META-ANALYSIS

Prognostic role of the Donor Risk Index, the Eurotransplant Donor Risk Index, and the Balance of Risk score on graft loss after liver transplantation

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SUMMARY

This study aimed to identify cutoff values for donor risk index (DRI), Eurotransplant (ET)-DRI, and balance of risk (BAR) scores that predict the risk of liver graft loss. MEDLINE and Web of Science databases were searched systematically and unrestrictedly. Graft loss odds ratios and 95% confidence intervals were assessed by meta-analyses using Mantel–Haenszel tests with a random-effects model. Cutoff values for predicting graft loss at 3 months, 1 year, and 3 years were analyzed for each of the scores. Measures of calibration and discrimination used in studies validating the DRI and the ET-DRI were summarized. DRI $\geq$ 1.4 (six studies, n = 35 580 patients) and ET-DRI $\geq$ 1.4 (four studies, n = 11 666 patients) were associated with the highest risk of graft loss at all time points. BAR > 18 was associated with the highest risk of 3-month and 1-year graft loss (n = 6499 patients). A DRI cutoff of 1.8 and an ET-DRI cutoff of 1.7 were estimated using a summary receiver operator characteristic curve, but the sensitivity and specificity of these cutoff values were low. A DRI and ET-DRI score $\geq$ 1.4 and a BAR score > 18 have a negative influence on graft survival, but these cutoff values are not well suited for predicting graft loss.

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Key words
balance of risk score, donor risk index, Eurotransplant, graft loss, liver transplantation, major extended donor criteria

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Introduction

Liver transplantation is the standard treatment for patients with advanced liver disease and prolongs the recipients' life expectancy. Improved outcome after transplantation has increased the number of recipients on the waiting lists and transplant centers, but has also raised the issue of fair and adequate organ allocation [1,2]. Because of the dire need for liver grafts, strict donor criteria have been relaxed in recent years [3]. Model of end-stage liver disease (MELD) score-based allocation has reduced mortality on the waiting lists, but has increased the one-year mortality following transplantation [4]. According to OPTN, 20% of patients with a chronic liver disease and high MELD score either drop out from the waiting list because of disease progression or die waiting for transplantation [5]. In Eurotransplant (ET), up to 30% of patients drop out from the waiting list because of death or because their condition deteriorates [6]. Therefore, donor–recipient matching has become crucial in achieving reasonable outcomes after transplantation, especially when allocating extended donor criteria (EDC) organs to sicker recipients [2,7]. The donor risk index (DRI) is a scoring system that was found to significantly influence outcomes after liver transplantation in a large cohort of 20 023 deceased donor transplants from the Scientific Registry of Transplant Recipients database [8]. The DRI was validated within the ET network, but because of differences in donor age, cause of death, donation after cardiac death, split liver donation, and organ allocation, the DRI values were different between the Organ Procurement and Transplantation Network (OPTN) and the ET region. To accommodate these differences, a scoring system tailored to the ET region (ET-DRI) was implemented [9,10]. The balance of risk (BAR) scoring system is a simple model that was calculated based on 37 255 patients in the United Network for Organ Sharing (UNOS) database [11]. The BAR score identified six donor and recipient factors that best predicted the outcome of liver transplantation. These predictors were found to be superior to the model for end-stage liver disease (MELD) score, the D-MELD (donor age multiplied by recipient MELD) score, and the DRI at predicting transplant outcome [11].

The DRI, ET-DRI, and BAR scores are continuous scoring systems that include donor, graft, and recipient parameters available at the time of organ allocation. As such, they allow information about graft-associated risk to be shared during the allocation procedure. These scores all use just a few covariates, which makes them more applicable than other more complex scoring systems. However, different cutoff values have been suggested for the DRI, ET-DRI, and BAR scores, and no consensus has been reached. This systematic review and meta-analysis aimed to evaluate at which cutoff values the DRI, ET-DRI, and BAR scores would predict an increased risk for graft failure after liver transplantation.

Methods

The study was conducted according to a predefined protocol, which is available upon request, and adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

Literature search

MEDLINE and Web of Science databases were searched systematically and without any restrictions on date of publication as previously reported [13]. Studies comparing the effect of different DRI, ET-DRI, and BAR cutoff values on graft loss published until December 2020 were identified. Citations of relevant articles were also screened for additional eligible studies. The search terms used for the DRI and the ET-DRI were ("Index" OR "DRI") AND "Transplant*" AND ("Liver" OR "Hepatic") AND "Donor". The search terms used for the BAR score were "Transplant*" AND ("Liver" OR "Hepatic") AND "Donor" AND ("Balance of Risk" OR "BAR" OR "Retransplantation" OR "Life support" OR "Recipient Age" OR "Cold Ischemia" OR "Cold Ischaemia" OR "Donor Age").

Terminology and definitions

The DRI considers donor age, cause of death, race, donation after cardiac death (DCD), split liver graft, donor's height, organ location (local, regional, or national), and cold ischemia time [8]. The ET-DRI considers donor age, cause of death, donation after cardiac death, split liver graft, organ location (regional or national), cold ischemia time, rescue allocation, and gamma-glutamyltransferase levels [9]. The BAR score considers recipient MELD score, recipient age, donor age, retransplantation, cold ischemia time, and recipient's life support dependence at the time of allocation [11].

Eligibility criteria

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

• Population: patients with end-stage liver disease undergoing primary liver transplantation.
• Intervention: patients transplanted with grafts from donors with higher DRI/ET-DRI/BAR score.
• Comparator: patients transplanted with grafts from donors with lower DRI/ET-DRI/BAR score.
• Outcomes: postoperative graft loss.
• Time: predictive ability of the DRI, ET-DRI, and BAR scores at three months, one year, and three years after 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 [14].

Studies not meeting these inclusion criteria and studies that did not report the outcomes of interest were excluded. Articles were carefully reviewed to exclude overlapping reports and duplicate publications. Studies that assessed the same patient collective more than once without providing additional information were excluded and only the study with the largest patient collective was included. Studies in languages other than English and German were also excluded. 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. A third reviewer resolved any discrepancies. Study data were extracted using the CHARMS checklist (checklist for critical appraisal and data extraction for systematic reviews of prediction modeling studies) [15].

Outcomes

Differences in graft loss rates following liver transplantation from donors with different DRI, ET-DRI, and BAR score cutoff values were assessed. Based on previously reported cutoff values, the main outcome of the meta-analysis was to identify the DRI, ET-DRI, and BAR scores that predicted the best possible 3-month, 1-year, and 3-year graft survival. Graft loss was a combined endpoint, defined as the time from liver transplantation to either patient's death or retransplantation (whichever came first).

Quality assessment and assessment of bias

Risk of bias and study applicability were evaluated using the prediction model risk of bias assessment tool (PROBAST). The risk of bias was considered high, and the evidence quality was considered low if the study did not address the issues in each domain. Studies with the lowest risk of bias were considered to have highest quality evidence. The risk of bias, the study methodology, and the relevance of the findings to the research question (applicability) were rated "high," "low," or "unclear" based on a predefined questionnaire and scoring guide [16].

Statistical analysis

Review Manager (RevMan, version 5.3.5, The Cochrane Collaboration, The Nordic Cochrane Center, Copenhagen, Denmark) was used to conduct the meta-analyses. R (a language and environment for statistical computing, R Core Team, 2020, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) was used to evaluate the discrimination of the evaluated scores and to perform the SROC analysis. Dichotomous data were presented as odds ratios (OR) with 95% confidence intervals (CI). Pairwise meta-analyses were performed using the Mantel–Haenszel random-effects model to account for between-trial heterogeneity [17,18]. The statistical heterogeneity between included studies was evaluated using the I^2. Values of I^2 between 50% and 75%, heterogeneity were regarded as moderate, while I^2 values > 75% were regarded as considerable. To evaluate score discrimination, the area under the receiver operating curve (AUC) value was used. Pooled AUC values were estimated for the DRI, ET-DRI, and BAR scores for each endpoint at different time points. Measures of calibration, such as sensitivity and specificity along with the reported cutoffs, were extracted. To estimate an optimal cutoff, summary receiver operator characteristics curve (SROC) analyses were performed [19]. A P value < 0.05 was considered significant in all analyses.

Results

Study selection and selection criteria

The literature search yielded 5492 potentially eligible articles. After excluding duplicates and screening titles and abstracts, the full texts of 106 articles were further assessed for eligibility. Of these, 57 articles were excluded because they presented no quantitative data about the endpoints of interest (n = 17), because the patients did not meet the inclusion criteria (n = 13), or because they did not evaluate the DRI, the ET-DRI, or the BAR score (n = 27). This left 49 studies that were

included in the qualitative analysis (Fig. 1). Only studies that clearly defined cutoff values for DRI, ET-DRI, and BAR scores, evaluated the impact of these cutoffs on graft survival, provided enough data on donor numbers and survival, and did not analyze overlapping collectives were eligible for analysis. Nine studies fulfilled these criteria and were included in the quantitative analysis. Six studies were included in the meta-analysis of the DRI [3,7–9,20,21], four studies were included in the meta-analysis of the ET-DRI [9,20–22], and two studies were included in the meta-analysis of the BAR score [23,24].

Studies and patients

All included studies were retrospective cohort analyses conducted in Europe, Asia, Africa, South America, Canada, and the United States between 2006 and 2020 [3,7–11,20–22,24–53]. A total of 35 580 liver transplant patients were included in the DRI meta-analysis, and 11 666 liver transplant patients were included in the ET-DRI meta-analysis (Tables 1 and 2). A total of 6499 liver transplant patients were included in the meta-analysis of BAR scores (Table 3). The follow-up ranged from 1 month to 240 months.

Qualitative analysis

Thirty-four retrospective studies assessed the effect of DRI on 3-month, 1-year, and 3-year graft loss [3,7–9,11,20,21,24–31,33–41,43–46,48–53]. Seven studies evaluated the relationship between ET-DRI and 3-month, 1-year, and 3-year graft loss [9,10,20–22,32,42]. Two studies evaluated the effect of the BAR score on 3-month and 1-year graft loss [23,24]. Schlegel *et al.* evaluated two databases (UNOS and Zurich), which were analyzed separately [24]. No studies evaluated the relationship between the BAR score and 3-year graft loss.

