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Risk factors for recurrent autoimmune liver diseases after liver transplantation

A meta-analysis

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Abstract

Background: Autoimmune liver disease (ALD) is a chronic liver disease caused by immune dysfunction in the body. However, no causative or curative medical treatment with proven efficacy exists to cure ALDs, and liver transplantation (LT) remains the only effective treatment available. However, the problem of recurrence of ALDs (rALDs) still remains after LT, which seriously affects the survival rate of the patients. Therefore, clinicians need to be aware of the risk factors affecting rALDs after LT. Therefore, this meta-analysis aims to define the risk factors for rALDs, which include the recurrence of primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis.

Methods: A systematic search in Pubmed, Embase, Cochrane library and Web of Science databases was performed from 1980 to 2019. The inclusion criteria were risk factors for developing rALDs after LT. However, case series, case reports, reviews, meta-analysis and studies only including human immunodeficiency virus cases, children, and pregnant patients were excluded.

Results: The electronic database search yielded 1728 results. Sixty-three retrospective cohort studies met the inclusion criteria and 13 were included in the meta-analysis. The final cohort included 5077 patients, and among them, 21.96% developed rALDs. Colectomy before LT, HR 0.59 (95% confidence interval [CI]: 0.37-0.96), cholangiocarcinoma, HR 3.42 (95% CI: 1.88–6.21), multiple episodes of acute cellular rejection, HR 2.07 (95% CI: 1.27–3.37), model for end-stage liver disease score, HR 1.05 (95% CI: 1.02–1.08), use of mycophenolate mofetil, HR 1.46 (95% CI: 1.00–2.12) and the use of cyclosporin A, HR 0.69 (95% CI: 0.49–0.97) were associated with the risk of rprimary sclerosing cholangitis. In addition, the use of tacrolimus, HR 1.73 (95% CI: 1.00–2.99) and cyclosporin A, HR 0.59 (95% CI: 0.39–0.88) were associated with the risk of rALD.

Conclusions: Multiple risk factors for rALDs were identified, such as colectomy before LT, cholangiocacinoma, multiple episodes of acute cellular rejection, model for end-stage liver disease score, and especially the use of mycophenolate mofetil, cyclosporin A and tacrolimus.

Abbreviations: AIH = autoimmune hepatitis, ALD = autoimmune liver disease, CCA = cholangiocarcinoma, CI = confidence interval, ELTR = European liver transplant registry, HR = hazard ratio, IBD = inflammatory bowel disease, LDLT = living donor liver transplantation, LT = liver transplantation, MELD = model for end-stage liver disease, PBC = primary biliary cirrhosis, PSC = primary sclerosing cholangitis, rALDs = recurrence of autoimmune liver diseases, rPBC = recurrence of primary biliary cirrhosis, rPSC = recurrence of primary sclerosing cholangitis, UDCA = ursodeoxycholic acid.

Keywords: autoimmune hepatitis, autoimmune liver disease, liver transplantation, primary biliary cirrhosis, primary sclerosing cholangitis, recurrence

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) represent the classic autoimmune liver diseases (ALDs). According to epidemiological characteristics associated with ALDs, ALDs represent approximately 5% of all liver diseases and the incidence of PSC, PBC and AIH is 0.33–5.8/100000, 0–1.3/100000, 0.08-3/100000, respectively.[1] The target of the autoimmune attack in ALDs is represented by the biliary epithelial cells and the hepatocytes. Persistent liver lesion associated with chronic ALDs leads to unresolved inflammation, cell proliferation and the deposition of extracellular matrix proteins by hepatic stellate cells and portal myofibroblasts, leading to liver cirrhosis, and consequent loss of normal liver function. Patients with cirrhosis have high risks of morbidity and mortality, and decompensated cirrhosis together with complications of portal hypertension and/or liver dysfunction lead to rapid deterioration.[2]

At present, no causative or curative medical treatment with proven efficacy to cure ALDs exists, and liver transplantation (LT) is the well-accepted treatment modality to solve ALDs.[3] As regard PBC, up to 10% of the patients listed for LT in North America and Europe have a diagnosis of PBC and the 5-year survival of PBC patients after LT is greater than 80%.[4–7] As regard PSC, it also has satisfactory post-transplantation results and patient survival, reaching 80% at 5 years after orthotopic liver transplantation.[8–10] As regard AIH, in 2012 the European liver transplant registry report revealed that only 0.6% of the patients transplanted because of AIH eventually died due to recurrent AIH.[11] The survival rate of AIH at 1 and 5 years is approximately 90% and 80% respectively.[12–15]

Even though LT is considered as the best therapeutic option in patients with end-stage liver disease secondary to ALDs, this disease can recur after LT with a reported rate of 18% for PBC, 11% for PSC, and 22% for AIH.[16] However, risk factors associated with recurrence of ALDS (rALDs) after LT have not been completely described. Previous studies mainly reported several potentially modifiable risk factors for rALDs such as:

(1) colectomy before LT;
(2) presence of inflammatory bowel disease (IBD);
(3) cholangiocarcinoma (CCA) before LT;
(4) donor age;
(5) any episode of acute rejection;
(6) multiple episodes of acute cellular rejection;
(7) model for end-stage liver disease (MELD) score.

However, results were inconsistent among studies. Therefore, it is still unclear which clinical and/or pathologic variables, if any, may be predictive of disease recurrence after transplantation. In 2006, Gautam et al performed a systematic review aiming to pool all described risk factors, but due to the lack of adequate information, they were unable to perform a meta-analysis.[16] Up to now, many new studies of ALDs patients undergoing orthotopic liver transplantation exist to identify risk factors for rALDs. Therefore, enough data are available to perform an exact and systematic data analysis of the rALDs after LT. Furthermore, a meta-analysis was also performed to determine the risk factors for rALDs after LT.

2. Method

2.1. Search strategy

The literature search was performed considering the risk factors for rALDs after LT. Pubmed, Embase, Cochrane library and Web of Science databases were used from 1980 to July 2019, without any country or language restriction, using the terms ('Autoimmune Hepatitis', 'Primary Biliary Cirrhosis', 'Primary Sclerosing Cholangitides', 'Autoimmune Hepatitides' AND 'Liver Transplantation' AND 'Recurrence').[17] Two authors (CFC and RSK) independently reviewed all found studies.

2.2. Study inclusion and exclusion

The inclusion criteria of our research were the risk factors for developing rALDs after LT, such as:

(1) Diagnosis of ALD, PBC, PSC, and AIH before LT;
(2) Sample size not less than 45;
(3) Must include both rALDs and the risk factors for the recurrence;
(4) Must be cohort studies or randomized controlled trial.

Furthermore, the following article were excluded:

(1) Case series;
(2) Case reports;
(3) Reviews;
(4) Meta-analyses;

Studies only including human immunodeficiency virus cases, children, and pregnant patients.

2.3. Data extraction

(1) Baseline data: first author, publication year, publication type, number of PBC/PSC, number of female patients, donor age.
(2) Preoperative data: age at diagnosis, gender mismatch, MELD score.
(3) Intraoperative data: recipient age, deceased donor liver transplantation/ living donor liver transplantation Domino LT, ABO incompatible, biliary anastomosis, cold ischemic time.
(4) Postoperative data: acute rejection, immunosuppressants, UC/Crohn disease/other, median time to follow up and recurrence, rate of recurrence and survival.

All data with corresponding hazard ratio (HR), *P* value, and confidence interval were extracted from the included articles. Due to the lack of results of multivariate analysis, only the results of univariate analysis were used in our analysis.

2.4. Statistical analysis

Two authors evaluated the quality of the included articles using the Newcastle Ottawa Scale for cohort studies. Risk factors containing no less than 5 study data were evaluated by funnel plots for risk of publication bias. Statistical analysis was performed using Review Manager version 5.3 software (https://community.cochrane.org/help/tools-and-software/rev man-5/). The HR and the mean difference with 95% confidence interval were respectively calculated for binary data and continuous variables. Data are described as median and range, or mean and standard deviation. Random and fixed-effect models were used to calculate the combined outcomes of both binary and continuous data. As I^2 value of 30% or less was set as Low heterogeneity, fixed-effects were use when meeting the condition of low heterogeneity instead of using random models. Cochrane Handbook was used as a reference when standard deviation was

not available, thus, it was calculated according to the method described in the Cochrane Handbook. Forest plots were primarily used for the graphical presentation of the univariate analysis of the results.

