META-ANALYSIS

Considering extended right lobe grafts as major extended donor criteria in liver transplantation is justified

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SUMMARY

The outcomes of split-liver transplantation are controversial. This study compared outcomes and morbidity after extended right lobe liver transplantation (ERLT) and whole liver transplantation (WLT) in adults. MEDLINE and Web of Science databases were searched systematically and unrestrictedly for studies on ERLT and its impact on graft and patient survival, and postoperative complications. Graft loss and patient mortality odds ratios (OR) and 95% confidence intervals (CI) were assessed by meta-analyses using Mantel–Haenszel tests with a random-effects model. Vascular and biliary complications, primary nonfunction, 3-month, 1-, and 3-year graft and patient survival, and retransplantation after ERLT and WLT were analyzed. The literature search yielded 10 594 articles. After exclusion, 22 studies (n = 75 799 adult transplant patients) were included in the analysis. ERLT was associated with lower 3-month (OR = 1.43, 95% CI = 1.09–1.89, P = 0.01), 1-year (OR = 1.46, 95% CI = 1.08–1.97, P = 0.01), and 3-year (OR = 1.37, 95% CI = 1.01–1.84, P = 0.04) graft survival. WL grafts were less associated with retransplantation (OR = 0.57; 95% CI = 0.41–0.80; P < 0.01), vascular complications (OR = 0.53, 95% CI = 0.38–0.74, P < 0.01) and biliary complications (OR = 0.67; 95% CI = 0.47–0.95; P = 0.03). Considering ERLT as major Extended Donor Criteria is justified because ERL grafts are associated with vasculobiliary complications and the need for retransplantation, and have a negative influence on graft survival.

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Key words
extended right lobe liver transplantation, major extended donor criteria, meta-analysis, split-liver transplantation

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Introduction

In times of organ shortage and longer waiting lists for organ transplants with high mortality rates, split-liver transplantation has become an attractive way for two recipients to benefit from one deceased donor graft. This technically complex and challenging procedure was introduced in 1988 and has become more significant as experience with liver splitting techniques has increased [1–3]. After the donor liver is split conventionally, a pediatric recipient receives the left lateral liver graft and the extended right liver lobe is transplanted into an

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adult patient with end-stage liver disease [2]. Only optimal, high-quality organs are considered for split-liver transplantations [4,5]. In addition, an optimal donor-recipient match, short cold ischemia time, and technical expertise are essential for a successful split-liver transplantation [5,6].

Donor quality has continuously decreased since the model of end-stage liver disease (MELD) score was introduced and the donor organ shortage has dire consequences for patients with end-stage liver disease [7]. OPTN data indicate that 20% of patients with a non-fulminant course of liver disease and high MELD score either die waiting for transplantation or drop out from the waiting list because their condition deteriorates [8]. In Eurotransplant, up to 30% of patients drop out from the waiting list because of death or disease progression [9]. The shortage of donor organs, especially in Eurotransplant, has encouraged the use of major extended donor criteria (maEDC: macrovesicular steatosis >40%, donor age >65 years, and cold ischemia time >14 h) organs, despite reports that these organs produce non-optimal results and affect graft and patient survival after transplantation [10–12]. Split-liver transplantation is an established procedure and an attractive way of expanding the limited organ pool for pediatric and adult graft recipients that may offer solution to the problem of chronic organ shortage. However, choices to perform split-liver transplantation are made on case-by-case basis and the procedure's outcomes are controversial. In Eurotransplant, deceased donor split-liver transplantation is ~5% of all liver transplantation cases, and OPTN reported a similar rate [6,13]. The 50/50-rule considers each liver from a donor who meets the conditions ≤50 years of age and ≥50 kg body weight for splitting, and increases awareness for split-liver transplantation in Eurotransplant [14]. Organs considered for splitting are allocated primarily to recipients with highest priority (mostly children) and unused splits are reallocated to another center, but this reduces the rates of in situ split and prolongs cold ischemia [4].

The comparison of outcomes following extended right lobe liver transplantation (ERLT) and whole liver transplantation (WLT) is retrospective. Graft and patient survival after ERLT are comparable to those after WLT, but higher biliary and vascular complication rates were reported following ERLT [6,15–20]. With an evident lack of prospective and randomized controlled trials, this systematic review and meta-analysis aimed to evaluate and compare graft and patient survival following ERLT and WLT in adult transplant recipients, and to assess differences in retransplantation and biliary and vascular complication rates between the two procedures.

Methods

This systematic review and meta-analysis adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. The analysis was conducted according to a pre-defined protocol, which is available upon request.

Literature search

MEDLINE and Web of Science databases were searched systematically and without any restrictions on date of publication as previously reported [22]. Studies comparing the effect of ERLT on graft and patient survival in adult transplant recipients published until December 2020 were identified. Citations of relevant articles were also screened for additional eligible studies. The search terms used were: ("transplantation" OR "transplant") AND ("liver" OR "hepatic") AND ("split" OR "partial" OR "extended right-split" OR "extended right lobe" OR "right extended lobe" OR "right extended graft" OR "full right").

Terminology and definitions

A conventional split divides the liver along the umbilical fissure to the extended right lobe (including Couinaud segments I, IV–VIII) and the left lateral lobe (including Couinaud segments II and III).

Eligibility criteria

The Population, Intervention, Comparison, Outcome, Time, and Study design (PICOTS) strategy was used to select studies with the following inclusion criteria:

- Population: adult transplant recipients over the age of 18 years with end-stage liver disease undergoing ex vivo ERLT or WLT for the first time.
- Intervention: ERLT.
- Comparator: WLT.
- Outcome: overall vascular complications, portal vein complications, hepatic artery thrombosis, overall biliary complications, anastomotic bile leakage, anastomotic and non-anastomotic biliary strictures, primary non-function (PNF), graft and patient survival, and retransplantation.
- Time: 3-month, 1-, and 3-year following liver transplantation.

• Study design: any study design (cross-sectional, case-control, and cohort studies) except study protocols, narrative or systematic reviews, common overviews, letters, case reports, experimental studies, and conference abstracts [23].

Studies without these inclusion criteria were excluded. Studies that did not report outcomes of interest and, therefore, did not contribute data suitable for meta-analysis were excluded. Studies that assessed the same patient collective more than once without providing additional information were also excluded. Full left split-liver transplantations were excluded because this procedure involves central dissection to give two smaller liver grafts, so it is not comparable to the conventional ERL split-liver technique. Articles were carefully reviewed to exclude overlapping reports and duplicate publications. Studies in languages other than English and German were also omitted. Two reviewers screened article titles and abstracts according to the inclusion and exclusion criteria, and the resulting full-text articles were further assessed for eligibility based on the inclusion criteria. Study data were extracted using a standardized data sheet. A third reviewer resolved any discrepancies.

Outcomes

Differences in vascular and biliary complications between the ERLT and WLT groups were assessed. Based on previous reports, portal vein thrombosis, hepatic artery thrombosis, and vascular complications in general were analyzed. We also analyzed anastomotic and non-anastomotic biliary leaks, anastomotic and non-anastomotic biliary strictures, and biliary complications in general. The main outcome of this meta-analysis was the influence of ERLT on PNF, 3-month, 1-, and 3-year graft and patient survival, and retransplantation. Graft survival was a combined endpoint, defined as the time from liver transplantation to either patient's death or retransplantation (whichever came first). Patient survival was defined as the time between the initial (primary) liver transplantation and death or last known contact.