Risk of bias assessment

According to PROBAST, 20 studies included in the DRI analysis were rated low risk of bias, 10 studies were rated high risk of bias, and in 8 studies the risk of bias was rated unclear. The risk of bias was high in five studies (50%) in the domain "Participants" [21,31,41,52,54]. In the domain "Predictors," the risk of bias was rated high in eight studies (80%) [11,31,37,41,44,51,52,55]. The risk of bias was rated high in the domain "Outcomes" in one study (10%) [54]. Also, in the domain "Analysis," the risk of bias was rated high in only one study (10%) [52]. Thirty studies had high applicability concerns, and 8 studies had low applicability concerns. One study had high applicability concerns in the domain "Participants" (3%) [54]. In the remaining 29 studies (97%), high applicability concerns were observed only in the domain "Outcomes" [11,20,26–29,31,33–39,41,43–46,48–53,55–57]. According to PROBAST, seven studies included in the ET-DRI analysis were rated low risk of bias, and one was rated high risk of bias [9,10,20–22,32,42,58]. In the study by Winter *et al.*, the domain "Participants' was rated high risk of bias [21]. Five studies had low applicability concerns, and three studies had high applicability concerns in the domain "Outcomes" [10,32,42]. Nine studies included in the BAR score analysis were rated low risk of bias [10,20,23,24,59–63]. Only one study was rated high risk of bias in the domain "Predictors" [11]. Applicability concerns were low in three studies included in the BAR score analysis [20,23,24]. Seven studies had high applicability concerns in the domain "Outcomes" [11,59–64]. The quality assessment of the included studies is shown in Supporting Table S1.

Quantitative analysis

Meta-analysis of DRI

Based on six studies with a total of 35 580 patients that reported on different DRI values and intervals, and graft loss following liver transplantation, we were able to stratify the DRI into three groups (Table 4) [3,7–9,20,21]. We analyzed DRI < 1.2, 1.2 ≤ DRI < 1.4, and DRI ≥ 1.4 and compared 3-month, 1-year, and 3-year graft loss between the groups.

Graft loss in DRI < 1.2 vs. 1.2 ≤ DRI < 1.4 groups. Three-month graft loss was not different between recipients of DRI < 1.2 grafts and 1.2 ≤ DRI < 1.4 grafts (five studies with 14 849 patients; OR = 1.12, 95% CI = 0.92–1.36, $P = 0.26$, $I^2 = 28\%$, $P = 0.23$). One-year and 3-year graft loss were higher if the DRI was < 1.2 compared with graft loss of recipients who were transplanted with 1.2 ≤ DRI < 1.4 grafts (six studies with 16 574 patients; OR = 1.16, 95% CI = 1.03–1.31, $P = 0.02$, $I^2 = 20\%$, $P = 0.28$ and OR = 1.16; 95% CI = 1.01–1.33, $P = 0.04$, $I^2 = 40\%$, $P = 0.14$, respectively) (Fig. 2).

Graft loss in 1.2 ≤ DRI < 1.4 vs. DRI ≥ 1.4 groups. The DRI ≥ 1.4 group had poorer 3-month graft loss than that in the 1.2 ≤ DRI < 1.4 group (five studies with 19 691 patients; OR = 1.45, 95% CI = 1.31–1.60, $P < 0.00001$, $I^2 = 0\%$, $P = 0.83$). Also, 1-year and 3-year graft loss were poorer in the DRI ≥ 1.4 group

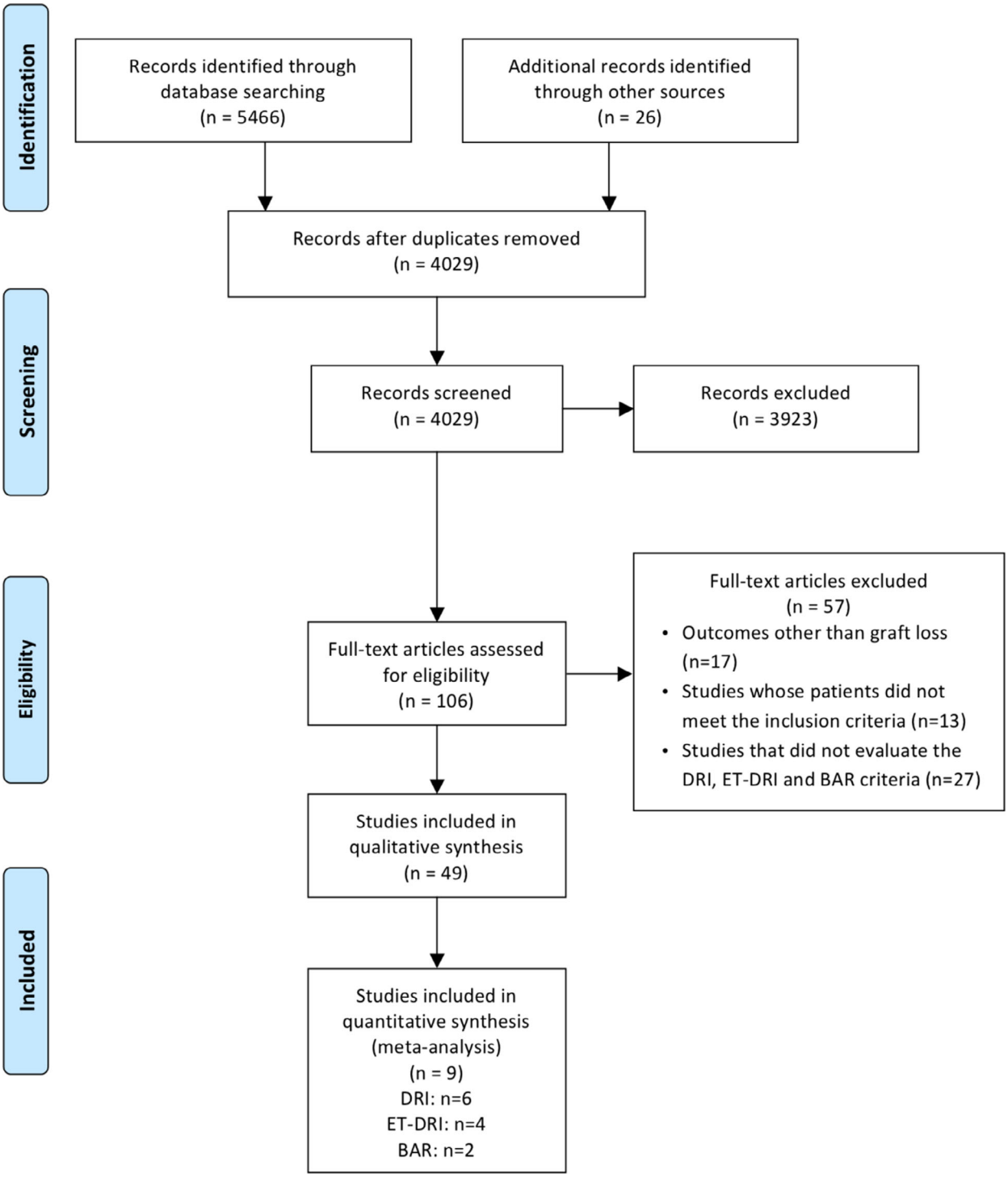

Figure 1 PRISMA flowchart.

compared with the $1.2 \leq \text{DRI} < 1.4$ group (six studies with 24 858 patients; OR = 1.36, 95% CI = 1.25–1.48, $P < 0.00001$, $I^2 = 10\%$, $P = 0.35$ and OR = 1.36; 95% CI = 1.19–1.55, $P < 0.00001$, $I^2 = 55\%$, $P = 0.05$, respectively) (Fig. 3).

Analysis of discrimination and estimation of an optimal cutoff value for the DRI

Area under the receiver operator characteristic curve (ROC) for 3-month graft loss was reported in eight

Table 1. Study characteristics of included trials that analyzed DRI-associated graft loss.

First author and year	Study period	Nr. of patients	Age (median or mean ± SD)	Gender (male/female)	Race	Study groups	Outcome	Follow-up
Feng, 2006* [8]	01.1998–12.2002	20 023	0–17: 2394 18–39: 7852 40–49: 3752 50–59: 3273 60–69: 1896 70 + 85: 6	11 911/8112	Caucasian: 17 143 African American: 2337 Other: 523	0.0 < DRI ≤ 1.0, 1.0 < DRI ≤ 1.1, 1.1 < DRI ≤ 1.2, 1.2 < DRI ≤ 1.3, 1.3 < DRI ≤ 1.4, 1.4 < DRI ≤ 1.5, 1.5 < DRI ≤ 1.6, 1.6 < DRI ≤ 1.8, 1.8 < DRI ≤ 2.0, 2.0 < DRI	Graft survival	3 years
Maluf, 2006* [37]	06.2002–06.2005	12 056	NA	NA	NA	EDC vs. no-EDC graft recipients (DRI = 1.7 used to define EDC grafts)	Graft survival	1 year
Volk, 2008* [52]	01.1997–08.2007	47 985	NA	NA	NA	pre-MELD vs. post-MELD era	Patient survival	5 years
Avolio, 2008* [27]	NA	223	NA	NA	NA	low-risk DRI (DRI < 1.7), high-risk DRI (DRI ≥ 1.7)	Graft survival	5 years
Boin. 2008* [30]	01.1994–12.2006	232	NA	NA	NA	HCV- and HCV + graft recipients Patient survival of HCV + recipients transplanted with grafts from donors older or younger than 50 years. *DRI = 1.7 used as cutoff	Patient survival	5 years
Schaubel, 2008* [44]	09.2001–07.2005	26 165	NA	NA	NA	low-risk DRI: 0 < DRI ≤ 1.075, medium risk DRI: 1.075 < DRI ≤ 1.65, high-risk DRI: DRI > 1.65	Patient survival	3 years
Bonney, 2009* [31]	01.1995–12.2005	1090	50 ± 4.61	NA	Caucasian: 1035 African American: 11 Other: 44	low-risk MELD < 15, intermediate MELD = 15–30; high-risk MELD > 30 low-risk DRI: DRI < 1.8, high-risk DRI: DRI ≥ 1.8	Graft survival, patient survival	1–125 months
Maluf, 2009* [38]	01.2000–06.2006	16 678	NA	9940/6738	Caucasian: 12 178 African American: 2138 Hispanic: 1859 Asian: 198 Other: 523	HCV- and HCV + graft recipients Effect of MELD score on HCV-DRI interaction	Graft survival	5 years

Table 1. Continued.