2.5. Ethics

This study did not involve the use of human participants or access to personal identifying information, therefore approval by an institutional review board was not required.

3. Results

In total, 2065 citations were screened, and 63 were selected to retrieve the full-text. After reading the full text, eighteen articles were included in the qualitative analysis and univariate analysis results of 13 articles were used to establish the basis of this meta-analysis. The 13 articles were retrospective studies and 5077 study participants in 13 retrospective series were included. In addition, the quality scores of the Newcastle-Ottawa Scale of the 13 articles were above 6 points, indicating that the quality of the included retrospective studies was considered relatively high. Unfortunately, no literature is available on AIH, thus, it was not possible to include any study regarding AIH after this systematic search. The inclusion process is illustrated in Figure 1 and the characteristics of the studies are described in Tables 1 and 2. Table 1 mainly describes these features in detail: author, age at diagnosis, MELD score, cold ischemic time, biliary anastomosis, immunosuppressants, median time to follow up, and median time to recurrence. Table 2 describes the rate of recurrence and survival between 1 and 20 years.

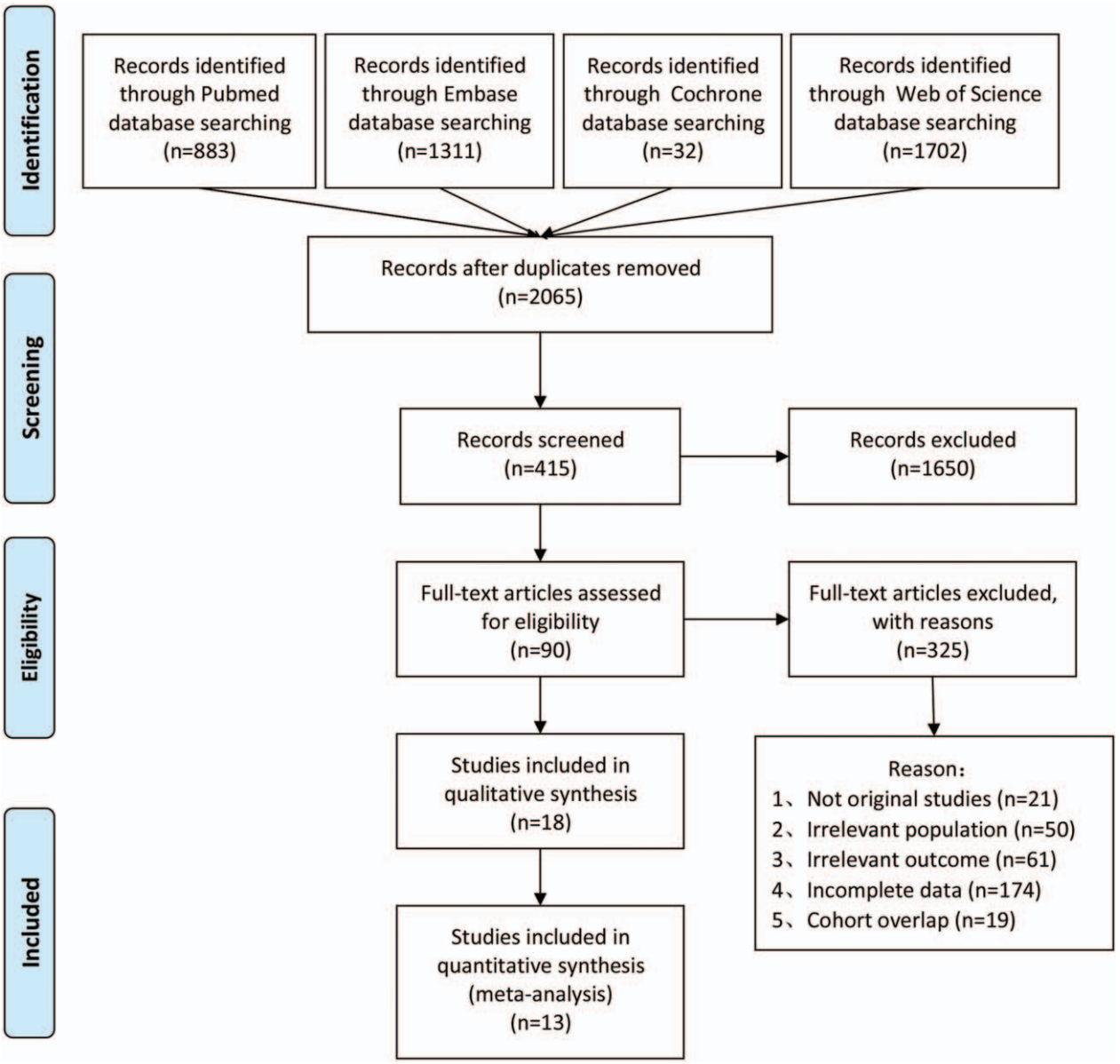

Figure 1. Inclusion process.

Table 1

Baseline characteristics of the studies.