Quality assessment

Study quality was evaluated using a checklist of the methodological quality of non-randomized studies (NRS) and healthcare interventions. Quality of data reporting, external and internal validity, and study power were determined [24]. The methodological index for NRS (MINORS) was used to assess study quality according to eight items (study aim, inclusion of consecutive patients, prospective data collection, endpoints appropriate to the aim, unbiased evaluation of endpoints, prospective sample size calculation, duration of follow-up, and loss to follow-up) which were scored as 0 (not reported), 1 (inadequately reported), or 2 (adequately reported) [25]. Studies with more than 12 points were considered high quality, studies with 8–12 points were considered intermediate quality, and studies with less than eight points were considered low quality. The risk of bias was considered high and the evidence quality was considered low if the study did not address the issues for each specific domain. Studies with low risk of bias were considered to provide high quality of evidence.

Statistical analysis

R(R Foundation for Statistical Computing, Vienna, Austria, 2019; https://www.R-project.org) was used for statistical analysis. Potential publication bias was evaluated using funnel plots and funnel plot's symmetry was evaluated using the Egger's test. Dichotomous data were presented as odd ratios (OR) with 95% confidence intervals (CI). The results of studies were pooled and an overall estimate of OR was obtained from a random-effects model, as this methodology takes into account any differences between studies even if there is no statistically significant heterogeneity. As previously reported, the Mantel–Haenszel random-effects model was used because the study samples were heterogeneous [26,27]. The statistical heterogeneity between included studies was evaluated using the I^2 index. If the I^2 index was between 50% and 75%, heterogeneity was moderate, and if the I^2 index was >75%, heterogeneity was considerable. A P value <0.05 was considered significant in all analyses.

Results

Study selection and selection criteria

The literature search yielded 10 594 potentially eligible articles. After excluding duplicates and screening titles and abstracts, the full texts of 228 articles were further assessed for eligibility. Of these, 202 articles were excluded because they presented no quantitative data about the endpoints (n = 63) and because the patients did not meet the inclusion criteria (n = 139). This left 26 studies that were included in the qualitative analysis (Fig. 1). Only studies that clearly described the splitting techniques, evaluated outcome of ERL liver grafts compared with WL grafts, and did not analyze overlapping collectives were eligible for analysis of ERLT and WLT outcomes [6,15,18,19,28–45]. Despite the high quality,

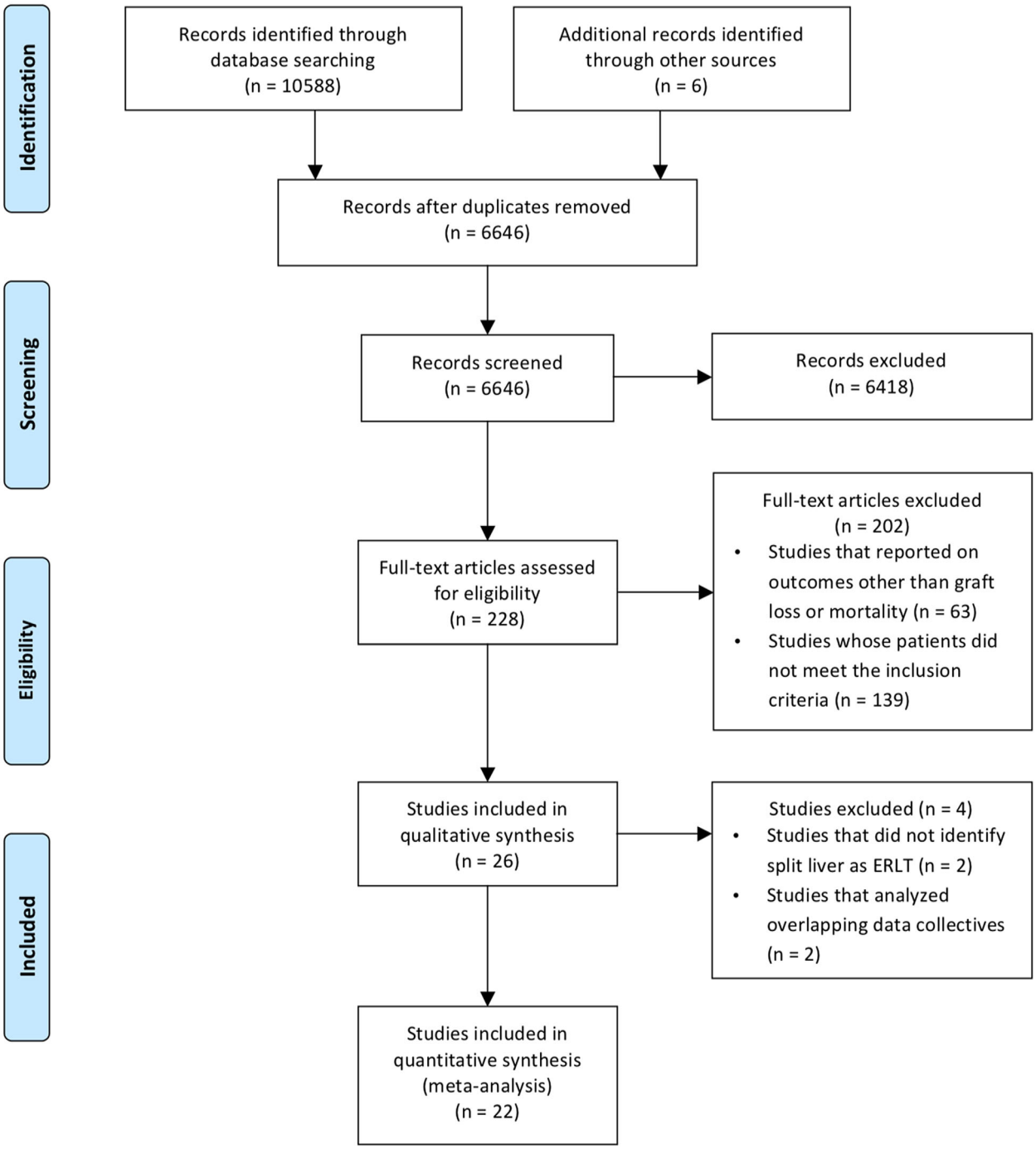

Figure 1 PRISMA flow-chart.

the study of Adam et al. did not provide precise definition of the splitting liver technique and their study was therefore excluded from the analysis [46].

Studies and patients

All included studies were retrospective cohort analyses that were published until December 2020 [6,15,18,19,28–45]. A total of 75 799 adult transplant patients were included in the ERLT meta-analysis, with follow-up ranging from 1 to 240 months (Table 1).

Qualitative analysis

Twenty-six studies evaluated the influence of ERLT on vascular and biliary complications, 3-month, 1-, and 3-

year graft and patient survival, and retransplantation [6,15,18,19,28–49]. The methodological index for non-randomized studies (MINORS) criteria evaluated the quality of the included studies as low to high (Table S1). According to the MINORS criteria, four of the analyzed retrospective studies were low quality [18,32,38,47], 20 studies were intermediate quality [6,15,19,28–31,33–37,39–45,48], and also one study was high quality [46], rendering the overall quality of the evaluated evidence as intermediate. All studies were adequately designed and the reported follow-up periods were sufficient to evaluate the endpoints of the meta-analysis. The aims and endpoints were comprehensively defined in all included studies. Three studies provided PNF definitions [29,37,44]. Ten studies analyzed PNF but did not provide PNF definitions [15,28,31,34,35,39–43]. Eight studies reported consecutive patient sampling [30,33,35,36,40,43,46,48]. Data was collected prospectively in six studies [19,34,37,41,42,46]. Unbiased assessment of endpoints was adequately reported in 10 studies [6,15,28,29,31,37,39,44–46]. In four studies bias reports were inadequate [18,33,35,40]. Eleven studies did not report bias [19,30,32,34,36,38,41–43,47,48]. None of the included studies reported on prospective sample size calculation and number of patients lost to follow-up. Detailed characteristics and outcomes of the included studies are shown in Table 1.