First author and year	Study period	Nr. of patients	Age (median or mean ± SD)	Gender (male/female)	Race	Study groups	Outcome	Follow-up
Vitale, 2009* [51]	12.2006–03.2008	74	53.25 ± 18.18	NA	NA	NA	PGD	1 year
Palmiero, 2010* [41]	07.2004–06.2006	1786	38.4	998/788	NA	pre- and post-MELD era	Patient survival	6 years
						low-risk DRI: DRI < 1.7 high-risk DRI: DRI ≥ 1.7		
Ghinolfi, 2011* [34]	08.2006–11.2007	148	51.2 ± 20.3	80/68	NA	temporary portocaval shunt (TPCS) and (no-TPCS).	Graft survival	2.5 years
						low-risk DRI: DRI < 1.8 high-risk DRI: DRI ≥ 1.8		
Ozhathil, 2011* [55]	01.2002–12.2008	31 576	NA	18 798/12 778	Caucasian: 21 928 African American: 4798 Other: 4850	low-risk DRI: DRI ≤ 1.63 moderate risk DRI: 1.64 < DRI ≤ 1.90 high-risk DRI: 1.90 < DRI ≤ 2.26 very high-risk DRI: DRI > 2.26	Graft survival	6 years
Dutkowski, 2011* [11]	12.1987–09.2010	37 255 (UNOS) 200 (Zurich)	41.75 ± 8.36	25 554/11 934	NA	MELD < 10, MELD = 10–19, MELD = 20–29, MELD ≥ 30 0.0 < DRI ≤ 1.2, 1.2 < DRI ≤ 1.4, 1.4 < DRI ≤ 1.6, 1.6 < DRI ≤ 1.8, DRI > 1.8	Patient survival	7 years
Uemura, 2012* [50]	02.2002–12.2007	7508	52.25	5653/1855	Caucasian: 5487 African American: 706 Hispanic: 1066 Asian: 179 Other: 70	low-risk DRI: DRI < 2.0 high-risk DRI: DRI ≥ 2.0	Graft survival, patient survival	5 years
Schrem, 2012* [45]	01.2007–03.2011	291	47 ± 17.89	177/114	NA	low-risk DRI: DRI < 1.7 high-risk DRI: DRI ≥ 1.7	Graft survival, patient survival	3 months
Braat, 2012* [9]	01.2003–12.2007	5148	48	2770/2378	NA	0.0 < DRI ≤ 1.0, 1.0 < DRI ≤ 1.2, 1.2 < DRI ≤ 1.4, 1.4 < DRI ≤ 1.6, 1.6 < DRI ≤ 1.8, 1.8 < DRI ≤ 2.0, DRI > 2.0	FFS†	3 years
Blok, 2012* [3]	01.2003–12.2007	5939	48	3194/2745	NA	0.0 < DRI ≤ 1.0, 1.0 < DRI ≤ 1.2, 1.2 < DRI ≤ 1.4, 1.4 < DRI ≤ 1.6, 1.6 < DRI ≤ 1.8, 1.8 < DRI ≤ 2.0, DRI > 2.0	FFS†	5 years

Table 1. Continued.

First author and year	Study period	Nr. of patients	Age (median or mean ± SD)	Gender (male/female)	Race	Study groups	Outcome	Follow-up
Croome, 2012* [33]	01.2006–09.2010	310	45.82 ± 10.07	NA	NA	low MELD: MELD < 15 intermediate MELD: 15 ≤ MELD<26) high MELD: MELD > 30	EAD[§] graft survival	6 months
Silberhumer, 2013* [46]	2000–2005	4701	43.25 ± 7.21	2628/2073	NA	low-risk DRI: DRI ≤ 1.17 moderate risk DRI: 1.17 < DRI ≤ 1.67 high-risk DRI: DRI > 1.67	Patient survival	1 year
Rauchfuss, 2013* [53]	12.2006–05.2011	45	NA	NA	NA	low DRI: DRI < 1.8 high DRI: DRI ≥ 1.8	Patient survival	1 year
Stey, 2013* [48]	01.1994–12.2004	1289	47	NA	NA	DRI ≤ 1.6, 1.6 < DRI ≤ 1.8, 1.8 < DRI ≤ 2.0, 2.0 < DRI ≤ 2.25, 2.25 < DRI ≤ 2.5, 2.5 < DRI ≤ 2.75, 2.75 < DRI≤3.0, 3.0 < DRI ≤ 3.5, 3.5 < DRI ≤ 4.0	Graft survival	3 years
Sarkut, 2014* [43]	12.2007–05.2012	47	45	NA	NA	low-risk DRI: DRI < 1.7, high-risk DRI: DRI ≥ 1.7	EAD[§]	6 months
Mathur, 2014* [39]	03.2002–12.2008	19 249	41.45	11 817/7432	Caucasian: 14 427 African American: 1727 Hispanic: 2395 Asian: 521 Other: 179	low-risk DRI: DRI < 1.0 medium risk DRI: 1.0 < DRI ≤ 1.7 high-risk DRI: DRI > 1.7	Graft survival	Follow-up until the earliest of graft failure[#]
Aranzana, 2015* [26]	07.2006–07.2009	1006	40.79 ± 16.1	NA	NA	NA (*DRI = 2.25 as the best cutoff value)	Patient survival	2 years
Adler, 2015* [56]	2002–2009	NA	NA	NA	NA	NA	Graft survival	NA
Jesudian, 2016* [35]	1998–2013	312	<50: 188 50–59: 53 60–69: 47 >70: 24	187/125	Caucasian: 161 African American: 110 Other: 41	low-risk DRI: DRI < 1.7 high-risk DRI: DRI ≥ 1.7 (for assessing fibrosis progression) low-risk DRI: DRI < 1.5 high-risk DRI: DRI ≥ 1.5 (for assessing patient survival)	Patient survival, progression of fibrosis	1–180 months
Stine, 2016* [49]	02.2002–03.2015	60 404	41.55	35 582/24 822	African American: 9923 Other: 50 481	low-risk DRI: DRI < 1.7 high-risk DRI: DRI ≥ 1.7	Graft loss due to HAT	3 months
Lau, 2017* [36]	01.1988–11.2013	180	45.8 ± 16.8	95/85	Caucasian: 157 Other: 15 Not recorded: 8	NA	Prediction of graft failure[#]	3 months

Table 1. Continued.

First author and year	Study period	Nr. of patients	Age (median or mean ± SD)	Gender (male/female)	Race	Study groups	Outcome	Follow-up
Benko, 2017* [29]	NA	116	63.2 ± 1.26	68/68	NA	16 < POP-MELD ≤ 16 on 5th postoperative day DRI = 1.79 as the best cutoff value	PNF$, EAD§, graft survival, patient survival	1 year
Beal, 2017* [28]	02.2002–12.2015	48 958	54.66	33 563/15 395	Caucasian: 35 227 African American: 4769 Other: 9160	high-risk DRI: DRI ≥ 1.9	Graft survival, patient survival	1 year
Schlegel, 2017* [24]	01.2003–12.2014	100 (Zurich) 3229 (UNOS)	50	NA	NA	low-risk DRI: DRI ≤ 1.8 high-risk DRI: DRI > 1.8 low-risk MELD: MELD < 30 high-risk MELD: MELD ≥ 30	Graft survival, patient survival	5 years
Winter, 2017* [21]	2009–2013	3677	54.2 ± 18.4	2033/1643	Caucasian: 3677	0.0 < DRI ≤ 1.0, 1.0 < DRI ≤ 1.1, 1.1 < DRI ≤ 1.2, 1.2 < DRI ≤ 1.3, 1.3 < DRI ≤ 1.4, 1.4 < DRI ≤ 1.5, 1.5 < DRI ≤ 1.6, 1.6 < DRI ≤ 1.8, 1.8 < DRI ≤ 2.0, DRI > 2.0	Graft survival	3 years
Lozanovski, 2018* [7]	12.2006–03.2014	465	59.2 ± 16.9	259/206	NA	0.0 < DRI ≤ 1.0, 1.0 < DRI ≤ 1.2, 1.2 < DRI ≤ 1.4, 1.4 < DRI ≤ 1.6, 1.6 < DRI ≤ 1.8, 1.8 < DRI ≤ 2.0, DRI > 2.0	Graft survival, patient survival	5 years
Boecker, 2019* [20]	05.2010–11.2017	328	56 ± 15	174/154	NA	0.0 < DRI ≤ 1.2, 1.2 < DRI ≤ 1.4, 1.4 ≤ DRI	Graft survival, patient survival	5 years
Scheuermann, 2019* [75]	02.2002–03.2016	63 906	<40: 28 312 40–49: 12 288 50–59: 12 777 60–69: 7412 70+: 3117	NA	Caucasian: 42 870 African American: 10 694 Other: 10 342	0 < DRI ≤ 1.08, 1.08 < DRI ≤ 1.27, 1.27 < DRI ≤ 1.49, 1.49 < DRI ≤ 76, DRI > 1.76	Graft survival	10 years
de Boer, 2019* [58]	01.2005–12.2015	62294	41	37 202/25 092	Caucasian: 49 078 African American: 11 232 Other: 1984	0 < DRI ≤ 20%, 20%<DRI ≤ 40%, 40%<DRI ≤ 60%, 60%<DRI ≤ 80%, DRI > 80%	Graft survival, patient survival	5.5 years
Cherchi 2020* [57]	01.2010–06.2018	77	NA	NA	NA	ICG-PDR < 16%/min ICG-PDR ≥ 16%/min	EAD, patient survival	5 years

Table 1. Continued.