First author	Publication year	Publication type	PBC/ PSC,N	Age at diagnosis, mean±SD (range,yr)	Female, N (%)	MELD score, mean±SD (range)	Donor Age, mean±SD (range, yr)	Recipient Age, mean±SD (range, yr)	DDLT/ LDLT/ Domino, N	Gender Mismatch, N	Cold Ischemic Time, Mean±SD (Range, min)	Biliary anastomosis, N	Acute rejection, N	Immunosuppressants, N	UC/CD/ other,N	Median time to follow up, (range,mo)	Median time to recurrence, (range, month)
A. J. Montano-Loza[7]	2010	Retrospective study, single center	PBC, 108	rPBC, 42±4; No-rPBC, 44±2	84%	rPBC, 16±2; No-rPBC, 17±1	rPBC, 37±4; No-rPBC,38±2	53±1 (21–72)	LDLT: rPBC, 0; No-rPBC,3	rPBC,9; No-rPBC,45	-	(1)End-to-end: rPBC, 22; No-rPBC, 66; (2)Roux-en-Y: rPBC, 6; No-rPBC, 14	rPBC, 28; No-rPBC, 80	-	-	88±6	70 (6–189)
A. J. Montano-Loza[26]	2019	Retrospective study, multicenter	PBC, 785	47±1	89%	-	40±1	54 (53–56)	DDLT, 757; LDLT, 28	331	-	End-to-end, 750; Roux-en-Y, 35	134	Tacrolimus, 527; Cyclosporine, 220; Sirolimus, 631; Prednisone, 15; Mycophenolate Mofetil,267; Azathioprine, 265; Everolimus, 1	-	82.8 (73.2–94.8).	52.8 (IQR,40.8–61.2)
Alexie Bosch[24]	2015	Retrospective study, multicenter	PBC, 90	45.7±9.9	85.60%	15.4±5.5 (6.4–37.9)	-	54.3±8.3	-	41	492±162	-	53	-	-	140.4±66 (18–307.2)	76.8±60 (12.0–259.2)
Christophe Corpechot[29]	2019	Retrospective conference abstract, multicenter	PBC, 941	54	88%	-	-	54	-	-	-	-	-	-	-	116.4±92.4	116.4±92.4
El Moghazy, W.[52]	2015	Retrospective conference abstract, single center	PSC, 94	-	-	-	-	41	-	-	-	-	-	-	-	>240	-
Fredric D. Gordon[21]	2016	Retrospective study, single center	PSC, 307	-	-	-	-	-	DDLT, 65; LDLT, 242	-	-	-	-	-	-	60 (0–180)	-
H. Egawa[28]	2016	Retrospective study, single center	PBC, 444	-	89%	20 (2–57)	35 (18–66)	52 (28–70)	-	297	72 (10–314)	-	-	Azathioprine, 29; Cyclophosphamide, 5; Mizoribine, 12; Mycophenolate, 106; Cyclosporine A, 12; Tacrolimus, 53	-	97.4	-
James Neuberger[25]	2004	Retrospective study, single center	PBC, 485	-	88%	-	37 (0–73)	55	-	213	694 (112–1387)	-	Cyclosporine,272; Tacrolimus, 223	Cyclosporine, 266; Tacrolimus, 90; Corticosteroids, 68	-	79	-
Jeffrey Campsen[23]	2008	Retrospective Study, Single Center	PSC, 130	-	23%	-	-	46	LDLT, 19	-	384 (16.2–918)	-	-	Sirolimus, 26	92	66	-
KJ Moncrief[19]	2010	Retrospective Study, Single Center	PSC, 59	38 (29–47)	22%	14(10–20.5)	-	46 (37–53)	-	-	-	-	-	-	42	68 (33–106)	40.2 (19.5–66.1)
Lina Lindström[18]	2018	Retrospective Study, Single Center	PSC, 440	35 (6–70)	30%	-	-	43 (11–70)	-	-	-	-	-	-	368	103.2 (0–348)	-
Lukas Bajer[51]#	2018	Retrospective Study, Single Center	PSC, 47	-	34%	15 (8–32)	37 (10–61)	36 (15–68)	-	23	319 (175–637)	End-to-end, 7; Roux-en-Y, 40	25	Tacrolimus, 32; Cyclosporine, 15	28	122 (60–249)	63 (12–180)
M. Carbone[50]#	2013	Retrospective Conference Abstract, Single Center	PBC, 248	-	-	-	-	-	–	-	-	-	-	-	-	61.8	61.8(IQR, 16.7–103.8).
Pinelopi Manousou[31]#	2010	Retrospective Study, Single Center	PBC, 103	-	92%	-	rPBC,39(19–62); No-rPBC, 40 (22–65)	rPBC,54.4; No-rPBC,52.2;	-	-	rPBC, 667 (200–1100); No-rPBC, 630 (230–1170)	-	-	Cyclosporine-based, 38; Tacrolimus-based, 62; Azathioprine, 70	-	108.5 (10–239)	72.4 (6–189)
Reena Ravikumar[20]	2015	Retrospective Study, Single Center	PSC,565	-	28.26%	-	-	49 (40–57)	DDLT: rPSC, 80; No-rPSC,467	-	-	-	-	Tacrolimus, 366; Cyclosporin, 75; Azathioprine, 238; Prednisolone, 323; Mycophenalate Mofetil,77	347	108 (60–168)	-
Tatiana Hildebrand[22]	2016	Retrospective Study, Multicenter	PSC, 335	30.1±11.3	31%	14.2±7.1	40.9±16.8	38.9±11.3	-	132	-	Biliary-enteric,291; Duct-to-duct, 33	rPSC, 20; No-rPSC, 37	-	246	100.13±60.87	55.2 (6.03–171.6)
Tomomi Kogiso[27]	2017	Retrospective Study, Multicenter	PBC, 388	-	100%	20 (2–57)	35 (18–66)	51 (28–70)	-	267	71 (10–314)	-	-	-	-	-	55.2 (9.6–174)
Yoshihide Ueda[49]#	2017	Retrospective Study, Single Center	PSC, 45	23 (1–60)	60%	-	48 (16–62)	30 (5–67)	LDLT, 39; DDLT, 2; Domino LT,4	-	-	Duct-to-duct, 6; Roux-en-Y, 39	-	Tacrolimus, 44; Cyclosporine, 1; Prednisolone, 38; Antimetabolites, 20	26	62.7(0.5–243.9)	30 (9–70)

CD = Crohn disease, DDLT = deceased donor liver transplantation, IQR = Inter Quartile Range, LDLT = living donor liver transplantation, LT = liver transplantation, MELD = model for end-stage liver disease, N = sample size, No-rPBC = the group of no PBC recurrence, No-rPSC = the group of no PSC recurrence, PBC = primary biliary cholangitis, PSC = primary sclerosing cholangitis, SD = standard deviation, UC = ulcerative colitis.

These studies met the inclusion criteria, but were not included in meta-analysis because there was no univariate factor analysis result available.

(A) Studies met the inclusion criteria; (B) Mean±standard deviation; (C) Interquartile range.

Table 2

Recurrence and survival rates over time in included studies.

	The rate of recurrence									The rate of survival								
First author	1 yr	2 yr	3 yr	5 yr	6 yr	10 yr	15 yr	20 yr	Overall	1 yr	2 yr	3 yr	5 yr	7 yr	10 yr	15 yr	20 yr	Overall
A. J. Montano-Loza (2010)[7]	-	-	-	13%	-	29%	-	-	26%	-	-	-	No-rPBC:83%; rPBC:96%	-	No-rPBC:74%; rPBC:83%	-	-	-
A. J. Montano-Loza (2019)[26]	-	-	-	22%	-	36%	50%	55%	30.5%	-	-	-	90%	-	81%	70%	53%	-
Alexie Bosch[24]	-	-	-	27%	-	47%	61%	68%	53%	-	-	-	98%	-	94%	75%	-	-
Christophe Corpechot[29]	-	-	-	-	-	-	-	-	28%	-	-	-	-	-	-	-	-	-
El Moghazy, W.[52].*	-	-	-	-	-	-	-	-	44%	95%	-	-	89%	-	85%	-	-	81%
Fredric D. Gordon[21]	0.30%	-	4.0%	8.70%	-	22.40%	-	-	11.1%	92.7%†	-	87.7%†	82.5%†	-	67.0%†	-	-	-
H. Egawa[28]	-	-	-	10%	-	21.30%	40%	-	14.6%	-	-	-	76.6%	-	71.20%	52.60%	-	-
James Neuberger[25]	-	-	-	-	-	-	-	-	23%	-	-	-	-	-	-	-	-	-
Jeffrey Campsen[23]	2%	12%	20%	-	-	-	-	-	16.9%	-	-	-	84%	-	-	-	-	81.5%
KJ Moncrief[19]	-	-	-	-	-	-	-	-	25%	97%	95%	-	85%	-	79%	-	-	-
Lina Lindström[18]	-	-	-	-	-	-	-	-	19%	-	-	-	-	-	-	-	-	-
Lukas Bajer[51].*	-	-	-	-	-	-	-	-	44.7%	95%	-	-	94.20%	-	91.40%	84.60%	-	-
M. Carbone[50],*	-	-	-	-	-	-	-	-	42.3%	-	-	-	-	-	-	-	-	-
Pinelopi Manousou[31]*	-	-	-	-	-	-	-	-	35%	-	-	-	-	-	-	-	-	-
Reena Ravikumar[20]	-	-	-	-	-	-	-	-	14.3%	97%	-	-	89%	-	79%	-	-	-
Tatiana Hildebrand[22]	-	-	-	-	-	-	-	-	18.5%	90.70%	-	-	84.80%	-	79.40%	-	-	-
Tomomi Kogiso[27]	-	-	-	-	-	-	-	-	14.9%	-	-	-	-	-	-	-	-	-
Yoshihide Ueda[49]*	2.50%	-	24.50%	39.30%	45.80%	-	-	-	40%	77.80%	-	73.20%	63.00%	57.50%	54.60%	-	-	-

No-rPBC = the group of no PBC recurrence, No-rPSC = the group of no PSC recurrence, PBC = primary biliary cholangitis, PSC = primary sclerosing cholangitis.

* These studies met the inclusion criteria, but were not included in this meta-analysis because there was no univariate factor analysis result available.

† Recurrence-free survival probabilities (alive with original graft and no PSC recurrence).

3.1. Colectomy before LT

A significant correlation was found between colectomy before LT and recurrence of primary sclerosing cholangitis (rPSC) after LT, with an HR of 0.59 [0.37, 0.96]; $I^2 = 0\%$; $Z = 2.12$ ($P = .03$). Four studies with 1377 patients were analyzed with 214 events.[18–21] The Forest plot of colectomy before LT is represented in Figure 2A.

3.2. Presence of IBD

No significant correlation was found between the presence of IBD and rPSC after LT with an HR of 1.58 [0.98, 2.54]; $I^2 = 48\%$; $Z = 1.87$ ($P = .06$). Four studies were included in the analysis, with 1647 patients and 262 events.[18,20–22] The Forest plot of the presence of IBD is represented in Figure 2B.