Publication bias assessment

No publication bias was detected for all outcomes (funnel plots, $P > 0.05$ in all analyses) (Supplementary Figures S1–S6).

Quantitative analysis

Nineteen studies with a total of 50 801 adult transplant recipients reported graft and patient survival following ERLT. We assessed postoperative morbidity and analyzed vascular and biliary complications reported in 16 studies ($n = 7174$) [15,19,28,29,31,32,34–36,39–45]. We analyzed ERLT vs. WLT and compared PNF, 3-month, 1-year, and 3-year graft and patient survival between the groups [6,15,18,19,28–33,36,37,39–44]. We also compared re-transplantation rates between the groups and analyzed 9 studies [6,15,31,34,36–38,41,44].

Vascular complications after ERLT

Nine studies ($n = 2515$) reported higher vascular complication rates in the ERLT group. Seven studies ($n = 6060$) reported on portal vein thrombosis rates, and these did not differ between ERLT and WLT groups (OR = 0.51, 95% CI = 0.26–0.99, $P = 0.05$; $I^2 = 0\%$, $P = 0.44$; Fig. 2a). Seven studies ($n = 3635$) reported on overall arterial complications including hepatic artery thrombosis after ERLT and WLT. Although the difference was not significant, there was a trend toward lower association with overall arterial complications after WLT compared to ERLT (OR = 0.67, 95% CI = 0.44–1.00, $P = 0.05$, $I^2 = 0\%$, $P = 0.48$). Hepatic artery thrombosis rates were reported in 12 studies ($n = 6711$). All studies showed lower association with hepatic artery thrombosis in the WLT group (OR = 0.51, 95% CI = 0.37–0.71, $P < 0.01$; $I^2 = 0\%$, $P = 0.79$) (Fig. 2b). In support of this, pooled data with a random-effects model suggested lower association with overall vascular complications following WLT versus following ERLT (OR = 0.53, 95% CI = 0.38–0.74, $P < 0.01$; $I^2 = 0\%$, $P = 0.83$) (Fig. 2c). Vascular complications' time points are summarized in Table 1.

Biliary complications after ERLT

Overall biliary complication rates were reported in 12 studies ($n = 5712$) (Fig. 3). Anastomotic biliary leak rates were reported in three studies ($n = 1797$) and did not differ between the groups (OR = 1.25, 95% CI = 0.58–2.73, $P = 0.57$; $I^2 = 0\%$, $P = 0.58$) (Fig. 3a). Non-anastomotic biliary leak rates were reported in three studies ($n = 1785$) and they all occurred after ERLT (OR = 0.02, 95% CI = 0.00–0.19, $P = 0.0009$; $I^2 = 53\%$, $P = 0.12$). Anastomotic biliary strictures were reported in three studies ($n = 1968$) and were significantly more common after WLT (OR = 1.84, 95% CI = 1.05–3.20, $P = 0.03$; $I^2 = 0\%$, $P = 0.75$) (Fig. 3b). In contrast, the association with non-anastomotic stricture did not differ between the groups (OR = 0.81, 95% CI = 0.37–1.77, $P = 0.60$; $I^2 = 0\%$, $P = 0.54$) (Fig. 3c). Because of the high non-anastomotic biliary leak rates in the ERLT group pooled results of a random-effects model revealed that WLT was less associated with overall biliary complications than ERLT (OR = 0.67, 95% CI = 0.47–0.95, $P = 0.03$; $I^2 = 29\%$, $P = 0.16$) (Fig. 3d). Biliary complications' time points are summarized in Table 1.

Graft survival after ERLT

Thirteen studies ($n = 5390$) provided data on PNF. Pooled results revealed equivalent association with PNF in both groups (OR = 0.87, 95% CI = 0.56–1.35, $P = 0.53$; $I^2 = 0\%$, $P = 0.78$) (Fig. 4). Five studies

Table 1. Studies included in the qualitative and quantitative analysis.

First author, year	ERL splitting technique	Data collection period	Country (data collection sources)	Number of patients	Recipient age (year/ range) ± SD	Donor age (year/range) ± SD	Outcome/morbidity	Complications and follow-up
Ghobrial, 2000 [33]	*In-situ*	1996–1999	USA (University of California)	52 ERLT 628 WLT	NA NA	NA NA	1- and 3-year graft/patient survival	NA
Broering, 2002 [29]	*Ex-situ*, *in-situ*	1993–1999	Germany (University of Hamburg)	40 ERLT 40 WLT	51 (20–65) 51 (20–65)	32 (15–61) 34 (16–65)	3 months and 1-year graft/patient survival, re-LT, biliary complications	3 months after ERLT
Merion, 2004 [38]	NA	1995–2002	USA (SRTR*)	436 ERLT 21 913 WLT	50 50	NA NA	Re-LT	NA
Baccarani, 2005 [48]	*In-situ*	1998–2004	Italy (University Hospital of Udine)	14 ERLT 194 WLT	54 NA	32 ± 18 45 ± 18	1- and 3-year graft/patient survival, re-LT, vascular and biliary complications	NA
Maggi, 2005 [36]	*In-situ*	1983–2004	Italy (Ospedale Maggiore Policlinico (IRCCS), Milano)	20 ERLT 261 WLT	46 ± 12 45 ± 10	31 ± 14 41 ± 17	Graft survival, patient survival, re-LT, biliary complications	NA
Cardillo, 2005 [15]	*In-situ*	1997–2002	Italy (Centers of the NITp[†])	154 ERLT 1126 WLT	48 ± 13 46 ± 15	31 ± 15 44 ± 20	3-year graft/patient survival, re-LT, biliary complications, HAT, PVT	NA
Spada, 2005 [42]	*In-situ*	1997–2003	Italy (Ospedali Riuniti di Bergamo (M.St.), Palermo)	15 ERLT 87 WLT	51 (24–62) 52 (19–65)	26 (13–60) 53 (5–78)	3-month, 1- and 3-year graft/patient, re-LT	NA
Corno, 2006 [47]	*In-situ*	1997–2005	Italy (Ospedali Riuniti, Largo Barozzi, Bergamo)	22 ERLT 48 WLT	5 (23–63) 55 (19–65)	22 (12–61) 54 (17–79)	1-year graft/patient survival, biliary complications, HAT	NA
Wilms, 2006 [44]	*Ex-situ*, *in-situ*	1993–2005	Germany (University of Hamburg)	70 ERLT 70 WLT	51 (16–69) 51 (16–69)	34 (15–64) 38 (0–73)	Graft survival, re-LT patient survival, biliary complications	3 months after ERLT
Bonney, 2008 [28]	*Ex-situ*	2000–2006	United Kingdom (James's University Hospital)	27 ERLT 27 WLT	52 (22–68) 53 (34–74)	40 (15–54) 47 (19–79)	1- and 3-year graft survival, patient survival, vascular and biliary complications	NA

Table 1. Continued.