First author and year	Study period	Nr. of patients	Age (median or mean ± SD)	Gender (male/female)	Race	Study groups	Outcome	Follow-up
Freitas, 2020* [54]	01.2017–12.2018	520	42 ± 16	314/206	Caucasian: 392 African American: 34 Brown: 91 Asian: 3	low-risk DRI: DRI < 1.61 high-risk DRI: DRI ≥ 1.61 low MELD: MELD < 15 intermediate MELD: 15 ≤ MELD ≤ 30) high MELD: MELD > 30	Waiting list allocation	2 years

All studies included in the DRI meta-analysis are retrospective.

COD, cause of death; DRI, Donor Risk Index; EAD, Early Allograft Dysfunction; EDC, Extended Donor Criteria; FFS, Failure-free Survival; HAT, Hepatic Artery Thrombosis; HCV, Hepatitis C Virus; ICG-PDR, indocyanine green plasma disappearance rate; MELD, Model of End-stage Liver Disease; NA, not available; PGD, Primary Graft Dysfunction; PNF, Primary Nonfunction, POP-MELD, Postoperative MELD score; SD, standard deviation; UNOS, United Network for Organ Sharing.

*According to Feng *et al*. [8] Donor risk index = exp[(0.154 if 40 ≤ age < 50) + (0.274 if 50 ≤ age < 60) + (0.424 if 60 ≤ age < 70) + (0.501 if 70 ≤ age) + (0.079 if COD = anoxia) + (0.145 if COD = CVA) + (0.184 if COD = other) + (0.176 if race = African American) + (0.126 if race = other) + (0.411 if DCD) + (0.422 if partial/split) + (0.066 ((170–height)/10)) + (0.105 if regional share) + (0.244 if national share) + (0.010 × cold time)].

[†]FFS was defined as the period from date of transplantation until the date of retransplantation or recipient death, whichever occurred first.

[#]Graft failure was defined as recipient death or need for retransplantation.

[$]PNF was defined as post-transplant liver dysfunction requiring emergency retransplantation or leading to death within 7 days.

[§]EAD was defined as: bilirubin ≥ 10mg/dl on POD7 and/or INR ≥ 1.6 on POD7 and/or AST or ALT more than 2000 IU/l within the first 7 days.

Table 2. Study characteristics of included trials that analyzed ET-DRI-associated graft loss.

First author and year	Study period	Nr. of patients	Age (median or mean ± SD)	Gender (male/female)	Race	Study groups	Outcome	Follow-up
Braat, 2012[+] [9]	01.2003–12.2007	5013	48	2770/2378	NA	0.0 < ET-DRI ≤ 1.0, 1.0 < ET-DRI ≤ 1.2, 1.2 < ET-DRI ≤ 1.4, 1.4 < ET-DRI ≤ 1.6, 1.6 < ET-DRI ≤ 1.8, 1.8 < ET-DRI ≤ 2.0, ET-DRI > 2.0	Graft survival	3 years
Reichert, 2013[+] [42]	01.2007–12.2010	291	48.4	177/114	NA	ET-DRI = 2.06 cutoff as predictor of 3-month patient mortality ET-DRI = 1.95 cutoff as predictor of 3-month graft failure	Graft survival, patient survival	3.8 years
Blok, 2015[+] [10]	01.2008–12.2010	4466	56.5 ± 11.55	2342/2124	NA	0.0 < ET-DRI ≤ 1.0, 1.0 < ET-DRI ≤ 1.2, 1.2 < ET-DRI ≤ 1.4, 1.4 < ET-DRI ≤ 1.6, 1.6 < ET-DRI ≤ 1.8, 1.8 < ET-DRI ≤ 2.0, ET-DRI > 2.0	Graft survival, patient survival	4 years
Buescher, 2016[+] [32]	1988–1992	179	NA	NA	NA	low-risk: ET-DRI < 1.21 moderate risk: 1.21 < ET-DRI ≤ 1.4 high-risk: ET-DRI > 1.4	Patient survival	20 years
Schoening, 2016[+] [22]	09.1988–12.2012	1767	NA	NA	NA	1.0 < ET-DRI ≤ 1.2, 1.2 < ET-DRI ≤ 1.4, 1.4 < ET-DRI ≤ 2.0, ET-DRI > 2.0	Graft survival, patient survival	15 years
Winter, 2017[+] [21]	2009–2013	4558	54.2 ± 18.4	2033/1643	Caucasian: 3677	0.0 < ET-DRI ≤ 1.0, 1.0 < ET-DRI ≤ 1.2, 1.2 < ET-DRI ≤ 1.4, 1.4 < ET-DRI ≤ 1.6, 1.6 < ET-DRI ≤ 1.8, 1.8 < ET-DRI ≤ 2.0, ET-DRI > 2.0	Graft survival	3 years
Boecker, 2019[+] [20]	05.2010–11.2017	328	56 ± 15	174/154	NA	1.0 < ET-DRI ≤ 1.2, 1.2 < ET-DRI ≤ 1.4, ET-DRI ≥ 1.4	Graft survival, patient survival	5 years

Table 2. Continued.

First author and year	Study period	Nr. of patients	Age (median or mean ± SD)	Gender (male/female)	Race	Study groups	Outcome	Follow-up
de Boer, 2019[+] [58]	01.2005–12.2015	62 294	41	37 202/25 092	Caucasian: 49 078 African American: 11 232 Other: 1984	0 < ET-DRI ≤ 20%, 20%<ET-DRI ≤ 40%, 40%<ET-DRI ≤ 60%, 60%<ET-DRI ≤ 80%, ET-DRI > 80%	Graft survival, patient survival	5.5 years

All studies included in the ET-DRI meta-analysis are retrospective.
COD, cause of death; ET-DRI, Eurotransplant Donor Risk Index; NA, not available; SD, standard deviation.
[+]According to Braat *et al.* [9] ET-DRI = exp[0.960((0.154 if 40 ≤ age < 50) + (0.274 If 50 ≤ age < 60) + (0.424 if 60 ≤ age < 70) + (0.501 if 70 ≤ age) + (0.079 if COD = anoxia) + (0.145 × if COD = cerebrovascular accident) + (0.184 if COD = other) + (0.411 if DCD) + (0.422 if partial/split) + (0.105 if regional share) + (0.244 if national share)) + (0.010 × (cold ischemia time − 8 h)) + 0.06((latest laboratory gamma-glutamyltransferase (U/L)- 50)/100) + (0.180 if rescue offer)].

studies [20,21,24,29,36,45,46,64]. The ROC for 1-year graft loss was reported in three studies [23,46,64]. No AUC values were identified for 3-year graft loss and discrimination was generally low (3-month graft loss: 0.475–0.68; 1-year graft loss: 0.5–0.557). Consequently, pooled summary estimates and prediction intervals covered 0.5, indicating low discriminatory power of the DRI for predicting graft loss. The optimal summary DRI cutoff estimated using SROC was 1.8, with a sensitivity of 0.525 and a specificity of 0.73 (Supporting Figures S1 and S2).

Meta-analysis of ET-DRI

Four studies with a total of 11 666 patients reported graft loss following liver transplantation and analyzed different ET-DRI values (Table 4) [9,20–22]. Similar to the meta-analysis of DRI and based on available cutoff values, we stratified ET-DRI into three groups and compared 3-month, 1-year, and 3-year graft loss between them: 1 ≤ ET-DRI < 1.2, 1.2 ≤ ET-DRI < 1.4, and ET-DRI ≥ 1.4.

Graft loss in 1.0 ≤ ET-DRI < 1.2 vs. 1.2 ≤ ET-DRI < 1.4 groups. There were no differences in 3-month graft loss between recipients of 1 ≤ ET-DRI < 1.2 grafts and 1.2 ≤ ET-DRI < 1.4 grafts (three studies with 2121 patients; OR = 1.09, 95% CI = 0.79–1.50, $P = 0.61$, $I^2 = 13\%$, $P = 0.32$). Also, 1-year and 3-year graft loss did not differ between the ET-DRI < 1.2 and 1.2 ≤ ET-DRI < 1.4 groups (OR = 1.17, 95% CI = 0.80–1.70, $P = 0.41$, $I^2 = 54\%$, $P = 0.09$ (four studies with 2734 patients) and OR = 1.10, 95% CI = 0.76–1.59, $P = 0.62$, $I^2 = 53\%$, $P = 0.12$ (three studies with 2121 patients), respectively) (Fig. 4).

Graft loss in 1.2 ≤ ET-DRI < 1.4 vs. ET-DRI ≥ 1.4 groups. ET-DRI ≥ 1.4 grafts were associated with poorer 3-month graft loss than 1.2 ≤ ET-DRI < 1.4 grafts (three studies with 8914 patients; OR = 1.28, 95% CI = 1.08–1.53, $P = 0.005$, $I^2 = 0\%$, $P = 0.87$). Also, 1-year and 3-year graft loss were worse in the ET-DRI ≥ 1.4 group (OR = 1.32, 95% CI = 1.15–1.51, $P < 0.001$, $I^2 = 0\%$, $P = 0.40$ (four studies with 10 732 patients) and OR = 1.25, 95% CI = 1.07–1.47, $P = 0.006$, $I^2 = 21\%$, $P = 0.28$ (three studies with 8914 patients), respectively) (Fig. 5).

Analysis of discrimination and estimation of an optimal cutoff value for the ET-DRI

A ROC for 3-month graft loss was presented in four studies [20,21,42,64]. Two studies presented a ROC for

Table 3. Study characteristics of included trials that analyzed BAR score-associated graft loss.