3.3. CCA

A significant correlation was found between CCA and rPSC after LT with an HR of 3.42 [1.88, 6.21]; $I^2 = 0\%$; $Z = 4.03$ ($P < .0001$). Three studies were included in the analysis, with 1002 patients and 137 events.[20,21,23] The forest plot of CCA is represented in Figure 2C.

3.4. Donor age

No significant correlation was found between donor age and rALDs after LT with a total HR of 1.02 [0.98, 1.06]; $I^2 = 44\%$; $Z = 1.01$ ($P = .31$). Six studies were included in the analysis, with 1890 patients and 367 events. As regard PBC, donor age was not a significant risk factor for the recurrence of PBC (rPBC) after LT with an HR of 1.01 [0.90, 1.14]; $I^2 = 12\%$; $Z = 0.24$ ($P = .81$). Three studies were included in the analysis, with 683 patients and 190 events.[7,24,25] As regard PSC, donor age was not a significant risk factor for rPSC after LT with an HR of 1.03 [0.93, 1.13]; $I^2 = 68\%$; $Z = 0.54$ ($P = .59$). Three studies were included in the analysis, with 1207 patients and 177 events. The Forest plot of donor age is represented in Figure 2D.[20–22]

3.5. Any episode of acute rejection

No significant correlation was found between any episode of acute rejection and rALDs after LT, with a total HR of 1.10 [0.88, 1.37]; $I^2 = 12\%$; $Z = 0.81$ ($P = .42$). Five studies were included in the analysis, with 1730 patients and 435 events. As regard PBC, any episode of acute rejection was not a significant risk factor for rPBC after LT, with an HR of 1.00 [0.76, 1.30]; $I^2 = 13\%$; $Z = 0.03$ ($P = .98$). Three studies were included in the analysis, with 983 patients and 316 events.[7,24,26] As regard PSC, any episode of acute rejection was not a significant risk factor for

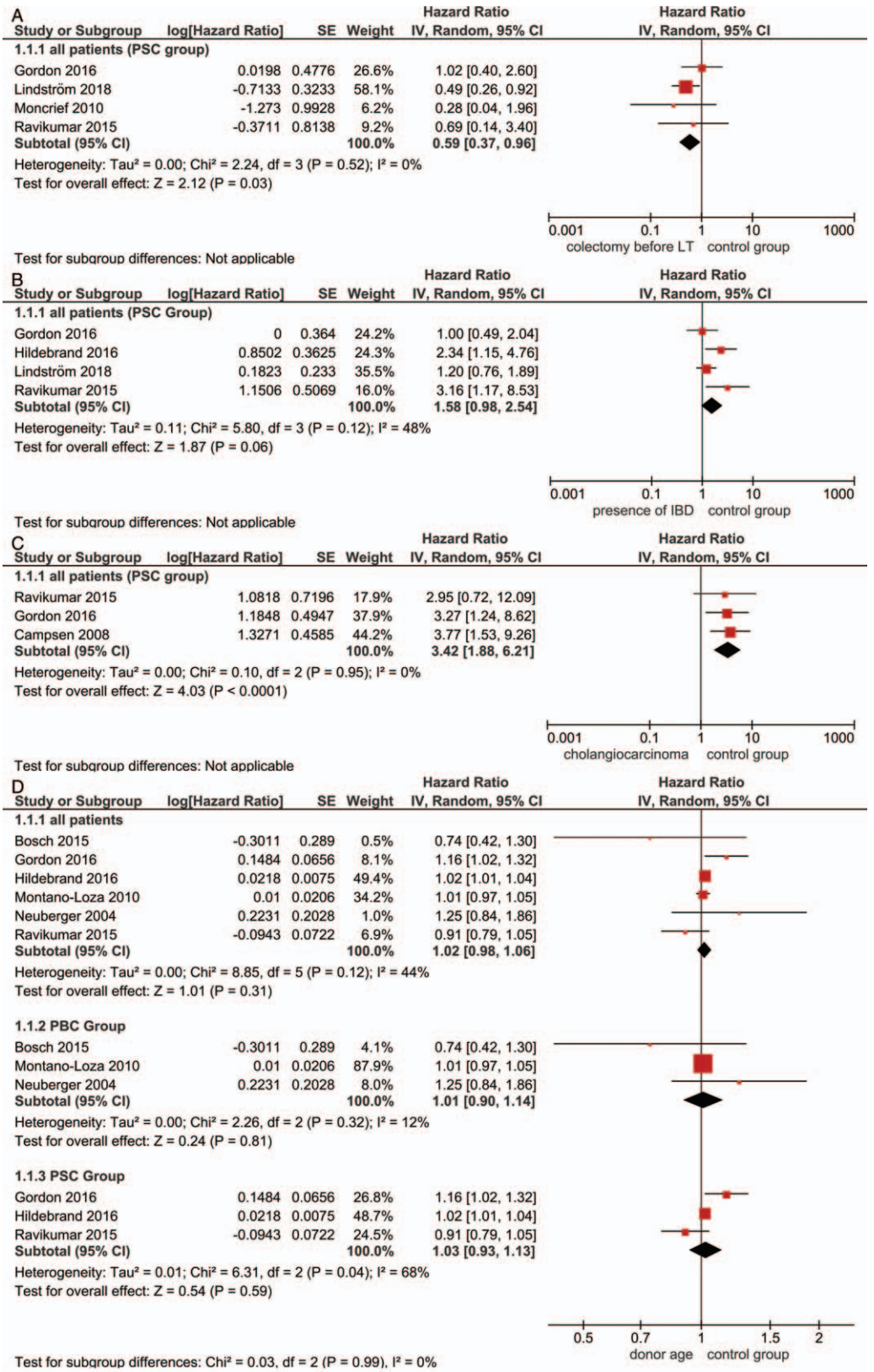

Figure 2. Potential risk factors for rALDs: A) colectomy before liver transplantation; B) presence of IBD; C) cholangiocacinoma; D) donor age. IBD = inflammatory bowel disease, rALDs = recurrence of autoimmune liver diseases.