First author, year	ERL splitting technique	Data collection period	Country (data collection sources)	Number of patients	Recipient age (year/ range) ± SD	Donor age (year/range) ± SD	Outcome/morbidity	Complications and follow-up
Sainz-Barriga, 2008 [40]	*Ex-situ*, *in-situ*	2001–2005	Belgium (Ghent University Hospital Medical School)	12 ERLT 12 WLT	52 ± 12 55 ± 7	33 (14–16) 44 (22–63)	1- and 3-year graft survival, patient survival	NA
Lee, 2008 [18]	*Ex-situ*, *in-situ*	1996–2006	USA (UNOS/OPTN‡)	568 ERLT 40 304 WLT	51 ± 11 51 ± 10	25 ± 10.3 40 ± 18	1- and 3-year graft survival, patient survival	NA
Hong, 2009 [34]	*In-situ*	1993–2006	USA (Dumont-UCLA Transplant Center)	72 ERLT 2433 WLT	51 52	20 37	Re-LT, vascular and biliary complications	NA
Takebe, 2009 [43]	*Ex-situ*	1998–2007	Germany (Medizinische Hochschule Hannover)	80 ERLT 80 WLT	42 (15–65) 43 (18–64)	33 (7–60) 38 (14–64)	1- and 3-year graft survival, patient survival, vascular and biliary complications	<3 months (early) and ≥3 months (late) after ERLT
Sandroussi, 2009 [41]	*Ex-situ*, *in-situ*	2002–2007	Australia (ANLTU§)	43 ERLT 182 WLT	53 (17–67) 52 (17–69)	39 (13–61) 47 (12–79)	Graft survival, patient survival	NA
Mallik, 2012 [37]	NA	2004–2010	United Kingdom (Addenbrooke's Hospital, Cambridge)	17 ERLT 32 WLT	50 (28–69) 58 (46–69)	23 (12–60) 34 (14–64)	1- and 3-year graft survival, patient survival	NA
Leithead, 2014 [35]	*Ex-situ*	2007–2011	United Kingdom (University of Birmingham)	72 ERLT 72 WLT	52 ± 13 52 ± 11	29 ± 10 48 ± 15	HAT, biliary complications	NA
Mourad, 2015 [19]	*Ex-situ*, *in-situ*	2000–2012	United Kingdom Queen Elizabeth Hospital (Birmingham, United Kingdom)	171 ERLT 1412 WLT	50 ± 13 51 ± 12	29 ± 10 46 ± 14	1- and 3-year graft/patient survival, HAT, PVT, biliary complications	3 months after ERLT
Adam, 2015 [46]	NA	1968–2012	France (ELTR¶)	1483 Split LT 37 428 WLT	NA NA	NA NA	1- and 3-year graft survival	NA
Gambaro, 2017 [32]	*Ex-situ*, *in-situ*	2009–2015	Argentina (Hospital Universitario Fundación Favaloro)	15 ERLT 30 WLT	43 ± 17 48 ± 16	22 ± 8 42 ± 15	1- and 3-year graft/patient survival, HAT, PVT, biliary complications	Early and late follow-up
Ross, 2017 [39]	*Ex-situ*, *in-situ*	1997–2001	Italy (Multicentric study**)	119 ERLT 119 WLT	50 ± 11 50 ± 11	32 ± 17 32 ± 16	1- and 3-year graft/patient survival, HAT, biliary complications	NA

Table 1. Continued.

First author, year	ERL splitting technique	Data collection period	Country (data collection sources)	Number of patients	Recipient age (year/range) ± SD	Donor age (year/range) ± SD	Outcome/morbidity	Complications and follow-up
Andrassy, 2018 [6]	NA	2007–2013	Germany (ET area[††])	269 ERLT 4744 WLT	44 ± 18 51 ± 15	32 ± 14 43 ± 15	1- and 3-year graft/patient survival	NA
Chul Yoon, 2018 [31]	*In-situ*	2005–2014	South Korea (KONOS[‡‡])	86 ERLT 303 WLT	54 (47–61) 53 (52–60)	26 (17–31) 44 (32–54)	1- and 3-year graft/patient survival	NA
Chan, 2019 [30]	NA	2003–2019	Taiwan (Chang Gung Memorial Hospital at Linkou)	100 ERLT 165 WLT	NA NA	NA NA	1- and 3-year patient survival	NA
Park, 2020 [45]	*In situ*	2016–2019	South Korea (Asan Medical Center)	7 ERLT 235 WLT	55 ± 10 52 ± 11	29 ± 7 47 ± 15	1-, 2- and 3-year graft/patient survival	NA

ERLT, extended right lobe liver transplantation; HAT, hepatic artery thrombosis; LT, liver transplantation; NA, not available; PVT, portal vein thrombosis; WLT, whole liver transplantation.

*Scientific Registry of Transplant Recipients.

[†]North Italian Transplant program.

[‡]UNOS/Organ Procurement and Transplantation Network (OPTN).

[§]Australian National Liver Transplantation Unit.

[¶]European Liver Transplant Registry.

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[††]Eurotransplant area.

[‡‡]Korean Network for Organ Sharing.