First author and year	Study period	Nr. of patients	Age (median or mean ± SD)	Gender (male/female)	Race	Study groups	Outcome	Follow-up
Dutkowski, 2011[§] [11]	12.1987–09.2010	37 255 (UNOS) 200 (Zurich)	41.75 ± 8.36	25 554/11 934	NA	low-risk BAR: BAR ≤ 18 high-risk BAR: BAR > 18	Patient survival	7 years
Angelico, 2014[§] [59]	06.2007–04.2009	1480	55.25 ± 7.79	817/663	NA	BAR (cutoff not defined)	Graft survival, patient survival	90 days
Schrem, 2014[§] [62]	01.2005–12.2010	687	NA	NA	NA	low-risk BAR: BAR ≤ 10 high-risk BAR: BAR > 10 low-risk BAR: BAR ≤ 16 high-risk BAR: BAR > 16 low-risk BAR: BAR ≤ 18 high-risk BAR: BAR > 18	Patient survival	90 days
Åberg, 2015[§] [23]	1982–2012	538	NA	NA	NA	low-risk BAR: BAR ≤ 18 high-risk BAR: BAR > 18	Graft survival	1 year
Ma, 2015[§] [60]	01.2001–05.2014	249	NA	NA	NA	Living donor BAR (cutoff not defined)	Patient survival	1 year
Schlegel, 2017[§] [24]	01.2003–12.2014	100 (Zurich) 5861 (UNOS)	55.25 ± 8.37	NA	NA	low-risk BAR: BAR ≤ 18 high-risk BAR: BAR > 18	Graft survival, patient survival	5 years
Blok, 2018[§] [64]	01.2002–12.2011	1012	48.25 ± 5.48	508/504	NA	BAR (cutoff not defined)	Graft survival, patient survival	5 years
Boecker, 2019[§] [20]	05.2010–11.2017	328	56 ± 15	174/154	NA	low-risk BAR: BAR ≤ 14 high-risk BAR: BAR > 14	Graft survival, patient survival	5 years
Martínez, 2019[§] [61]	01.2003–12.2015	202	41.6 ± 13.2	NA	NA	low-risk BAR: BAR ≤ 15 high-risk BAR: BAR > 15	Patient survival	5 years
Toledo, 2020[§] [63]	01.2012–07.2019	164	61.59 ± 16.02	NA	NA	low-risk BAR: BAR ≤ 7 high-risk BAR: BAR > 7	Patient survival	5 years

All studies included in the BAR meta-analysis are retrospective.

BAR, balance of risk; NA, not available; SD, standard deviation; UNOS, United Network for Organ Sharing.

[§]According to Dutkowski *et al.* [11].

Table 4. DRI-, ET-DRI, and BAR scores categorized graft survival.

First author and year	DRI / ET-DRI / BAR	3-month graft survival (%)	1-year graft survival (%)	3-year graft survival (%)
Feng, 2006 [8]	DRI < 1.2	90.88	85.74	78.88
	1.2 ≤ DRI < 1.4	88.65	82.78	74.72
	DRI ≥ 1.4	84.34	76.97	67.1
Blok, 2012 [3]	DRI < 1.2	NA	79.27	72.02
	1.2 ≤ DRI < 1.4	NA	77.05	70.53
	DRI ≥ 1.4	NA	72.16	62.44
Braat, 2012 [9]	DRI < 1.2	85.2	79.11	72.2
	1.2 ≤ DRI < 1.4	85.05	77.65	69.97
	DRI ≥ 1.4	80.13	71.49	62.24
	1 ≤ ET-DRI < 1.2	87.79	82.06	75.19
	1.2 ≤ ET-DRI < 1.4	83.94	76.54	70.08
	ET-DRI ≥ 1.4	80.76	71.68	62.75
Åberg 2015 [23]	BAR ≤ 18	NA	89.01	NA
	BAR > 18	NA	68.42	NA
Winter, 2017 [21]	DRI < 1.2	89.88	85.07	78.44
	1.2 ≤ DRI < 1.4	91.32	85.01	75.94
	DRI ≥ 1.4	87.88	83.44	75.61
	1 ≤ ET-DRI < 1.2	89.95	84.64	77.15
	1.2 ≤ ET-DRI < 1.4	90.75	84.33	75.86
	ET-DRI ≥ 1.4	87.84	81.37	73.74
Schoening, 2016 [22]	1 ≤ ET-DRI < 1.2	NA	92.17	NA
	1.2 ≤ ET-DRI < 1.4	NA	88.86	NA
	ET-DRI ≥ 1.4	NA	81.9	NA
Schlegel, 2017 (UNOS Data) [24]	BAR ≤ 18	87.9	78.78	NA
	BAR > 18	75.08	63.56	NA
Schlegel, 2017 (Zurich Data) [24]	BAR ≤ 18	86.11	80.55	NA
	BAR > 18	64.28	53.57	NA
Lozanovski, 2018 [7]	DRI < 1.2	97.3	94.59	94.59
	1.2 ≤ DRI < 1.4	93.18	88.64	88.64
	DRI ≥ 1.4	94.01	90.1	87.5
Boecker, 2019 [20]	DRI < 1.2	93.33	73.33	66.67
	1.2 ≤ DRI < 1.4	94.29	91.43	91.43
	DRI ≥ 1.4	85.61	79.5	74.46
	1 ≤ ET-DRI < 1.2	80	40	40
	1.2 ≤ ET-DRI < 1.4	88.24	82.35	79.41
	ET-DRI ≥ 1.4	86.85	80.97	76.12

DRI, Donor Risk Index; ET-DRI, Eurotransplant Donor Risk Index; BAR, The Balance of Risk score; NA, not available.

1-year graft loss [42,64]. No AUC values were identified for 3-year graft loss. Discrimination was low (3-month graft loss: 0.51–0.62; 1-year graft loss: 0.5–0.54). Pooled summary estimates and prediction intervals covered 0.5, indicating low discriminatory power of the ET-DRI for predicting graft loss. The optimal ET-DRI cutoff value estimated using SROC was 1.7, with a sensitivity of 0.723 and a specificity of 0.449 (Supporting Figures S3 and S4).

Meta-analysis of BAR score

Two studies with a total of 6499 patients reported graft loss following liver transplantation and analyzed the impact of different BAR score values on graft loss following liver transplantation (Table 4) [23,24]. Based on previously reported cutoff values, a BAR score of 18 was chosen as a cutoff for the purpose of the meta-analysis. We analyzed BAR ≤ 18 and BAR > 18 and compared 3-month and 1-year graft loss between the groups.

Graft loss in BAR ≤ 18 vs. BAR > 18 groups. A BAR score > 18 was associated with significantly worse 3-month graft loss (two studies with 5961 patients; OR = 2.44, 95% CI = 2.05–2.90, $P < 0.00001$, $I^2 = 0\%$, $P = 0.50$) and 1-year graft loss (two studies with 6499

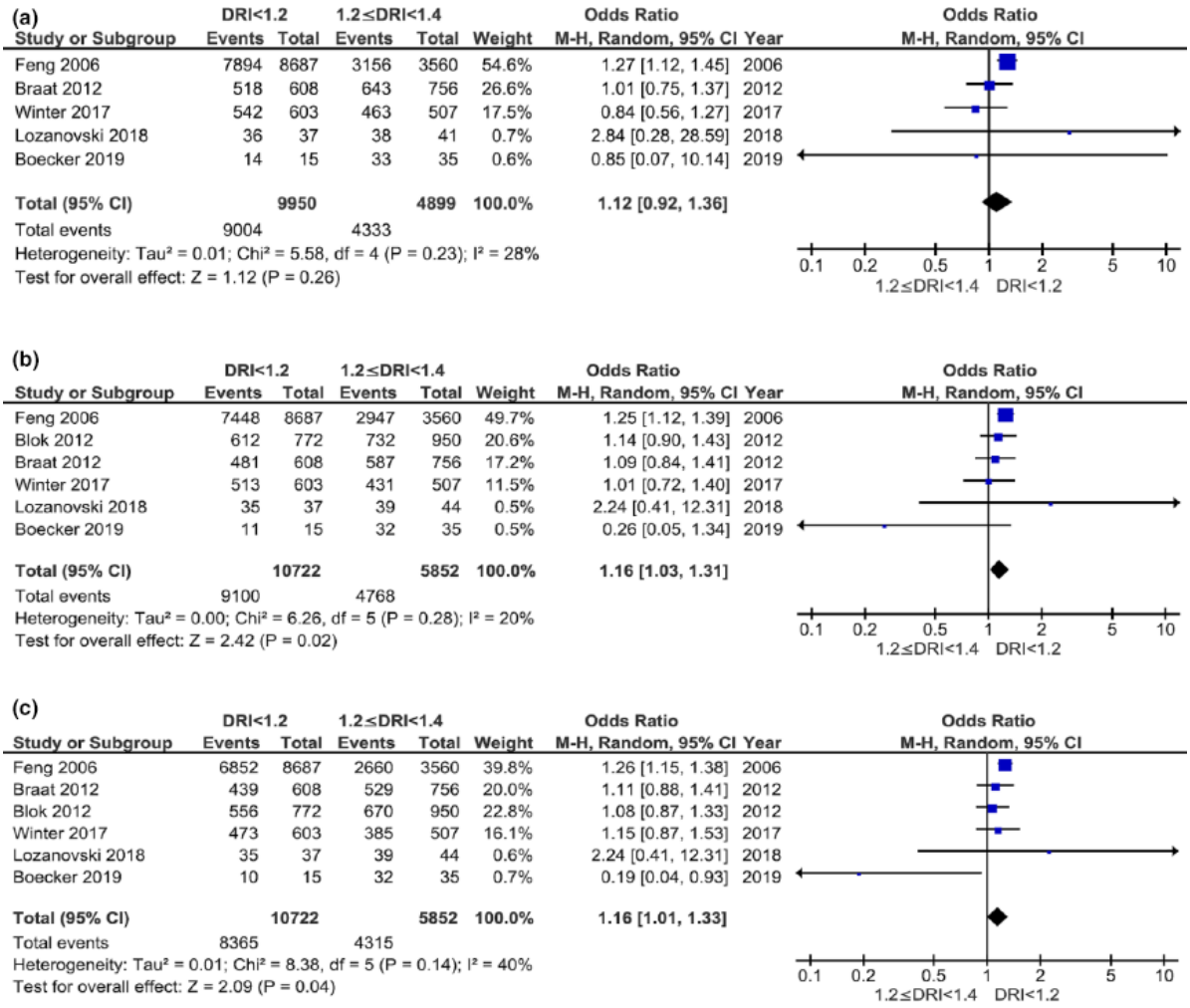

Figure 2 Individual study data, pooled effect estimates, and forest plot of the studies included in the meta-analysis. DRI < 1.2 vs. 1.2 ≤ DRI<1.4 (a) 3-month graft survival, (b) 1-year graft survival, and (c) 3-year graft survival (RevMan 5.3.5 output). DRI, Donor Risk Index; CI, confidence interval, Tau^2, true heterogeneity; df, degrees of freedom; I^2, inconsistency of the study results.

patients; OR = 2.31, 95% CI = 1.75–3.04, $P < 0.00001$, $I^2 = 12\%$, $P = 0.32$) (Fig. 6).