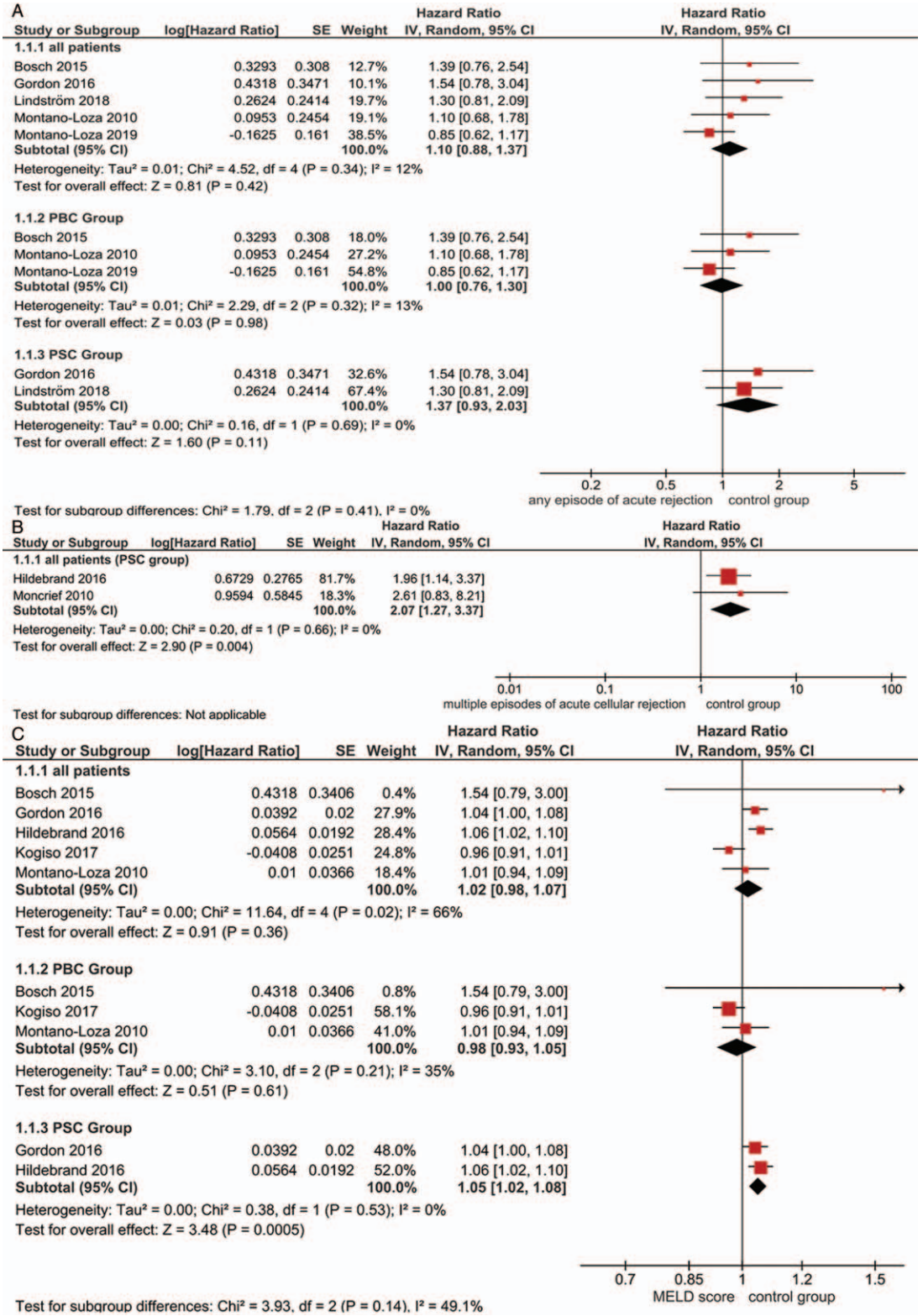

Figure 3. Potential risk factors for rALDs: A) any episode of acute rejection; B) multiple episodes of acute cellular rejection; C) MELD score. rALDs = recurrence of autoimmune liver diseases, MELD = model for end-stage liver disease.

rPSC after LT with an HR of 1.37 [0.93, 2.03]; $I^2 = 0\%$; $Z = 1.60$ ($P = .11$). Two studies were included in the analysis, with 747 patients and 119 events.[18,21] The Forest plot of any episode of acute rejection is represented in Figure 3A.

3.6. Multiple episodes of acute cellular rejection

A significant correlation was found between multiple episodes of acute cellular rejection and rPSC after LT with an HR of 2.07 [1.27, 3.37]; $I^2 = 0\%$; $Z = 2.90$ ($P = .004$). Two studies were

included in the analysis, with 394 patients and 76 events.[19,22] The Forest plot of multiple episodes of acute cellular rejection is represented in Figure 3B.

3.7. MELD score

No significant correlation was found between MELD score and rALDs after LT, with a total HR of 1.02 [0.98, 1.07]; $I^2 = 66\%$; $Z = 0.91$ ($P = .36$). Five studies were included in the analysis, with 1228 patients and 230 events. As regard PBC, MELD score was not a significant risk factor for rPBC after LT, with an HR of 0.98 [0.93, 1.05]; $I^2 = 35\%$; $Z = 0.51$ ($P = .61$). Three studies were included in the analysis, with 586 patients and 134 events.[7,24,27] As regard PSC, MELD score was significantly associated with the risk of rPSC after LT, with an HR of 1.05 [1.02, 1.08]; $I^2 = 0\%$; $Z = 3.48$ ($P = .0005$). Two studies were included in the analysis, with 642 patients and 96 events.[21,22] The Forest plot of the MELD score is represented in Figure 3C.

3.8. Mycophenolate mofetil

No significant correlation was found between the use of mycophenolate mofetil and rALDs after LT, with a total HR of 1.29 [0.82, 2.04]; $I^2 = 74\%$; $Z = 1.09$ ($P = .28$). Six studies were included in the analysis, with 2376 patients and 540 events. As regard PBC, the use of mycophenolate mofetil was not a significant risk factor for rPBC after LT, with an HR of 1.21 [0.54, 2.67]; $I^2 = 84\%$; $Z = 0.46$ ($P = .65$). Four studies were included in the analysis, with 1371 patients and 374 events.[7,24,26,27] As regard PSC, the use of mycophenolate mofetil was significantly associated with the risk of rPSC after LT, with an HR of 1.46 [1.00, 2.12]; $I^2 = 0\%$; $Z = 1.97$ ($P = 0.05$). Two studies were included in the analysis, with 1005 patients and 166 events.[18,20] The Forest plot of mycophenolate mofetil is represented in Figure 4A.

3.9. Azathioprine

No significant correlation was found between azathioprine and rALDs after LT with a total HR of 0.77 [0.56, 1.05]; $I^2 = 56\%$; $Z = 1.64$ ($P = 0.10$). Six studies were included in the analysis, with 2771 patients and 606 events. As regard PBC, azathioprine was not a significant risk factor for rPBC after LT, with an HR of 0.73 [0.46, 1.16]; $I^2 = 68\%$; $Z = 1.32$ ($P = 0.19$). Four studies were included in the analysis, with 1766 patients and 440 events.[7,25–27] As regard PSC, azathioprine was not a significant risk factor for rPSC after LT, with an HR of 0.83 [0.50, 1.38]; $I^2 = 47\%$; $Z = 0.72$ ($P = 0.47$). Two studies were included in the analysis, with 1005 patients and 166 events.[18,20] The Forest plot of azathioprine is represented in Figure 4B.

3.10. Tacrolimus

A significant correlation was found between tacrolimus and rALDs after LT, with a total HR of 1.73 [1.00, 2.99]; $I^2 = 87\%$; $Z = 1.95$ ($P = 0.05$). Six studies were included in the analysis, with 2541 patients and 587 events. As regard PBC, tacrolimus was not a significant risk factor for rPBC after LT, with an HR of 1.90 [0.82, 4.38]; $I^2 = 91\%$; $Z = 1.51$ ($P = 0.13$). Four studies were included in the analysis, with 1766 patients and 440 events.[7,25–27] As regard PSC, tacrolimus was not a significant risk factor for rPSC after LT, with an HR of 1.48 [0.98, 2.24]; $I^2 = 26\%$; $Z = 1.86$ ($P = 0.06$). Two studies were included in the analysis, with 775 patients and 147 events.[18,22] The Forest plot of tacrolimus is represented in Figure 5A.

3.11. Cyclosporine A

A significant correlation was found between cyclosporine A and rALDs after LT, with a total HR of 0.59 [0.39, 0.88]; $I^2 = 68\%$; $Z = 2.54$ ($P = 0.01$). Five studies were included in the analysis, with 2056 patients and 473 events. As regard PBC, cyclosporine A was not a significant risk factor for rPBC after LT, with an HR of 0.47 [0.20, 1.12]; $I^2 = 83\%$; $Z = 1.70$ ($P = 0.09$). Three studies were included in the analysis, with 1281 patients and 326 events.[7,26,27] As regard PSC, cyclosporine A was significantly associated with the risk of rPSC after LT, with an HR of 0.69 [0.49, 0.97]; $I^2 = 0\%$; $Z = 2.12$ ($P = 0.03$). Two studies were included in the analysis, with 775 patients and 147 events.[18,22] The Forest plot of cyclosporine A is represented in Figure 5B.

3.12. Tacrolimus vs cyclosporine A

No significant correlation was found between "tacrolimus *vs* cyclosporine A" and rALDs after LT, with a total HR of 1.32 [0.70, 2.50]; $I^2 = 67\%$; $Z = 0.86$ ($P = 0.39$). Four studies were included in the analysis, with 1158 patients and 208 events. As regard PBC, "tacrolimus *vs* cyclosporine A" was not a significant risk factor for rPBC after LT, with an HR of 1.17 [0.37, 3.69]; $I^2 = 80\%$; $Z = 0.26$ ($P = 0.79$). Two studies were included in the analysis, with 534 patients and 113 events.[24,28] As regard PSC, "tacrolimus *vs* cyclosporine A" was not a significant risk factor for rPSC after LT, with an HR of 1.60 [0.75, 3.39]; $I^2 = 44\%$; $Z = 1.23$ ($P = 0.22$). Two studies were included in the analysis, with 624 patients and 95 events.[19,20] The Forest plot of "tacrolimus *vs* cyclosporine A" is represented in Figure 6A.

