparoscopic approach, while the conversion occurred in three cases during a laparoscopic-assisted approach. In detail, the conversion during a pure laparoscopic approach was seen in 7/158 (4.4%) cases, followed by 3/290 (1.0%) donors approached with a laparoscopic-assisted technique. No conversions were reported in the 48 and 20 donors handled with a robotic or hand-assisted approach, respectively.

### Donor characteristics

The differences between the MILR and OLR group in terms of donor characteristics were reported in Table 2. As for the donor age, the MILR group showed a younger population ($P$ value = 0.008). Regarding the donor sex, more males were observed in the MILR group ($P$ value = 0.027). No differences were reported in terms of BMI value between the two groups ($P$ value = 0.472).

### Postoperative course

Table 3 reported the postoperative course of the donors. As expected, a shorter operative duration was required in the OLR cases ($P$ value = 0.020).

No other significant differences were observed between the MILR and OLR cases. Similar results were observed also when the estimated blood loss ($P$ value = 0.384) and the length of hospital stay ($P$ value = 0.972) were investigated.

### Complications after right hepatectomy

The number of donors experiencing a complication was clearly detailed in 14 studies (Table 3). In fact, in the study written by Choi et al. [21], only the total number of complications was reported instead of the number of donors experiencing a complication. Therefore, this study was not included for this meta-analysis.
A total of 100/528 MILR (18.9%) and 173/1057 OLR (16.4%) cases presented any grade of complication after donation. No statistical difference was reported between the two groups, with the MILR group only merging the statistical relevance in terms of advantage in terms of a lower number of complications (OR = 0.771, 95% CI 0.578–1.028; P value = 0.077) (Fig. 4). This datum was confirmed investigating separately the two sub-groups of MILR patients receiving a “hybrid” (laparoscopic-assisted and hand-assisted) or “pure laparoscopic” (robotic and pure laparoscopic) of MILR (Fig. 4).

Only investigating the complications ≥ IIIa according to the Dindo-Clavien classification, 38/528 MILR (7.2%) and 60/1057 OLR (5.7%) cases were reported (Table 3). Importantly, no grade IV or V cases were observed in all the reported series. Also in this case, no statistical difference was reported between the two groups (OR = 0.837, 95% CI 0.578–1.278; P value = 0.401) (Fig. 5). This datum was further confirmed by investigating separately the two sub-groups of MILR patients receiving a “hybrid” (laparoscopic-assisted and hand-assisted) or “pure laparoscopic” (robotic and pure laparoscopic) of MILR (Fig. 5).

Discussion

MILR has been introduced into clinical practice in the setting of living donation to reduce the potential risks of
morbidity and mortality for the donor. As clearly reported in several studies, MILR consents to achieve several results when compared with OLR: (a) to minimize tissue trauma, (b) to reduce postoperative pain, (c) to achieve better aesthetic results by improving the psychosocial outcome of the donor, and (d) to allow a faster postoperative recovery and an early return to normal daily activities [8–10].

In the setting of left lateral sectionectomy as part of an adult-to-child live donation, the benefits of MILR have been largely explored [31, 32]. As a further confirmation of this evidence, the recent guidelines published on MILR and liver donation stated that “pure laparoscopic” donor hepatectomy is applicable to left lateral sectionectomy and should be considered standard practice once the team has fulfilled the adequate learning” [11].

On the opposite, more controversial results exist on the benefits of MILR for right hepatectomy in the setting of A2ALDLT. Conflicting results exist even in the meta-analyses already published on this topic [33–35].

Berardi reported in a meta-analysis (number of studies = 6; MILR = 171 vs. OLR = 223) that mini-invasive and open cases had similar results in terms of blood loss rates (P value = 0.45), operative time (P value = 0.45), and overall donor morbidity (P value = 0.86). On the opposite, the hospital stay duration was shorter in the MILR group (P value = 0.30) [33].

Zhang et al. [34] published another meta-analysis (number of studies = 7; MILR = 187 vs. OLR = 499) in which the mini-invasive approach reduced the intraoperative blood loss rates (P value = 0.002). However, no significant differences were reported in postoperative complications (P value = 0.80) and length of hospital stay (P value = 0.35).

Lastly, a meta-analysis published by Li et al. [35] (7 studies; MILR = 220 vs. OLR = 709) showed no difference in terms of post-operative complications (P value = 0.21), surgery duration (P value = 0.43), and blood loss rates (P value = 0.96).