Analysis of discrimination and estimation of an optimal cutoff value for the BAR score

A ROC for 3-month graft loss was presented in three studies [20,59,64]. Two studies presented a ROC for 1-year graft loss [23,64]. No AUC values were identified for the 3-year graft loss. Discrimination was low (3-month graft loss: 0.57–0.73; 1-year graft loss: 0.64–0.65). The pooled summary estimate and prediction interval covered 0.5 for 3-month graft loss, indicating low discriminatory power of the BAR score for 3-month graft loss, while it did not cover 0.5 for 1-year graft loss. However, this finding was based only on two datasets. It was not possible to perform a SROC analysis of the BAR score because the number of included studies was low and the heterogeneity between data was high (Supporting Figure S5).

Discussion

In contrast to ideal grafts, EDC organs are heterogeneous and are associated with higher risk of graft failure, which will unlikely decrease unless organ preservation is improved [7,8,65]. As relative risks for a specific liver allograft and recipient, the DRI, the ET-DRI, and the BAR scores have helped in allocating organs to specific recipients, but clear cutoff values have not yet been defined.

Feng *et al.* identified eight donor and graft characteristics known at the time of organ offer that were associated with increased graft failure following deceased

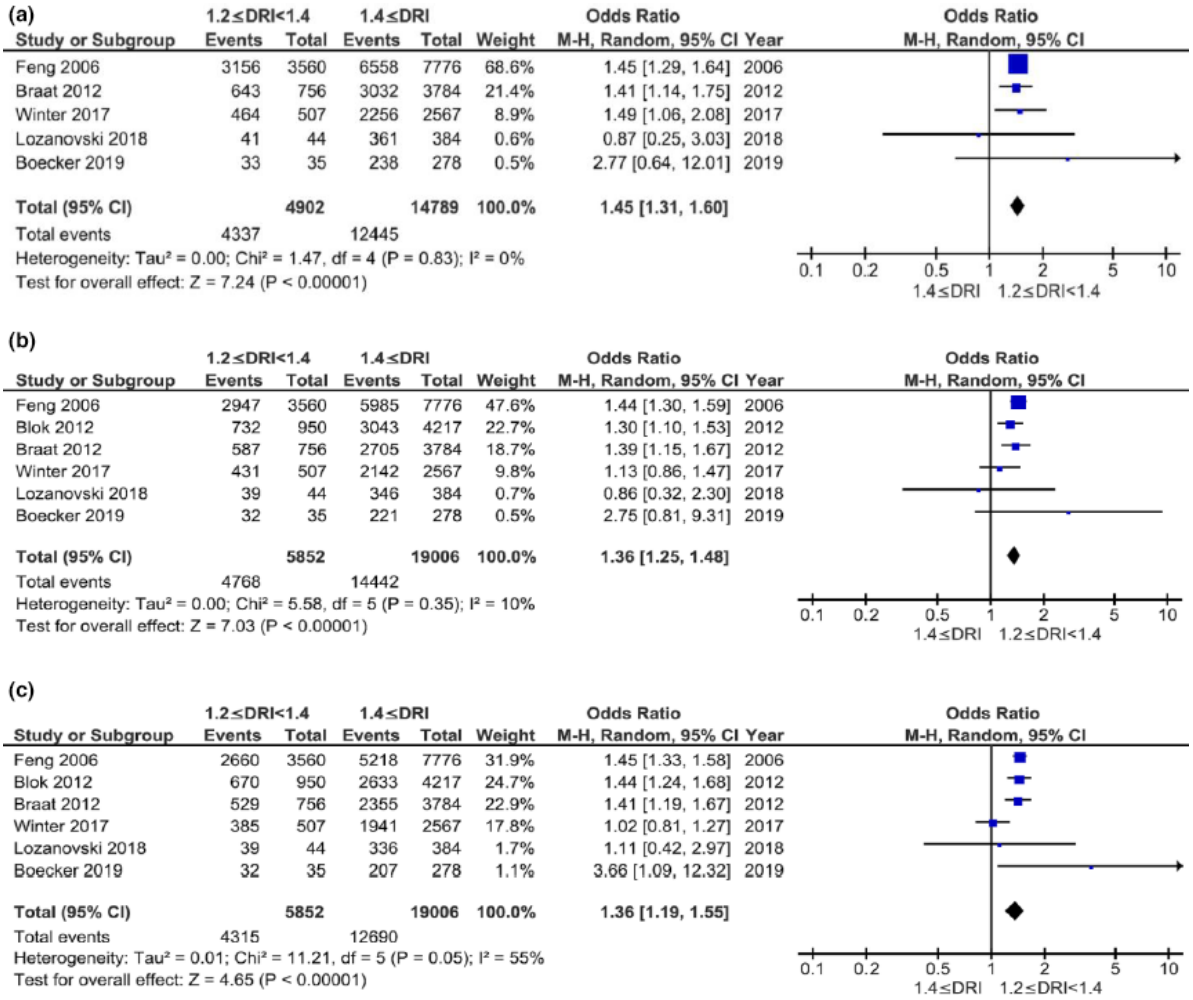

Figure 3 Individual study data, pooled effect estimates, and forest plot of the studies included in the meta-analysis. 1.2 ≤ DRI<1.4 vs. DRI ≥ 1.4 (a) 3-month graft survival, (b) 1-year graft survival, and (c) 3-year graft survival (RevMan 5.3.5 output). DRI, Donor Risk Index; CI, confidence interval, Tau^2, true heterogeneity; df, degrees of freedom; I^2, inconsistency of the study results.

donor liver transplantation [8]. Despite significant differences in donor quality between OPTN (mean DRI = 1.45) and ET (mean DRI = 1.71) regions, Blok *et al.* were able to validate the DRI within the ET [3]. The authors analyzed the failure-free survival by DRI category and found that outcome was strongly influenced by recipient parameters such as age, MELD score, and cause of liver disease—but they did not correct for these factors. In their study, they emphasized the striking difference in donor quality between OPTN and ET: 25% of ET grafts had a DRI ≥ 2.0, and 57.6% of all donors had a DRI > 1.5, which was the OPTN limit for twice as many discarded organs compared with donors with a DRI ≤ 1.1 [3,8,44]. Discrepancies between donor age, cause of death, donation after cardiac death, split liver donation, and extra-regional allocation contributed to these differences. The authors therefore suggested a specific scoring system for the ET region, and the ET-DRI was created to help estimate the risks of ET donor organs [9]. A recent French study provided data on 3-month, 1-year, and 3-year graft survival that was not affected by the DRI and failed to identify beneficial effects of lower DRI values. Moreover, the authors were not able to show that risk of graft failure increased with increasing DRI [21]. There are several possible reasons for this. The number of transplant cases used to create the DRI was more than sixfold larger than that of the French database (20 023 vs. 3681) and might have given the OPTN dataset more statistical power. Donor race was also missing in the French dataset, and donor age —a strong risk factor for graft failure—was different in the validation and the construction dataset. Furthermore, the authors had to create new variables such as local, regional, and national sharing. Finally, the French