3.13. Preventive ursodeoxycholic acid (UDCA)

No significant correlation was found between preventive UDCA and rPBC after LT, with an HR of 0.64 [0.23, 1.79]; $I^2 = 84\%$; $Z = 0.86$ ($P = 0.39$). Three studies were included in the analysis, with 1419 patients and 370 events.[24,27,29] The Forest plot of preventive UDCA is represented in Figure 6B.

3.14. Corticosteroid & steroid

No significant correlation was found between "Corticosteroid & steroid" and rALDs after LT, with a total HR of 0.88 [0.68, 1.14]; $I^2 = 63\%$; $Z = 0.97$ ($P = 0.33$). Eight studies were included in the analysis, with 2637 patients and 565 events. As regard PBC, "Corticosteroid & steroid" was not a significant risk factor for rPBC after LT, with an HR of 0.64 [0.38, 1.06]; $I^2 = 56\%$; $Z = 1.73$ ($P = 0.08$). Four studies were included in the analysis, with 1371 patients and 374 events.[7,24,26,27] As regard PSC, "Corticosteroid and steroid" was not a significant risk factor for rPSC after LT, with an HR of 1.03 [0.72, 1.49]; $I^2 = 64\%$; $Z = 0.18$ ($P = .86$). Four studies were included in the analysis, with 1266 patients and 191 events.[19–22] The Forest plot of corticosteroid and steroid is represented in Figure 6C.

In addition, all thirteen publications were retrospective analyzes, thus, funnel plots were used to assess the risk of publication bias across retrospective series for all outcome measures and represented in Figure 7 (A-H). However, the

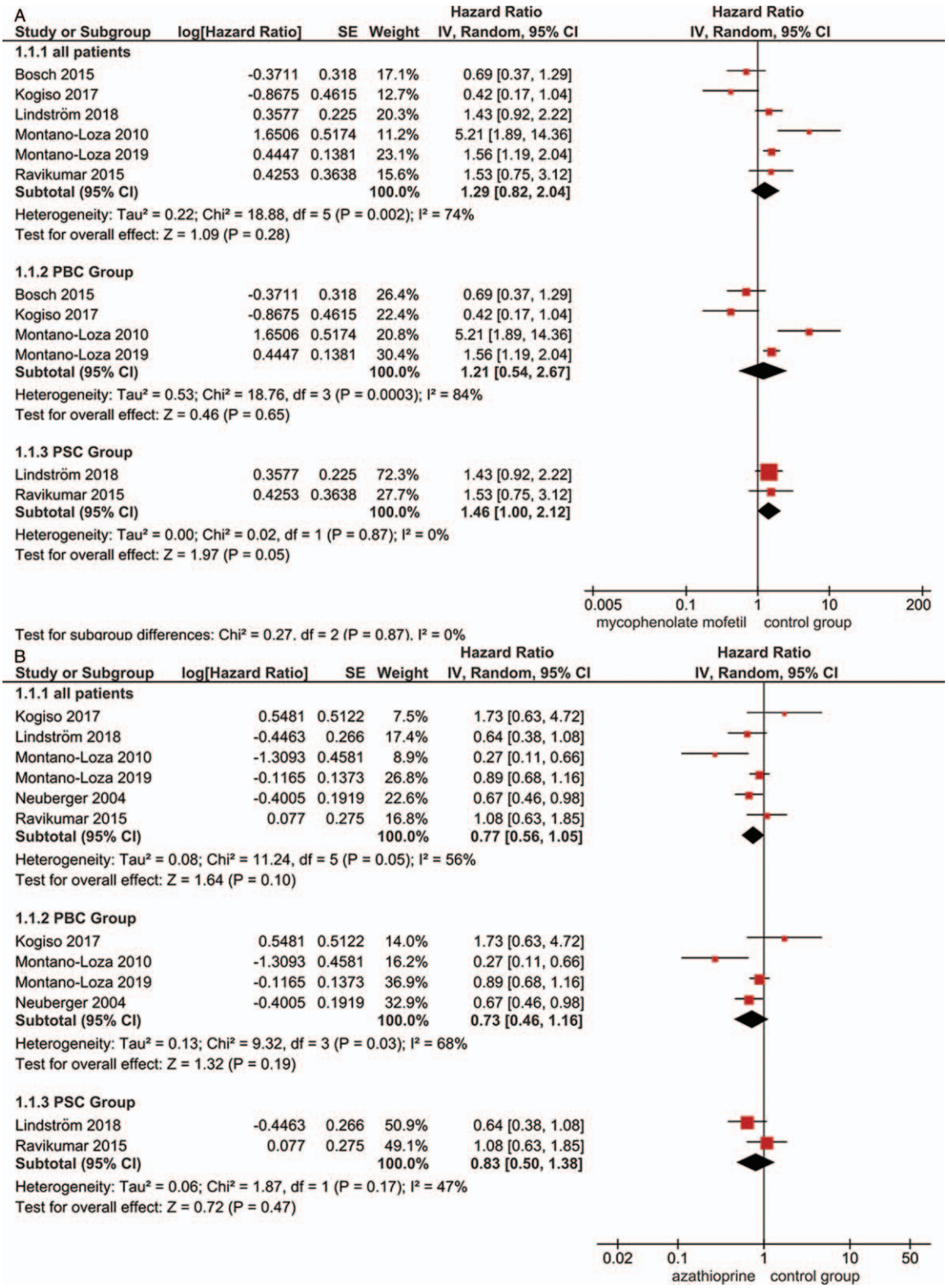

Figure 4. Potential risk factors for rALDs: A) mycophenolate mofetil; B) azathioprine. rALDs = recurrence of autoimmune liver diseases.

majority of the funnel plots of the HR for outcomes did not show any evidence of publication bias, except for the funnel plot of any episode of acute rejection and MELD score. As shown in Figure 7B and C, their scatter plots were near linear but not perfectly symmetrical, which attributes to potentially missing studies the cause of the asymmetry of the funnel plot of any episode of acute rejection. Fortunately, the other 6 funnel plots did not show any significant publication bias.