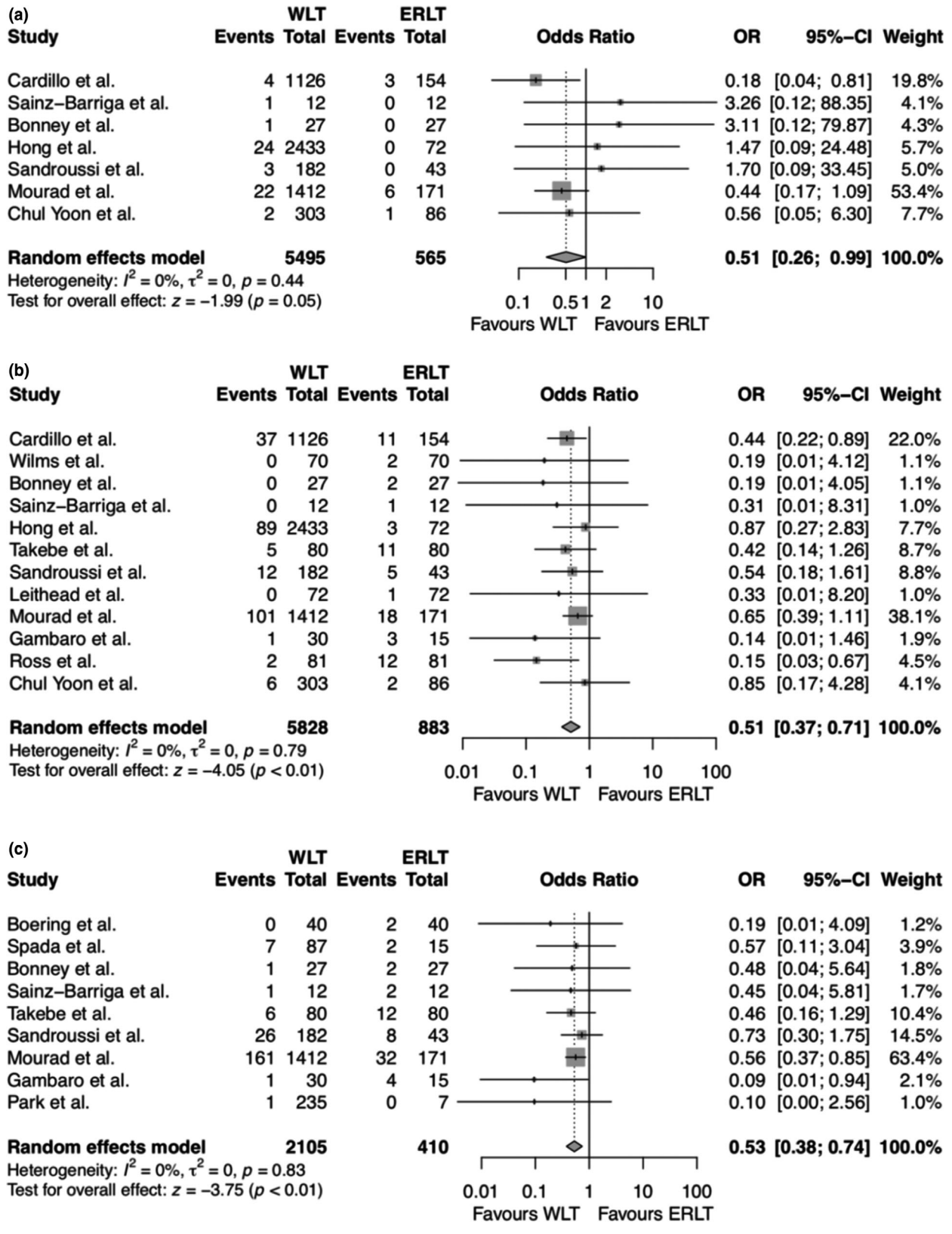

Figure 2 Meta-analysis of vascular complications after whole liver transplantation and extended right lobe liver transplantation. (a) Portal vein thrombosis; (b) hepatic artery thrombosis; (c) overall vascular complications.

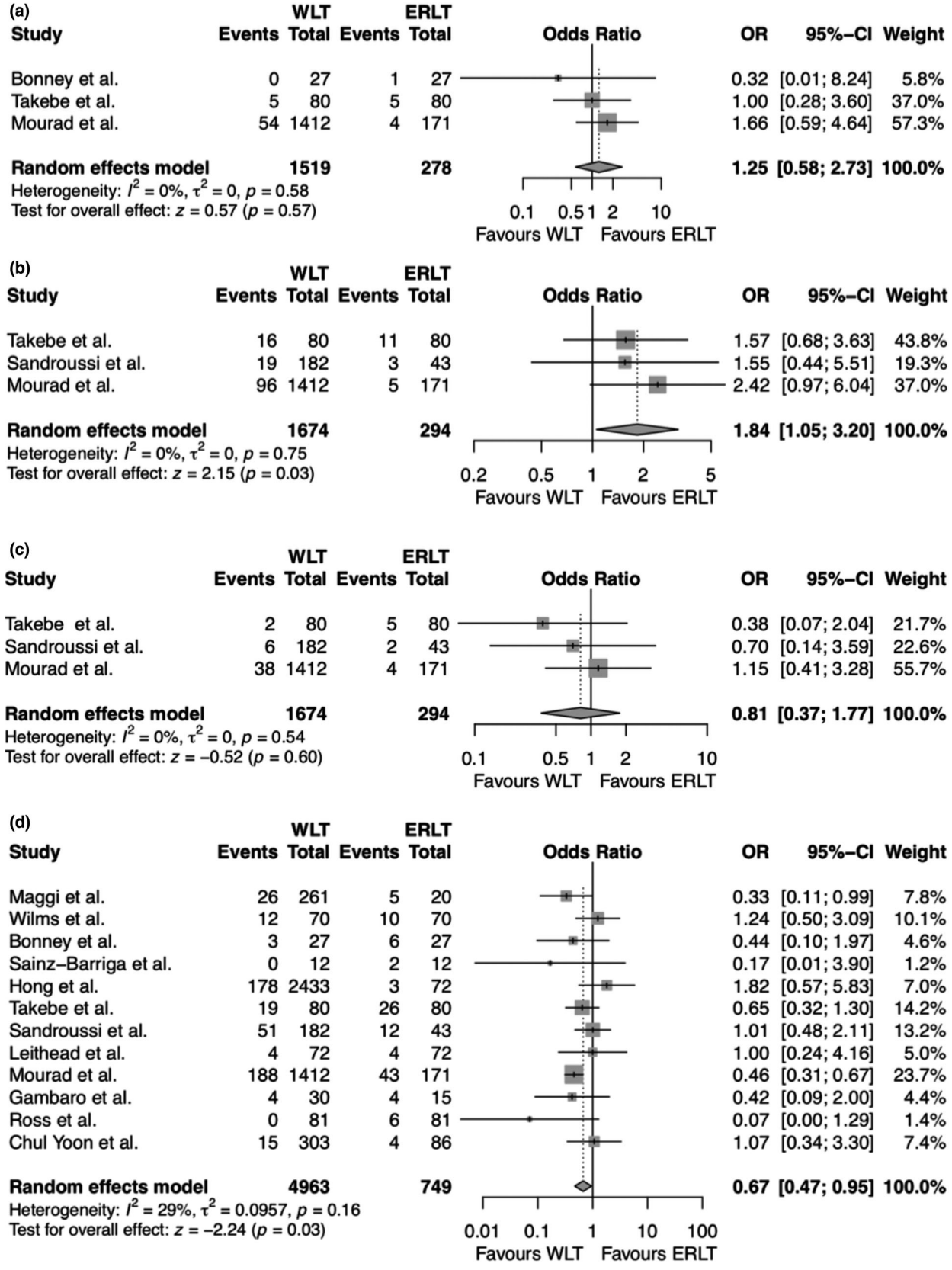

Figure 3 Meta-analysis of biliary complications after whole liver transplantation and extended right lobe liver transplantation. (a) Anastomotic biliary leaks; (b) anastomotic biliary strictures; (c) non-anastomotic biliary strictures; (d) overall biliary complications.

(n = 5521) provided data on 3-month graft survival, 12 (n = 47 904) provided data on 1-year survival, and 12 (n = 48 049) provided data on 3-year graft survival (Fig. 5). Heterogeneity between included studies varied from low to moderate. ERLT grafts were associated with lower 3-month, 1-year, and 3-year graft survival rates following liver transplantation compared with WLT cases (3 month: OR = 1.43, 95% CI = 1.09–1.89, P = 0.01; I^2 = 0%, P = 0.53; 1-year: OR = 1.46, 95% CI = 1.08–1.97, P = 0.01; I^2 = 52%, P = 0.02; 3-year: OR = 1.37, 95% CI = 1.01–1.84, P = 0.04; I^2 = 59%, P < 0.01; Fig. 5a–c).

Retransplantation after ERLT

Retransplantation rates were reported in nine studies (n = 32 231), and in six of them retransplantation rates were significantly higher after ERLT. Heterogeneity was moderate between studies included in the meta-analysis of retransplantation rates, but pooled results using a random-effects model showed significantly lower retransplantation rates following WLT than ERLT (OR = 0.57, 95% CI = 0.41–0.80, P < 0.01; I^2 = 46%, P = 0.06; Fig. 6).

Patient survival after ERLT

Six studies (n = 5910) provided data on 3-month patient survival, 12 (n = 8883) provided data on 1-year survival, and 13 (n = 9979) provided data on 3-year patient survival and were included in the analysis. Heterogeneity between studies included in the patient survival meta-analysis varied from low to moderate. Three-month and 3-year patient survival did not significantly differ after WLT and ERLT (3 month: OR = 1.35, 95% CI = 0.65–2.78, P = 0.42; I^2 = 64%, P = 0.02; 3-year: OR = 1.06, 95% CI = 0.90–1.25, P = 0.51; I^2 = 0%, P = 0.58; Fig. 7a,c). ERLT grafts were associated with lower 1-year patient survival rates following liver transplantation compared with WLT cases, but the difference between the groups was marginal (OR = 1.32, 95% CI = 1.01–1.72, P = 0.04; I^2 = 29%, P = 0.16; Fig. 7b).