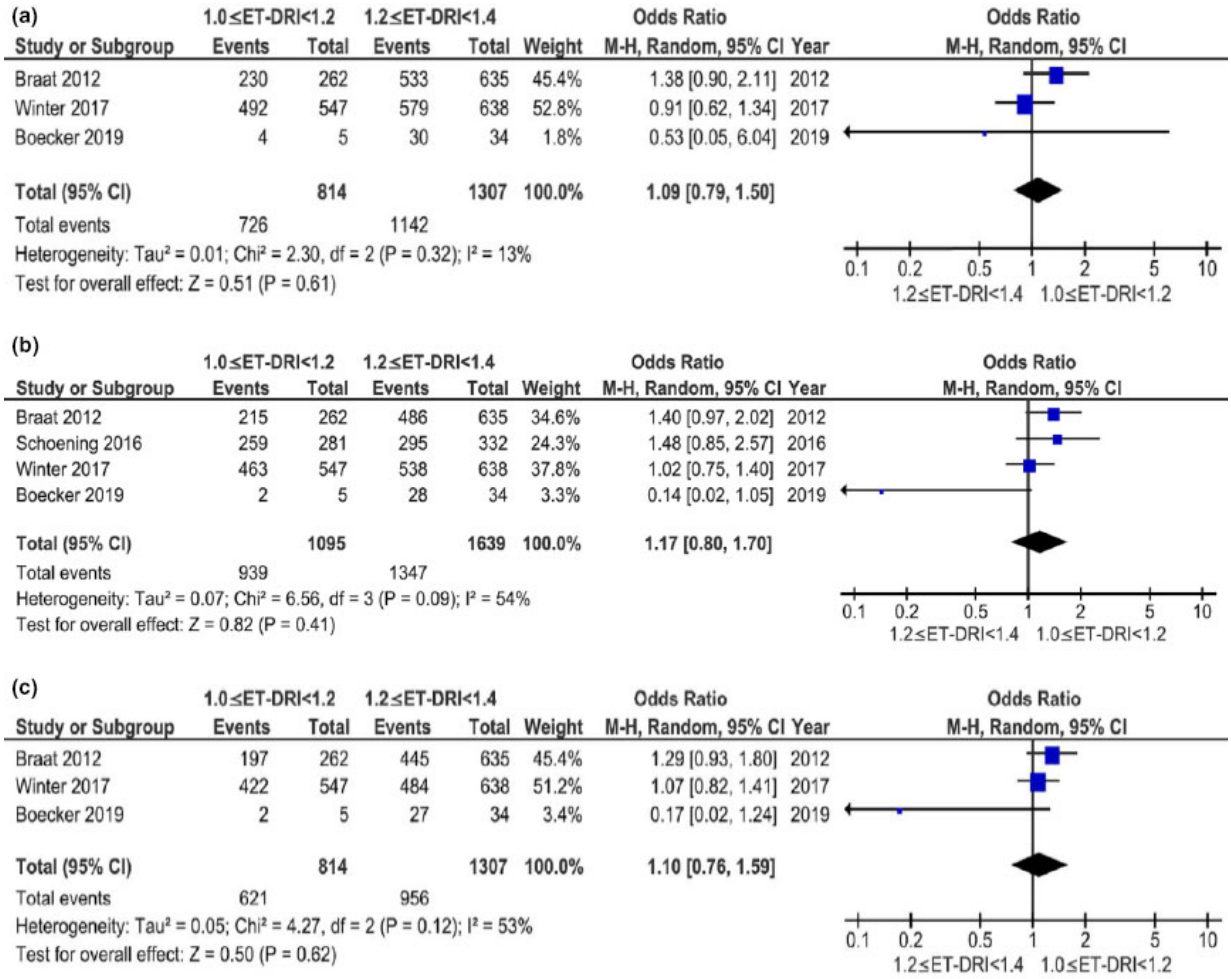

Figure 4 Individual study data, pooled effect estimates, and forest plot of the studies included in the meta-analysis. 1.0 ≤ ET-DRI < 1.2 vs. 1.2 ≤ ET-DRI < 1.4 (a) 3-month graft survival, (b) 1-year graft survival, and (c) 3-year graft survival (RevMan 5.3.5 output). ET-DRI, Eurotransplant Donor Risk Index; CI, confidence interval, Tau^2, true heterogeneity; df, degrees of freedom; I^2, inconsistency of the study results.

dataset showed diverse DRI with higher values than the OPTN dataset, which may have rendered the model inapplicable in the setting of the French collective [21]. We did not perform validation analysis in our previous study, but we found that the mean DRI increased significantly in our transplant collective from 1.53 for no-major EDC grafts (major maEDC: biopsy-proven macrovesicular steatosis > 40%, donor age > 65 years, and cold ischemia time > 14 hours) to 1.88 for grafts with one maEDC, and to 2.05 for grafts with two maEDC [7]. This indicated that DRI scores increase with the number of maEDC [7]. Because previously reported cutoffs were heterogeneous, three DRI clusters were used in this systematic review and meta-analysis. Grafts from donors with DRI < 1.2 have a zero to very low risk of graft failure three months following liver transplantation, but the risk increases at later time points. In the study of Feng *et al*., graft survival differed between grafts with high and lower DRI values three months after transplantation, and this risk increased over time [8]. This may be due to recipient factors that exert their effect after the initial phase of the transplantation. However, there are insufficient data to confirm this hypothesis. Grafts with DRI ≥ 1.4 had the greatest risk of failure and the poorest survival at every investigated time point. Grafts from donors with DRI between 1.2 and 1.4 had a higher risk of 1-year and 3-year failure than DRI < 1.2 grafts, but had lower failure rates than DRI ≥ 1.4 grafts at all investigated time points, suggesting that they have a moderate risk of failure.

Because the DRI factors are different between OPTN and ET, a specific scoring system was created for allocating organs within the ET region. Braat *et al*. removed donor height and race from DRI and added the latest

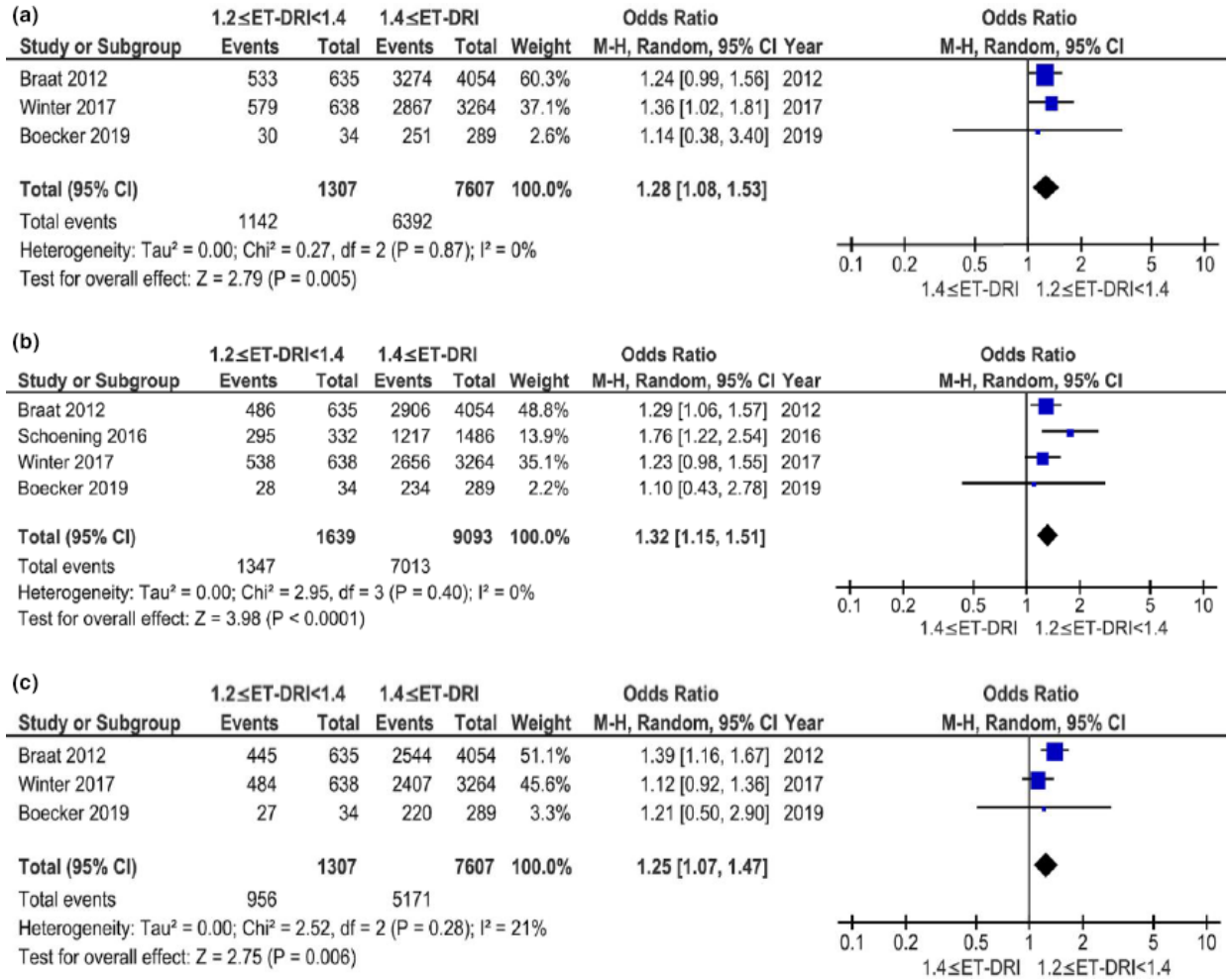

Figure 5 Individual study data, pooled effect estimates, and forest plot of the studies included in the meta-analysis. 1.2 ≤ ET-DRI < 1.4 vs. ET-DRI ≥ 1.4 (a) 3-month graft survival, (b) 1-year graft survival, and (c) 3-year graft survival (RevMan 5.3.5 output). ET-DRI, Eurotransplant Donor Risk Index; CI, confidence interval, Tau^2, true heterogeneity; df, degrees of freedom; I^2, inconsistency of the study results.

serum gamma-glutamyltransferase value and rescue allocation and created the ET-DRI—a scoring system that predicts the overall risk specific grafts have on outcome after liver transplantation in ET [9]. Winter *et al.* failed to validate the ET-DRI in a French database [21]. The authors had to create new variables such as local, regional, extra-regional sharing, and rescue allocation and proposed a re-calibration of the model. Also, Boecker *et al.* failed to validate the ET-DRI, but their study was limited by a very poor sample size [20]. In contrast, Schoening *et al.* showed that the ET-DRI can be used to allocate grafts and identified ET-DRI values of 1–1.2 as the best [22]. The present systematic review and meta-analysis showed a permanent increase in graft loss with increasing ET-DRI. Based on these findings, we suggest that grafts with an ET-DRI < 1.4 have a very low risk of failure following liver transplantation compared with livers with ET-DRI ≥ 1.4 that have the highest risk of failure at three months, one year, and three years after transplantation.