In the present study, similar results were observed. No clear differences were reported in the postoperative clinical course when MILR and OLR cases of right hepatectomy for A2ALDLT were compared. As previously reported in the other meta-analyses [33–35] the MILR and OLR cases showed similar blood losses (P value = 0.38), AST and ALT peaks after surgery (P value = 0.09 and 0.08, respectively), postoperative complications (P value = 0.08), complications ≥ IIIa (P value = 0.40), and lengths of hospital stay (P value = 0.97).

The only significant datum was the longer duration of the MILR with respect to the open approach (P = 0.02), being this latter evidence not completely surprising when complex laparoscopic approaches are compared with open ones, mainly at the beginning of the learning curve [36].

With respect to the previously reported meta-analyses, the present study has the great benefit of investigating a larger number of cases (15 studies, n = 2094), with a total of 553 MILR cases, the largest even explored so far.
Such a beneficial numerical effect has also been corroborated by the possibility of investigating different minimally invasive approaches. Consequently, we were able to perform, for the first time, specific sub-analyses exploring separately only the hybrid (laparoscopy-assisted and hand-assisted) and the "pure laparoscopic" types of MILR (robotic and pure laparoscopy).

Thanks to these separate analyses, further investigation was given to the impact of MILR vs. OLR concerning the postoperative complications. However, the sub-analyses focused on "pure laparoscopy" approaches only further failed to show any difference between MILR and OLR. If we consider the cut-off of 50 procedures proposed by Rhu et al. for surpassing the learning curve [36], only a limited number of series was able to overpass it [17, 29, 30]. Approximately 40% of the reported MILR cases have been published only during 2020, and the pure laparoscopic approaches started to be published only in the last 4 years. Therefore, we can postulate that the complications reported in the present analysis should be affected by the surgeons' relatively short learning curve. In many cases, the reported studies investigate the first "laparoscopic" series of experienced "open" centers [11]. For this reason, the recent already cited international guidelines strongly recommend considering the laparoscopic approach as "applicable to selected right liver grafts". We can only postulate that the growing experience in MILR will consent to observe a progressive reduction of complications in the next future.

Unfortunately, some critical issues were impossible to be investigated in the present study. As an example, it is strongly recommended in the international guideline, "large grafts and deviation from standard biliary and vascular anatomy may increase the difficulty of MILR procedure in right-lobe donation" [11]. These critical elements were impossible to be explored between the MILR and OLR groups, therefore adding a potential selection bias when the mini-invasive or open approach was decided. As a potential confirmation of a sort of selection of "easier" cases using the laparoscopic approach, we reported in our meta-analysis that younger cases were present in the MILR group (\(P\) value = 0.008).
Furthermore, one additional potential indirect observation comes from the result that more men were observed in the MILR group ($P$ value = 0.027). It has been suggested that women more frequently present variations of biliary anatomy, making more challenging a MILR in a patient with such an anatomical condition [37, 38].

Another important aspect requiring further investigations is the role of the robotic approach. Only two studies reported robotic series [24, 28], limiting our possibility of further exploring the role of robotic surgery in this field. Lastly, relevant aspects like the use of different surgical instruments, the use of the Pringle Maneuver, and the vascular/biliary division methods need further studies to explain better their impact in the setting of MILR A2AL-DLT donation.

In conclusion, MILR represents a novel and promising approach for improving adult-to-adult liver live donors' results. However, this surgery still pays the fee of having been only recently introduced. Therefore, no benefits have been reported regarding blood loss, length of stay, and post-operative complications. More extensive experiences are needed to re-evaluate the impact of MILR in right lobe live donation.
Fig. 4 Forest plots and meta-analyses on the appearance of any complication grade according to Dindo-Clavien: A hybrid (laparoscopic-assisted and hand-assisted) vs. open; B pure laparoscopic (robotic and pure laparoscopic) vs. open; C all MILR techniques vs. open
Fig. 5 Forest plots and meta-analyses on the appearance of complications ≥ IIIa according to Dindo-Clavien: A hybrid (laparoscopic-assisted and hand-assisted) vs. open; B pure laparoscopic (robotic and pure laparoscopic) vs. open; C all MILR techniques vs. open
Author contributions QL and FG contributed to the conception and design of the study; QL and FG contributed to the acquisition of data; QL, FG, and GB analyzed and interpreted the data; QL and FG drafted the article; GM, GB, and MR critically revised the manuscript; all authors approved the final version.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare about the present study.

Ethical approval This is a review study which has been conducted in accordance with the ethical standards as laid in the 1964 Helsinki Declaration.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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