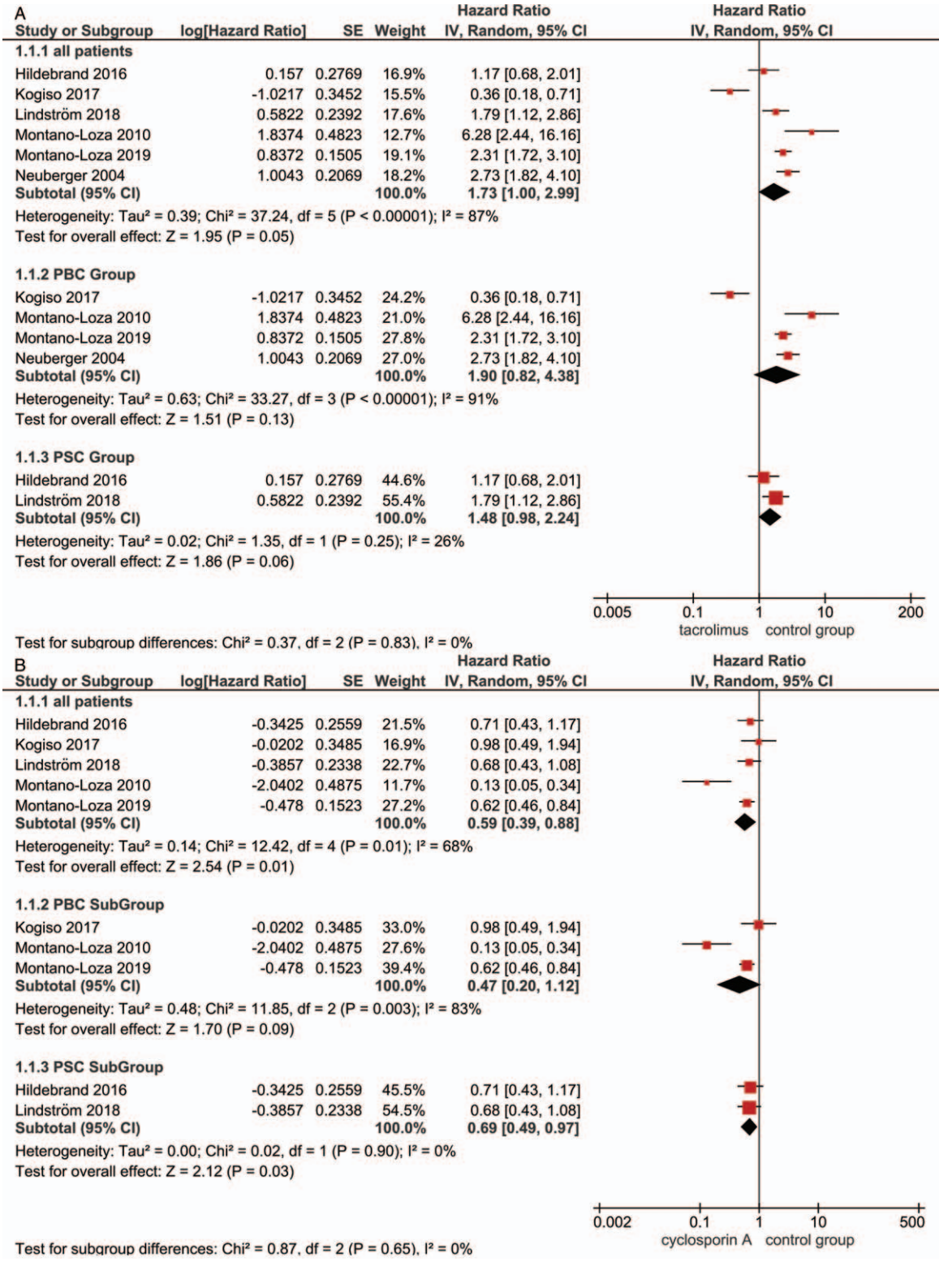

Figure 5. Potential risk factors for rALDs: A) tacrolimus; B) cyclosporine A. rALDs = recurrence of autoimmune liver diseases.

4. Discussion

ALDs is a relatively rare liver disease, accounting for 5% of chronic liver diseases.[1] The medical treatment does not improve the disease progression and to date, LT remains the only curative option.[3] Despite a reasonably good prognosis following transplantation, the post-transplant course of ALD patients can still be complicated by the rALDs.[19,30] Since more liver transplant recipients survive longer than ever before, the recurrence of the disease is becoming the primary cause of morbidity and mortality.[31] Until recently, no studies that

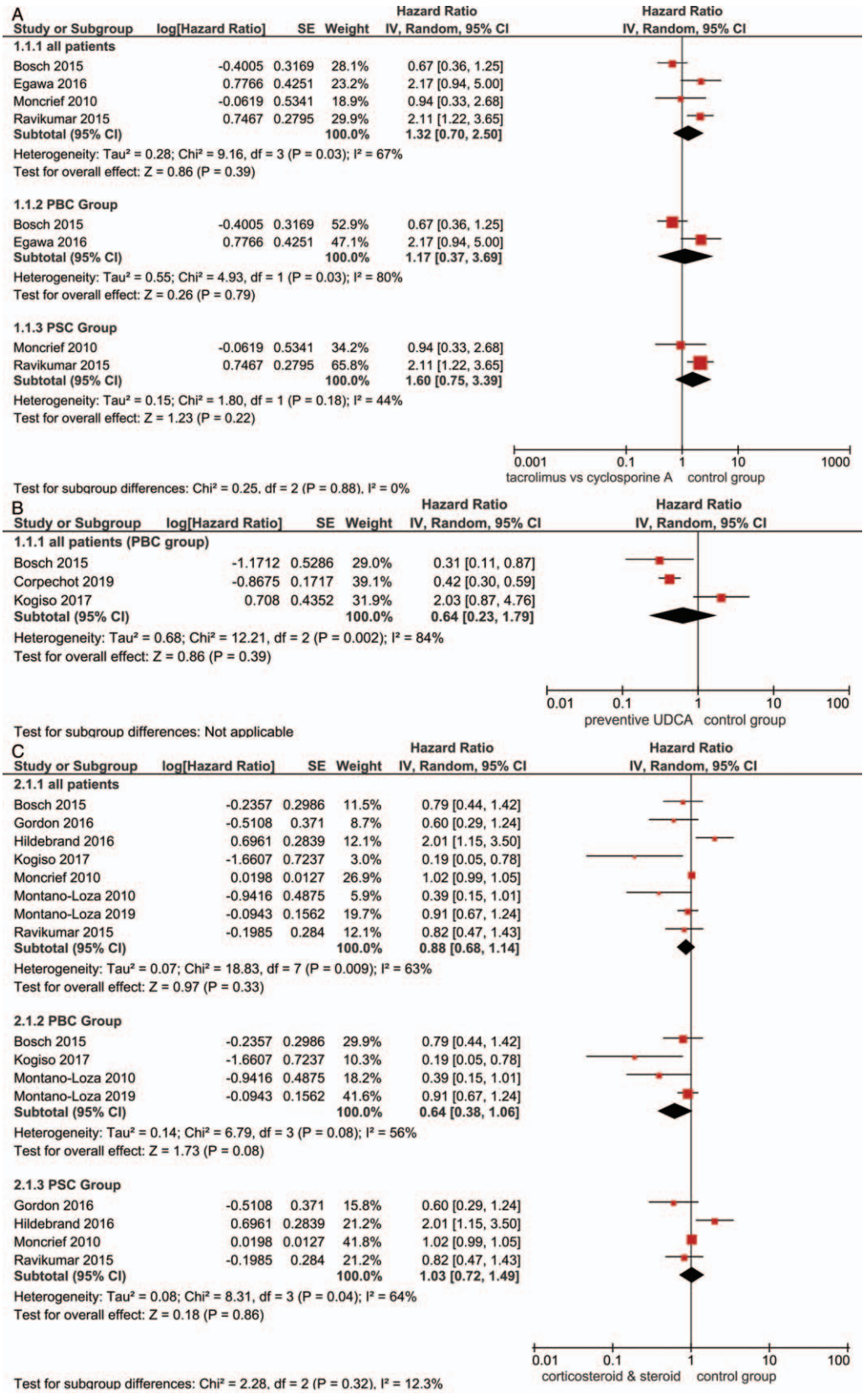

Figure 6. Potential risk factors for rALDs: A) tacrolimus vs cyclosporine A; B) preventive UDCA; C) corticosteroid & steroid. rALDs = recurrence of autoimmune liver diseases.