Discussion

The results of this systematic review and meta-analysis confirm that ERLT is significantly associated with vascular and biliary complications and indicate a negative influence of ERLT on graft survival in adult recipients. The absence of difference in portal vein thrombosis between ERLT and WLT is not surprising because the main portal vein is assigned to the ERL graft and its reconstruction in ERLT is just as challenging as in WLT. In contrast, hepatic artery thrombosis rates of up to 17% after ERLT have been reported [19,50]. This major complication may lead to acute, early graft loss, or cause ischemic biliary lesions. It can be attributed to technical complications, in which the splitting procedure may be directly or indirectly implicated [19]. Vascular

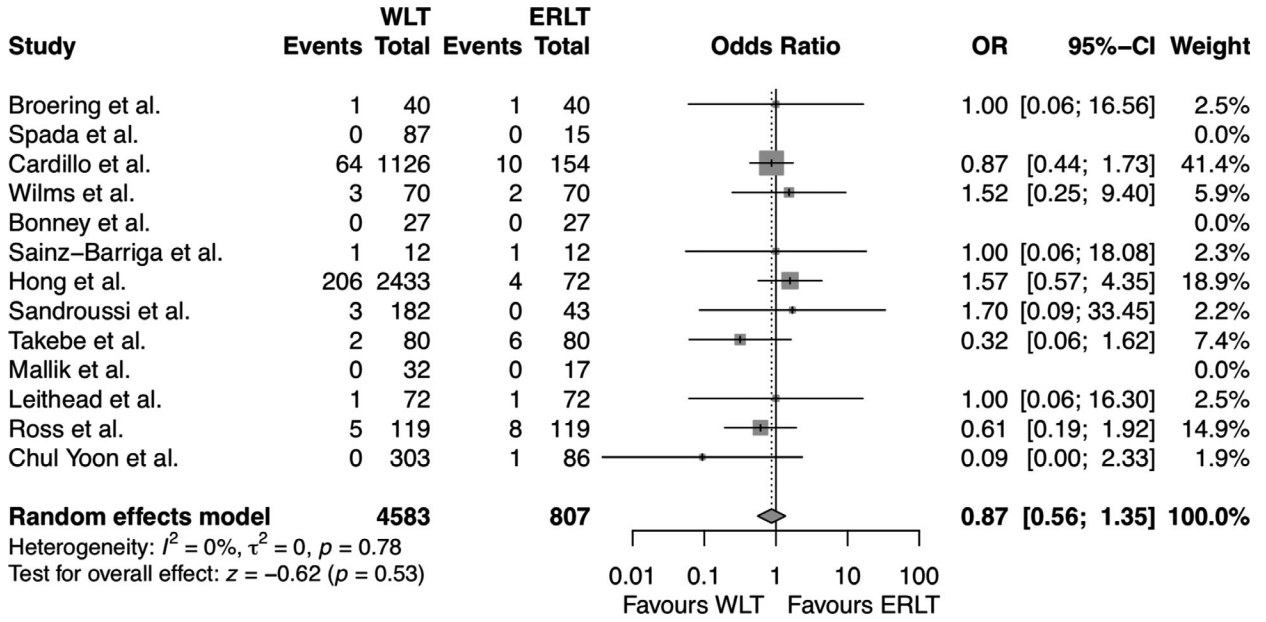

Figure 4 Meta-analysis of primary nonfunction after whole liver transplantation and extended right lobe liver transplantation.

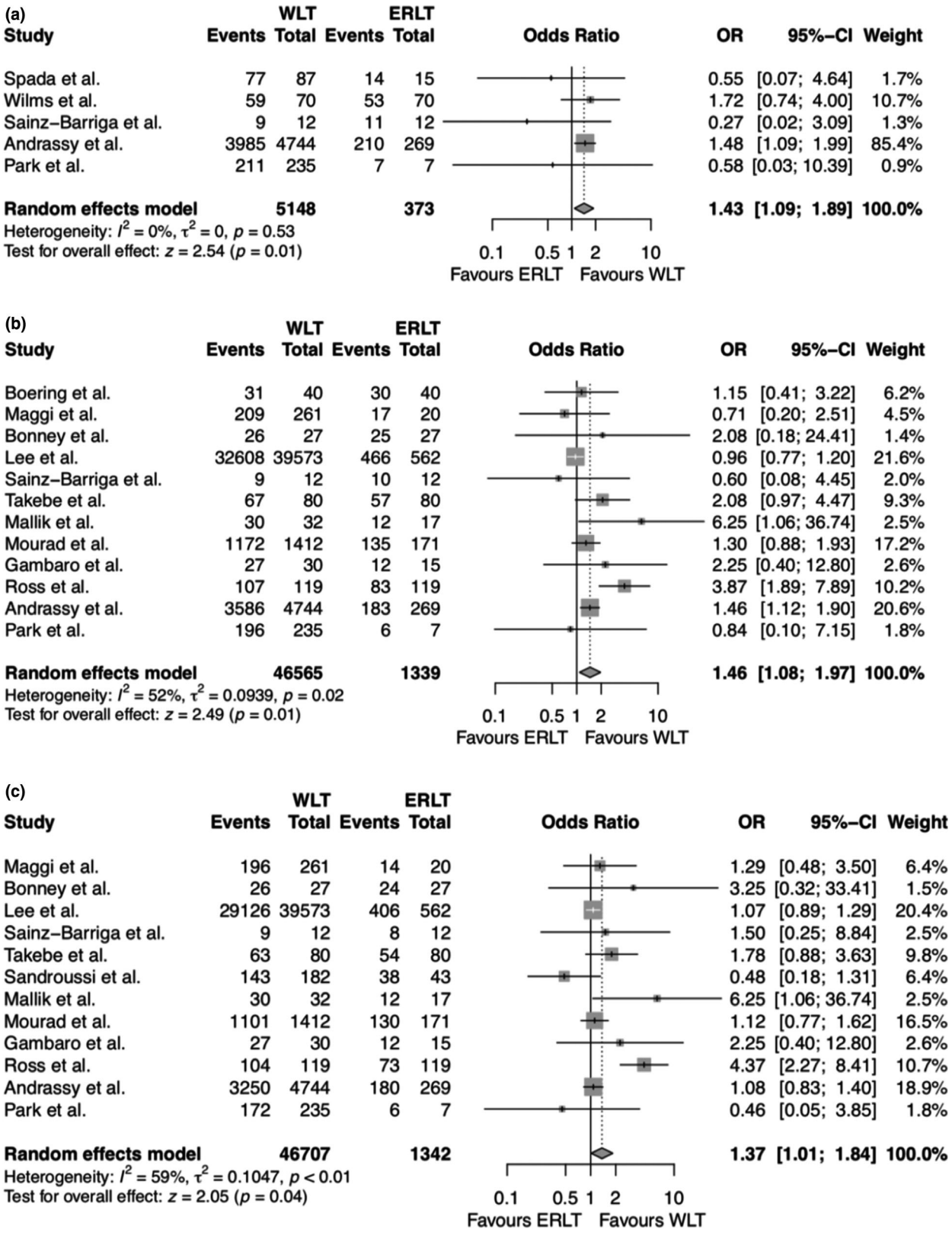

Figure 5 Meta-analysis of graft survival after extended right lobe liver transplantation and whole liver transplantation. (a) 3-month graft survival; (b) 1-year graft survival; (c) 3-year graft survival.