The DRI and ET-DRI are widely used, but their cut-off values are different. Included studies reported low AUC values suggesting that the scores cannot discriminate between graft loss and graft survival. Our SROC analyses confirmed that the DRI and the ET-DRI cannot accurately predict graft loss at 3 months and 1 year. The optimal pooled cutoff was 1.8 for the DRI and 1.7 for the ET-DRI, and both cutoffs had low sensitivity and specificity. This may be because one model might be preferable for the prediction of short-term graft survival and another model might be more suitable for prediction of long-term survival [64]. Therefore, although high-risk grafts have a negative impact on graft survival, simply discarding them is not a good

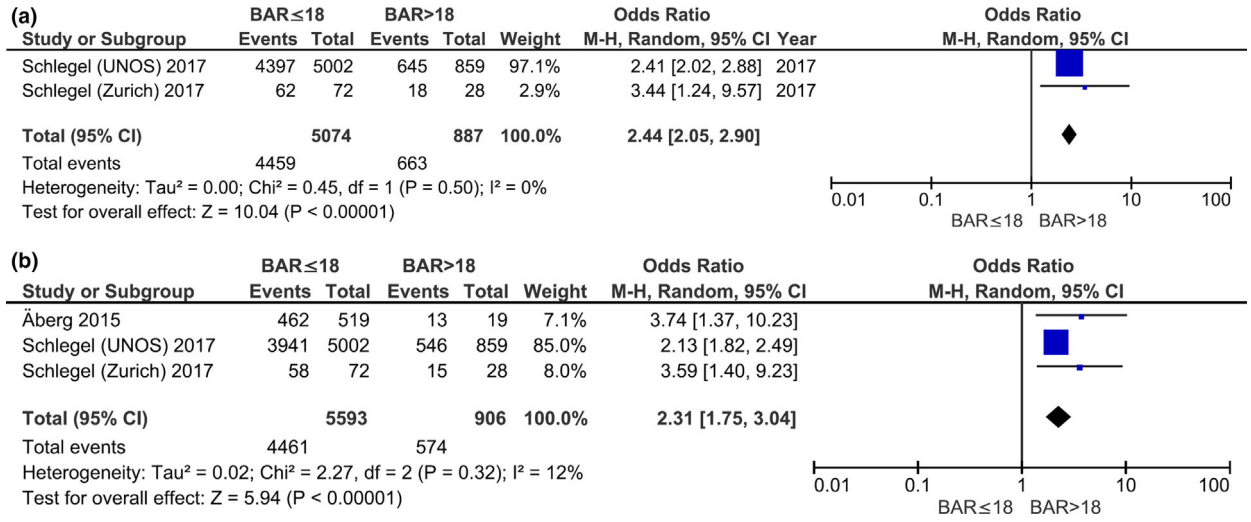

Figure 6 Individual study data, pooled effect estimates, and forest plot of the studies included in the meta-analysis. 18 ≤ BAR vs. BAR > 18 (a) 3-month graft survival and (b) 1-year graft survival (RevMan 5.3.5 output). BAR, Balance of Risk score; CI, confidence interval, Tau^2, true heterogeneity; df, degrees of freedom; I^2, inconsistency of the study results.

solution. In contrast to the US and because of chronic organ shortage, livers with DRI and ET-DRI scores between 1.2 and 1.4 have become standard grafts in most countries, especially in ET [66,67]. Moreover, DCD grafts usually have DRI and ET-DRI scores > 1.5 and often > 2.0 [66,68]. Hypothermic, normothermic, or combined machine perfusion resuscitates hepatocytes and cholangiocytes and allows EDC livers to be transplanted with excellent outcomes. Recently, De Vries *et al.* achieved excellent 3-month graft survival after transplanting ex situ perfused liver grafts with median DRI scores of 2.82 and median ET-DRI scores of 2.87 [68]. Limited by low case numbers, such excellent outcomes may be a result of an adequate hepatobiliary viability assessment during machine perfusion and before transplantation, and optimal graft selection and graft–recipient matching. Therefore, further multicenter studies with longer follow-ups are needed to clarify the effects of machine perfusion on grafts with DRI scores ≥ 1.8 and ET-DRI scores ≥ 1.7 and whether a proper donor–recipient match is prudent in such cases [69].

Dutkowski *et al.* identified six donor, graft, and recipient factors associated with the worse outcome following transplantation. They developed the BAR score using the UNOS database and validated it in the European Liver Transplant Registry [11,70]. Unlike other scores, the BAR score correlates with postoperative morbidity, hospital stay, and costs [24]. More importantly, a BAR score > 18 is associated with poor graft survival following liver transplantation [23,24]. Schlegel *et al.* evaluated UNOS and Zurich databases and emphasized the utility of the BAR score for predicting survival and postoperative morbidity [24]. The results of the present systematic review and meta-analysis are in alignment with previous reports that BAR scores > 18 are associated with significantly poorer 3-month and 1-year graft survival. However, the reported AUC values were low, suggesting that the BAR score did not discriminate between graft loss and graft survival. This may be because the number of included studies was low and data heterogeneity was high, both of which hindered the SROC analysis of the BAR score.

A limitation of this meta-analysis is the lack of randomized controlled trials. The present study is also affected by the limitations of the analyzed studies. These include overfitting—the risk that a survival model might describe random chance instead of true relationship between risk factors and survival. This might explain why Winter *et al.* could not validate the DRI [21]. This may also explain why our SROC analyses did not show that the scores can predict graft loss. However, this could also be explained by the different cutoff values among the included studies. Furthermore, ET is much smaller than the OPTN region, so distances for extra-regional sharing are not as far in ET [10]. These regional and allocation differences limit the individual studies and also our meta-analysis. Blok *et al.* validated the DRI in the ET database, but the model used in the validation dataset did not use the same covariates as the construction dataset [21,71]. In the present systematic review and meta-analysis, we were also not able to

confirm that better results could be achieved by better donor–recipient matching because recipient MELD scores were not available in the included studies. Moreover, we could not evaluate patient survival because the included studies did not report patient outcomes. Finally, inconsistent reporting of survival data hindered the SROC analysis of 3-year graft loss for the DRI and ET-DRI and the SROC analysis of 3-month, 1-year, and 3-year graft survival for the BAR score.

Mortality while waiting for a donor organ is the most important factor for accepting an EDC organ, and transplant surgeons have to balance the risks and benefits to the recipient. Patients who are most sick (MELD $\geq$ 20) have the greatest survival benefit from transplantation [4,8]. However, they also may have disproportionately poorer outcomes if they receive a higher risk graft, although the interaction between donor organ quality and recipient disease severity is still incompletely defined [8]. Schaubel *et al.* demonstrated that transplant candidates with MELD $\geq$ 20 who were transplanted with high-DRI livers (>1.65) had better survival. This was even observed in patients with MELD scores as high as 40. Therefore, the authors discouraged inversed matching of MELD score and DRI [44]. In contrast, Schoening *et al.* observed a significant increase in mean ET-DRI and laboratory model of end-stage liver disease score (labMELD) over time, showing that most donor organs are low quality and that low-quality organs are most often allocated to sicker recipients. By matching the ET-DRI with the labMELD scores, the authors suggested that good long-term graft survival can be achieved by allocating higher risk organs with ET-DRI > 1.4 to patients with cholestatic or autoimmune diseases or hepatitis C virus infection, whereas organs with ET-DRI > 2 should not be allocated to patients with a labMELD of > 25–35. In our previous study, we suggested that grafts with more than one maEDC could be allocated to recipients in a better clinical condition and with lower labMELD scores, such as transplant candidates with hepatocellular carcinoma [72]. This is in alignment with the findings of Schoening *et al.* who also showed that patients with hepatocellular carcinoma had the same long-term benefit from low and high ET-DRI grafts [7,22]. We previously showed that steatosis is the strongest predictive factor of negative outcomes after liver transplantation and that the DRI increases in the presence of maEDC. Therefore, we suggested that current DRIs be modified to include macrovesicular steatosis in their calculation [7]. DRI and ET-DRI calculations include cold ischemia time, but Feng *et al.* and Braat *et al.* did not consider indication for transplantation as confounder and assumed constant linear influence of cold ischemia time with a fixed coefficient (0.010) [8,9]. By doing so, the categorical effect of cold ischemia could not be observed, especially when opposite, nonlinear influence is evident [73]. In our recent study, we found that the influence of cold ischemia is nonlinear and important only during the first year after liver transplantation and that it also depends on the indication for liver transplantation [73]. This effect was especially strong in patients with hepatocellular carcinoma and alcoholic liver cirrhosis [73]. Therefore, we suggested that similar to donor age, a categorical model that also considers the underlying disease should be preferred to a linear one in the case of cold ischemia time, and that including cold ischemia time as categorical variable and different indications for transplantation with their respective coefficients might increase the specificity of the DRIs [73,74]. Indeed, large multicenter studies are needed to verify these results, but transplant trials with longer follow-up may not be necessary because, similar to cold ischemia time, the negative impact of higher scores is usually evident during the first year, and recipient characteristics such as underlying disease are more important than the graft quality at later time points.

In conclusion, despite data heterogeneity and risk of bias in the included studies, this systematic review and meta-analysis provides an important quantitative risk assessment based on DRI, ET-DRI, and BAR scores that can be used in graft allocation and reaffirms the profound benefits of choosing the right graft and identifying the most adequate recipient. It is obviously important to consider the quality of the donor organ because it is essential for optimal outcomes, but to be able to make the best decision, surgeons need to know the risk posed by the offered graft and the risk of death from progressive liver disease if the offer is declined. Therefore, DRI, ET-DRI, and BAR scores cannot replace subjective surgical experience, and using these scores and their currently proposed cutoff values alone to make decisions on graft allocation should be approached with caution.

Authorship

VJL: designed the study, collected and analyzed data, and wrote the manuscript. PP: co-designed the study, analyzed data, and revised the manuscript. AA, AR, EA, MN, EK, OG, SS, SAHAS, SS, and EK: collected and analyzed data. AN, ZC, GL, and MM: contributed knowledge and revised the manuscript. AM: co-designed

the study and revised the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPORTING INFORMATION

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

Figure S1. Pooled AUC values for the DRI. 3-month (a) and 1-year (b) follow-up.

Figure S2. Pooled analysis for the DRI with survival functions corresponding to the proportions of positive test results shown in the upper left panel (A), the Youden index shown in the upper right panel (B), study-specific ROC curves displayed in the lower left panel (C), and the SROC curve shown in the lower right panel (D).

Figure S3. Pooled AUC values for the ET-DRI. 3-month (a) and 1-year (b) follow-up.

Figure S4. Pooled analysis for the ET-DRI with survival functions corresponding to the proportions of positive test results shown in the upper left panel (A), the Youden index shown in the upper right panel (B), study-specific ROC curves displayed in the lower left panel (C), and the SROC curve shown in the lower right panel (D).

Figure S5. Pooled AUC values for the BAR score. 3-month (a) and 1-year (b) follow-up.

Table S1. Prediction model risk of bias assessment tool (PROBAST).

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