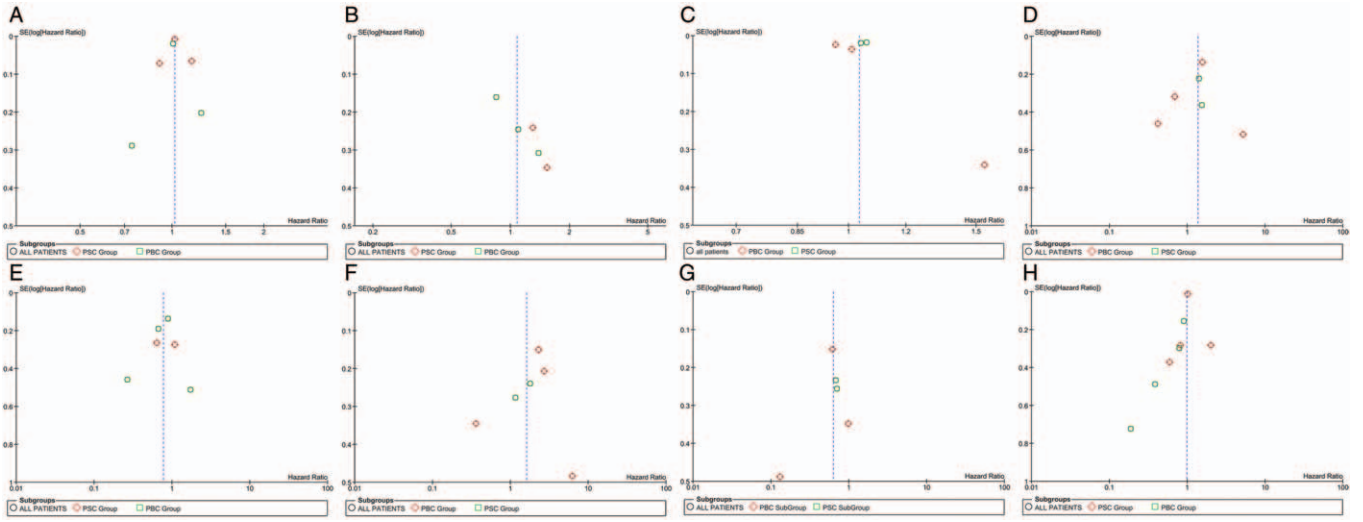

Figure 7. Funnel plots for the risk of publication bias: A) donor age; B) any episode of acute rejection; C) MELD score; D) mycophenolate mofetil; E) azathioprine; F) tacrolimus; G) cyclosporine A; H) corticosteroid & steroid. MELD = model for end-stage liver disease.

evaluated all of risk factors for post-LT rALDs were available in a meta-analysis. Therefore, identifying potential risk factors is essential to categorize and possibly develop interventions to reduce the chances of recurrent disease.

Thirteen included studies described 1115 (21.96%) cases of rALDs after LT and more use of immunosuppressants were included in this study compared with other relevant meta-analysis.[32] In addition, colectomy before LT, cholangiocarcinoma, multiple episodes of acute cellular rejection, MELD score, and the use of mycophenolate mofetil, tacrolimus, and cyclosporin A were significantly associated with the risk of rALDs.

The current meta-analysis showed that colectomy before LT was associated with the risk of rPSC after LT. The association between colectomy and PSC was also investigated in a recent study by Lina Lindström et al, demonstrating that colectomy before LT is associated with a decreased risk of rPSC.[18] Furthermore, some recent studies by Tomomi Kogiso et al and Fredric D. Gordon et al revealed that colectomy before LT is also associated with a decreased risk of rPSC.[21,27] Based on the current data, a better control of inflammatory activity should be adopted since it has been suggested as protective against rPSC, and a lower threshold for colectomy should be considered in PSC-IBD patients with persistent intestinal inflammation and progressive liver disease who probably need LT.

In addition, the current meta-analysis showed that the presence of CCA is significantly associated with disease recurrence. For example, Jeffrey Campsen et al demonstrated this finding using the database of the University of Colorado Health Sciences Center between 1988 and 2006.[23] Moreover, Fredric D Gordon et al (Lahey Hospital & Medical Center, Burlington) and Reena Ravikumar et al (Royal Free Hospital, London) stated that the presence of pre-transplant CCA had a statistically significant association with higher risk of rPSC.[20,21] However, other studies suggest that the presence of CCA in the explant is probably a byproduct of severe PSC.[23] In addition, the chemotherapy of pre-transplant CCA may induce changes in the native hepatic artery, resulting in secondary sclerosing cholangitis after LT, which makes difficult the differentiation from rPSC.[33] Therefore, the transplant for CCA is limited and may be only suitable for specific candidates.

The result of this meta-analysis also showed that multiple episodes of acute cellular rejection were significantly associated with the risk of rPSC after LT. For example, Tatiana Hildebrand et al and Karli J Moncrief MSc et al proved that acute cellular rejection was identified as an independent predictor of rPSC.[19,22] In addition, other studies suggested that the mechanism may result in the injury of biliary epithelium, which can lead to increased autoimmune epitopes and therefore immune-mediated ductal damage.[34] It has also been postulated that there may be a predisposition in these patients for rPSC as well as acute cellular rejection.

Pre-transplant MELD score was significantly associated with the risk of rPSC. A total of 2 articles were included in the study, 1228 patients were analyzed and an increased risk for rPSC per MELD point was found. MELD score assesses the severity of liver disease to determine priorities in allocating organs for LT. It also predicts the survival in patients with cirrhosis.[35] Thus, high MELD scores may reflect ongoing inflammation with corresponding septic episodes in PSC patients, indicating that a more severe disease course before LT predicts chances of rPSC after LT. Therefore, patients with high MELD scores are not candidates for LT for ALD.

The use of mycophenolate mofetil was significantly associated with the risk of rPSC after LT. Although only 2 studies were included, 642 patients were analyzed and an increased risk for rPSC was found.[18,20] In another study, the efficacy of mycophenolate mofetil in the treatment of rPSC after LT remained unkown.[36] However, there is a hypothesis that may explain this consequence: it has been suggested that mycophenolate mofetil may indirectly lead to the rPSC through the induction of high inflammatory activity.[37–39] This aspect is important because mycophenolate mofetil was used to treat the recurrence of PBC and AIH, whereas the efficacy of mycophenolate mofetil in PSC need urgent clarification.[40–42]

In the result of the present analysis, the use of tacrolimus and cyclosporin A was a risk factor associated with the risk of rALDs. In addition, tacrolimus used in previous studies was significantly

associated with a higher rate of PBC and PSC, as well as cyclosporin A.[18,22] However, in the subgroup analysis, it was puzzling that only one result was statistically significant: tacrolimus was a risk factor for rPSC after LT. Therefore, to establish whether tacrolimus and cyclosporin A have protective effects for rALDs needs further study; their role as first line standard for immunosuppression in ALDs also needs further study.[37,43,44]

A limitation of the current meta-analysis may be the size of the included studies. ALD is a rare disease and rALD occurs in a lesser proportion of patients after transplantation. Nevertheless, to date, this is the largest meta-analysis regarding this topic. Studies that meet the inclusion criteria are still rare, and the possibility of bias in the analysis results due to small samples is not excluded. Apart from this aspect, the 13 studies were all retrospective analyses with no blinding and concealment, thus being a potential risk of bias. Another limitation is the definition of rALDs. Although the criteria for rALDs has not been used to define rALDs in all studies, it remains challenging to discriminate between rALDs and other biliary diseases such as ischemic type biliary lesion or (ductopenic) chronic rejection.[45,46] Furthermore, due to the lack of data on the combination of multiple immunosuppressants, this study only analyzed the correlation between a single immunosuppressant and rALDs after LT. In addition, some unavoidable differences among outcomes were present that may result in different methods of HR calculation in MELD and donor age. Besides these aspects, two retrospective studies written by Montano-Loza, A. J. in 2010 and 2019 may have overlapped samples. Therefore, future studies should focus on the combination therapy of multiple immunosuppressants and finding a non-invasive measure to discriminate between rALDs and ischemic type biliary lesion.[10,47,48]

In conclusion, this meta-analysis revealed several risk factors for rALD and rPSC. Colectomy before LT, cholangiocacinoma, multiple episodes of acute cellular rejection, MELD score, and especially the use of mycophenolate mofetil and cyclosporin A were significantly associated with the risk of rPSC after LT. In addition, the use of tacrolimus and cyclosporin A were associated with the risk of rALD. Because the results of studies using immunosuppressants are contradictory to the clinical first-line treatment, the association between the risk factors they found and rALDs need to be confirmed in future studies. If possible, it would be better to suspend the first-line regimen of immunosuppressive therapy including mycophenolate mofetil, tacrolimus and cyclosporin A for rALDs, and then formulate the next treatment regimen after obtaining the results from relevant larger researches, so as to increase the survival rate and avoid the death of patients. Moreover, the data available at present are quite limited, and high-quality prospective studies in the future are urgently needed to verify our results and conclusions.

Author contributions

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Analysis and interpretation of data: Chongfa Chen, Fang Yang, Jianyong Liu.
Drafting the article: Chongfa Chen, Xinghua Huang, Jianwei Chen, Fengfeng Xu.
Revising it critically for important intellectual content: Chongfa Chen, Qiucheng Cai.
Final approval of the version to be submitted: Chongfa Chen, Yi Jiang.

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