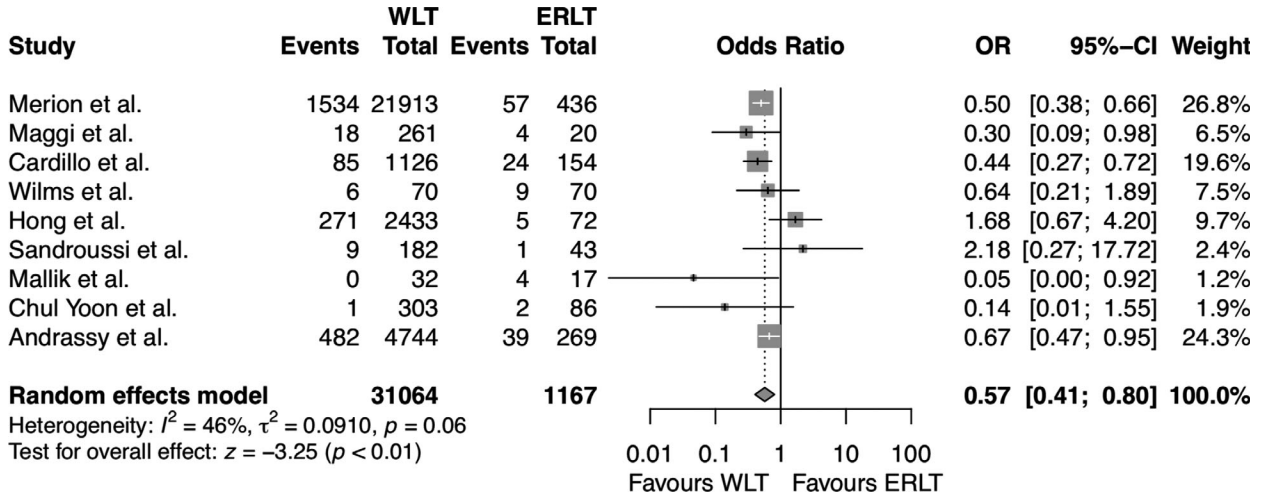

Figure 6 Meta-analysis of retransplantation after whole liver transplantation and extended right lobe liver transplantation.

reconstructions of the right hepatic artery increase the risk of thrombosis *per se* because of differences in the caliber of the right hepatic artery and common hepatic artery. In addition, the risk of early graft loss due to hepatic artery thrombosis depends on the vascular variations and is higher if more than one arterial reconstruction or interposition vascular grafts are needed [19]. Therefore, the decision whether to assign the celiac tripod to the ERL liver should be governed by donor's and recipient's arterial anatomy: number of branches, branch size, origin of liver segment 4 branches, retransplantation, and previous hepatic artery thrombosis [51]. The available data did not discriminate between the types of arterial reconstructions, but ERL grafts were more associated with hepatic artery thrombosis and vascular complications than WL grafts in general suggesting more complex vascular anatomy and reconstruction in the ERLT group.

Specific biliary complications were not evenly distributed between the groups. Anastomotic biliary leaks were predominantly seen after WLT. They are mostly of technical nature, but damage to the microvascular plexus supplying the bile duct which can also occur during hepatectomy or back table preparation, may lead to ischemia and necrosis, thus explaining the insignificantly higher anastomotic leakage rates following WLT [43]. In contrast, non-anastomotic biliary leaks were observed only in the ERLT group and were responsible for the higher overall biliary complication rates in this group. The distribution of this complication, which is almost always of technical nature, is not surprising, because ERLT includes liver transection and higher leakage rates from the large transection plane are expected [19,43,45]. Anastomotic biliary strictures affected ERL liver recipients less than they did WLT patients. Roux-en-Y hepaticojejunostomy, which is more often performed in ERLT, has been proven to be less prone to structures mainly because of the modifiability of the ostium of the jejunal loop, but also because the Roux-en-Y hepaticojejunostomy may protect the bile duct from ischemia by providing additional blood supply through the Roux loop [19]. Moreover, very experienced surgeons who also perform living-donor liver transplantation generally perform ERLT. This may explain the significantly lower association with anastomotic biliary strictures after ERLT. However, the included studies did not differentiate between duct-to-duct biliary reconstruction and Roux-en-Y hepaticojejunostomy and we could not verify this hypothesis. Ischemic-type biliary lesions occur when the arterial perfusion of the bile ducts is compromised. Despite the lack of statistical significance, non-anastomotic biliary strictures were more frequent after ERLT, which is in line with the higher rates of hepatic artery thrombosis seen in ERLT cases. Thanks to current technical developments, arterial occlusions can now be better managed by interventional radiology, which in turn may explain the comparable non-anastomotic biliary stricture rates, which are almost always of ischemic nature.

Only high-quality organs are considered for liver split [4,5]. This may be the reason why we observed no difference in PNF rates between the ERLT and WLT groups, but this may be also because of different PNF definitions. However, ERLT had a negative effect on graft survival at all other investigated time points. Although liver grafts from younger and hemodynamically more stable donors were predominantly used for ERLT in most studies, and despite that optimal donor quality suggests superior outcome after ERLT, the re-transplantation rates were significantly higher in the ERLT group.

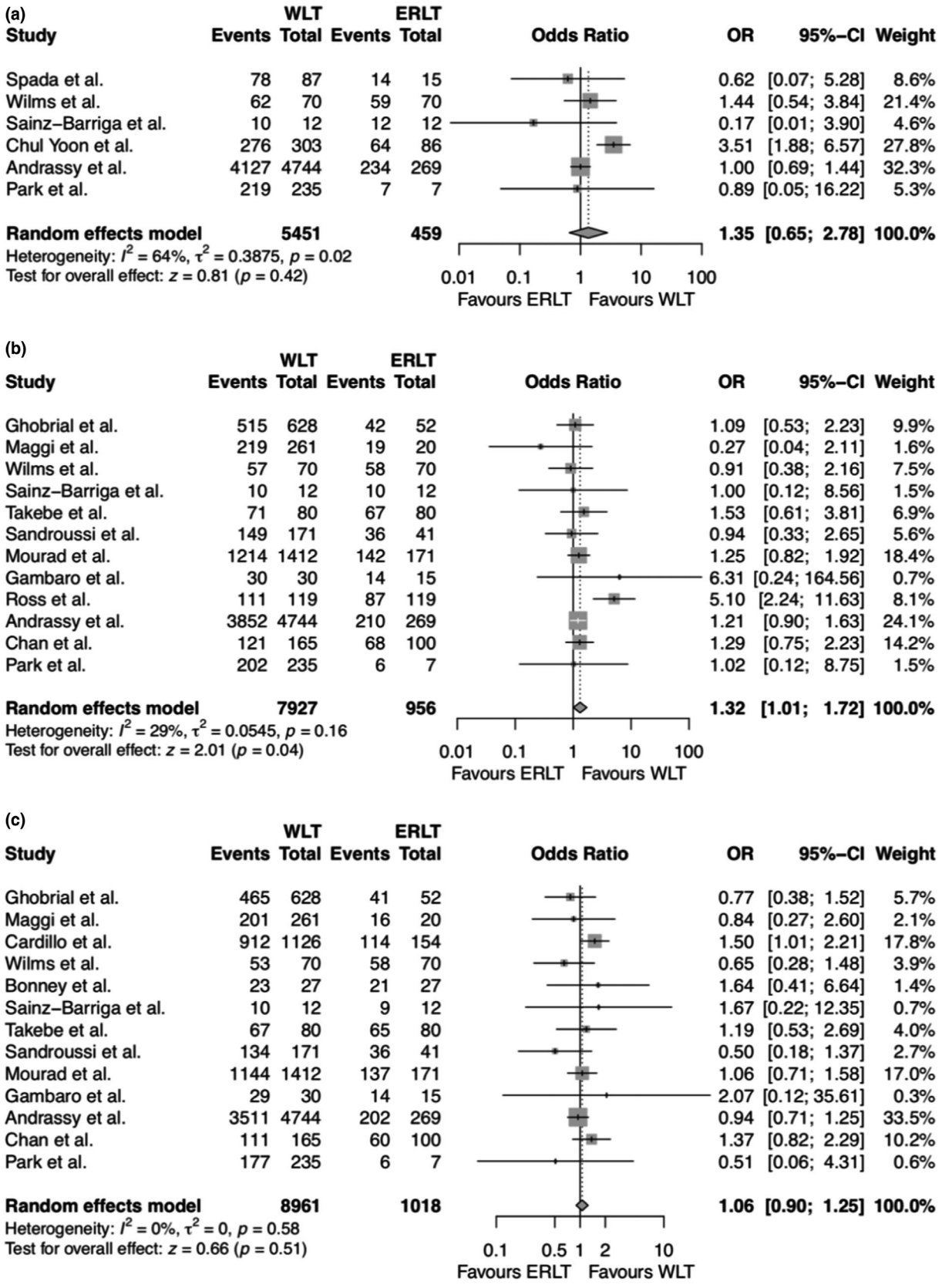

Figure 7 Meta-analysis of patient survival after extended right lobe liver transplantation and whole liver transplantation. (a) 3-month patient survival; (b) 1-year patient survival; (c) 3-year patient survival.

The significantly higher association with hepatic artery thrombosis and biliary complications, which can occur later and irrespective of PNF, could explain this. However, higher graft loss and retransplantation rates did not necessarily translate into worse patient survival. The better recipient's condition with lower laboratory MELD (labMELD) scores in the cases of ERLT may explain these results. In a recent Eurotransplant analysis of 5013 transplant cases, patient survival rates did not differ between ERLT and WLT groups thanks to optimal donor and recipient match [6]. The marginal difference in 1-year survival rates between the groups could be explained by the higher early recurrence rates of original disease (hepatitis C and hepatocellular cancer) after ERLT observed in the study by Ross *et al*. [39]. The study emphasized the need for optimal donor-recipient match to reduce waiting time and mortality rates on the waiting list. Indeed, similar to WLT, the risk of retransplantation after ERLT is higher in older donors and younger recipients and in recipients of ERL grafts with prolonged cold ischemia times [6,12,52]. Cold ischemia time influences graft and patient survival only during the first year after WLT indicating that once the liver has recovered from the ischemia-reperfusion injury – the duration of the cold storage becomes irrelevant [10]. Although the role of cold ischemia has been fueling intense debate for decades, it has not been addressed properly in ERLT so far. Because of lack of data on cold ischemia time we were not able to draw conclusion if the effect of cold storage after ERLT is similar to the effect of cold ischemia after WLT. However, the time it takes to split and transport the ERL graft to another center for transplantation prolongs the cold ischemia, and the conservation time is approximately 50% longer in ERLT than in WLT as a result. This has a major influence on the inferior graft outcome following *ex situ* graft splitting and ERLT [6,53]. Our results confirm that graft allocation and optimal donor-recipient match are essential for a successful split-liver transplantation and remain the main challenges in ERLT [1,20]. One solution to the problem of prolonged cold ischemia time in the case of *ex situ* ERLT may be to allocate both grafts to pediatric and adult transplant candidates at the center that performs the liver-split procedure thus reducing transport and longer conservation time, whereas *in situ* split-grafts may be allocated to different centers thus avoiding allocation and prioritizing bias. Moreover, donors of ERL grafts are younger and presumably healthier, but the split procedure has different influences on patients with different clinical conditions [4]. ERLT in patients with low labMELD scores may achieve similar outcomes to WLT, but ERLT becomes less tolerable with increasing MELD scores [6]. This finding is supported by the results of our previous studies, in which the negative influence of maEDC diminished as the labMELD score decreased, especially in recipients with hepatocellular carcinoma who are generally in a better condition [10–12]. However, we could not verify this hypothesis in the case of ERLT because we were not able to analyze the underlying disease, the clinical condition and the MELD score of the recipients, and whether ERL grafts should be preferably allocated to recipients with lower labMELD scores needs to be considered with caution. Moreover, in the light of organ shortage it should be evaluated whether modern technologies, such as machine perfusion, could reverse the negative outcome trend after ERLT [54,55].

The experience in liver splitting techniques has improved over the years. The unrestricted literature search and inclusion of data from a period where ERLT was pioneered to most recent data where outcomes could have been influenced by better understanding of the procedure and surgical technique modifications could result with the association with higher complications at the early stages of implementation of ERLT. However, we used strict inclusion criteria to minimize heterogeneity between studies, but limitations of the available data translate into limitations of our analysis. Not being able to differentiate between *ex situ* and *in situ* ERLT hindered the analysis of the differential influence of longer cold ischemia time in *ex situ* ERLT, and the influence of plausibly instable recipient with an increased blood loss during the *in situ* ERLT. Lack of data on donor quality, patient acuity, operative factors, vascular and biliary reconstruction, and variants hindered the analysis of outcome in these specific subgroups. Also, individual centers may have applied different donor-recipient matching criteria and different postoperative complications definitions thus reducing the significance of their results. These limitations and the lack of randomized studies emphasize the urgent need of further, more focused analyses and prospective trials to address the issues of a highly technical procedure such as the use of ERL liver grafts.

ERL grafts are associated with vasculobiliary complications and the need for retransplantation, and have a negative influence on graft survival. Therefore, considering ERLT as major EDC is justified and has to be addressed appropriately in the allocation algorithms. However, simply discarding these grafts does not offer a solution because split livers are an absolute necessity and represent great potential for creating value in liver transplantation in the current era of organ shortage.

ERL grafts effectively expand the donor organ pool especially for vulnerable populations, particularly children who benefit extremely from the transplantation procedure, and may provide a good alternative for adult recipients with lower labMELD scores and recipients with hepatocellular cancer who are generally in a better condition.

Authorship

VJL: designed the study, collected and analyzed data, and wrote the manuscript. PP: co-designed the study, analyzed data and revised the manuscript. AR, AA, OG, EA and EK: collected and analyzed data. AM: designed the study and revised the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Funnel plots for risk of publication bias. Vascular complications: portal vein thrombosis (A), hepatic artery thrombosis (B), and overall vascular complications (C).

Figure S2. Funnel plots for risk of publication bias. Biliary complications: anastomotic biliary leaks (A), anastomotic biliary strictures (B), non-anastomotic biliary strictures (C), and overall biliary complications.

Figure S3. Funnel plot for risk of publication bias: primary nonfunction.

Figure S4. Funnel plots for risk of publication bias: 3-month graft survival (A), 1-year graft survival (B), and 3-year graft survival (C).

Figure S5. Funnel plot for risk of publication bias: retransplantation.

Figure S6. Funnel plots for risk of publication bias: 3-month survival (A), 1-year patient survival (B), and 3-year patient survival (C).

Table S1. Methodological index for non-randomized studies (MINORS).

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