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Systematic review with meta-analysis: risk factors for recurrent primary sclerosing cholangitis after liver transplantation

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Summary

Background: After liver transplantation primary sclerosing cholangitis (PSC), the condition returns in the transplanted liver in a subset of patients (recurrent primary sclerosing cholangitis, rPSC).

Aim: To define risk factors for rPSC.

Methods: We searched Pubmed, Embase, Web of Science, and Cochrane library for articles published until March 2018. Studies addressing risk factors for developing rPSC were eligible for inclusion. A random effects meta-analysis was conducted using hazard ratios (HR) as effect measure. Study quality was evaluated with the Newcastle Ottawa scale. Statistical analysis was performed using Cochrane Review Manager.

Results: The electronic database search yielded 449 results. Twenty-one retrospective cohort studies met the inclusion criteria for the review; 14 were included in the meta-analysis. The final cohort included 2159 patients (age range 31-49 years, 68.8% male), of whom 17.7% developed rPSC. Colectomy before liver transplantation, HR 0.65 (95% CI: 0.42-0.99), cholangiocarcinoma before liver transplantation, HR 2.42 (95% CI: 1.20-4.86), inflammatory bowel disease, HR 1.73 (95% CI: 1.17-2.54), donor age, HR 1.24 (95% CI 1.0-1.45) per ten years, MELD score, HR 1.05 (95% CI: 1.02-1.08) per point and acute cellular rejection, HR of 1.94 (95% CI: 1.32-2.83) were associated with the risk of rPSC.

Conclusions: Multiple risk factors for rPSC were identified. Colectomy before liver transplantation reduced the risk of rPSC.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Peter Hayes, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic fibroinflammatory disorder of the biliary tree, typified by its strong association with inflammatory bowel disease (IBD), usually ulcerative colitis.[1–3] As to date, no specific treatment has been shown to attenuate the progressive course of disease, with orthotopic liver transplantation (OLT) remaining the only lifesaving therapy.

Unfortunately, PSC recurs after OLT (rPSC) in approximately 20%-25% of patients over a 10-year period, imparting significant morbidity, need for retransplantation and an increased mortality risk.[3–5] The aetiology of rPSC remains largely unknown but identifying possible risk factors may help to develop treatment strategies to reduce its incidence. rPSC impacts graft and recipient survival and, with donor livers being scarce, efficient usage is of upmost importance.[6] Previous studies have reported several potentially modifiable risk factors for rPSC including colectomy, use of extended criteria donor grafts, choice of primary immunosuppression and cold ischemic time. However, results were inconsistent between studies.[7] In 2006, Gautam et al performed a systematic review aiming to pool all described risk factors but, due to a lack of adequate information, they were unable to perform a meta-analysis.[8] In the past decade, larger cohorts of PSC patients undergoing OLT were analysed to identify risk factors for rPSC. The current systematic review and meta-analysis was conducted to summarise all available data in order to define risk factors for rPSC.

2 | METHODS

2.1 | Recurrence of PSC

In 1999 Graziadei et al proposed criteria for diagnosing rPSC: the Mayo Clinic criteria, which now serve as the gold standard for diagnosing rPSC.[9,10] The Mayo Clinic criteria consist of a confirmed diagnosis of PSC prior to liver transplantation; cholangiography showing intrahepatic and/or extrahepatic biliary stricturing, beading and irregularity after 90 days after transplantation or liver biopsy showing fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis or biliary cirrhosis. Moreover, conditions such as hepatic artery thrombosis/stenosis, established ductopenic rejection, anastomotic strictures alone, non-anastomotic strictures or ischemic type biliary lesions (ITBL) within 90 days and ABO incompatibility between donor and recipient must be excluded (Table S1).

2.2 | Search strategy

A literature search without any country or language restriction was performed to identify studies that described risk factors for recurrent PSC after liver transplantation. The search of the following databases was performed: Pubmed, Embase, Web of Science, Cochrane library for studies published until March 2018 using a combination and variation of the following key words and terms "primary sclerosing cholangitis" and "recurrence" and "liver transplantation" or "hepatic transplant" and "risk factor" or "risk." The inclusion process is depicted in Figure 1.

2.3 | Study selection

Two authors (ICS and KSK) independently reviewed all found articles for titles, abstracts and consulted full text when abstracts did not provide sufficient information about the study. Abstracts were independently checked for inclusion.

2.4 | Study inclusion and exclusion

Articles were selected by means of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11]

Studies addressing risk factors for developing rPSC after liver transplantation were eligible for inclusion in the review. Each study had to provide information regarding characteristics of patients at transplantation and describe rPSC as outcome as well as risk factors for rPSC. Excluded were case series, case studies, reviews and studies only including children. When studies used overlapping cohorts from the same institution addressing equivalent risk factors, the study with the smallest cohort was excluded from the analysis. Due to the low number of studies regarding risk factors for rPSC, studies with various criteria for diagnosing rPSC were included.

2.5 | Risk of bias and quality assessment

Quality of included studies was evaluated by two authors (ICS and KSK) with the Newcastle Ottawa Scale for cohort studies.[12] Studies were evaluated by selection with a maximum of four stars, comparability with a maximum of two stars and outcome with a maximum of three stars. Risk of publication bias would be assessed for each risk factor with funnel plots if more than 10 studies were included in the meta-analysis.[13]

2.6 | Data extraction

Extracted from articles were authors, country of origin, publication date, study design, number of patients, patient characteristics, recurrence in group, number of patients with and without risk factor and outcome, with corresponding odds ratios (OR), risk ratios, relative risks, hazard ratios, 95% confidence intervals and p-values for univariate analysis from tables and describing text. Multivariate analyses were not included due to lack of data and because different control factors were used across studies when a multivariate analysis was performed.

2.7 | Statistical analysis

Through pooled proportion meta-analysis using a random effects model, a pooled recurrence rate was calculated. Data regarding risk

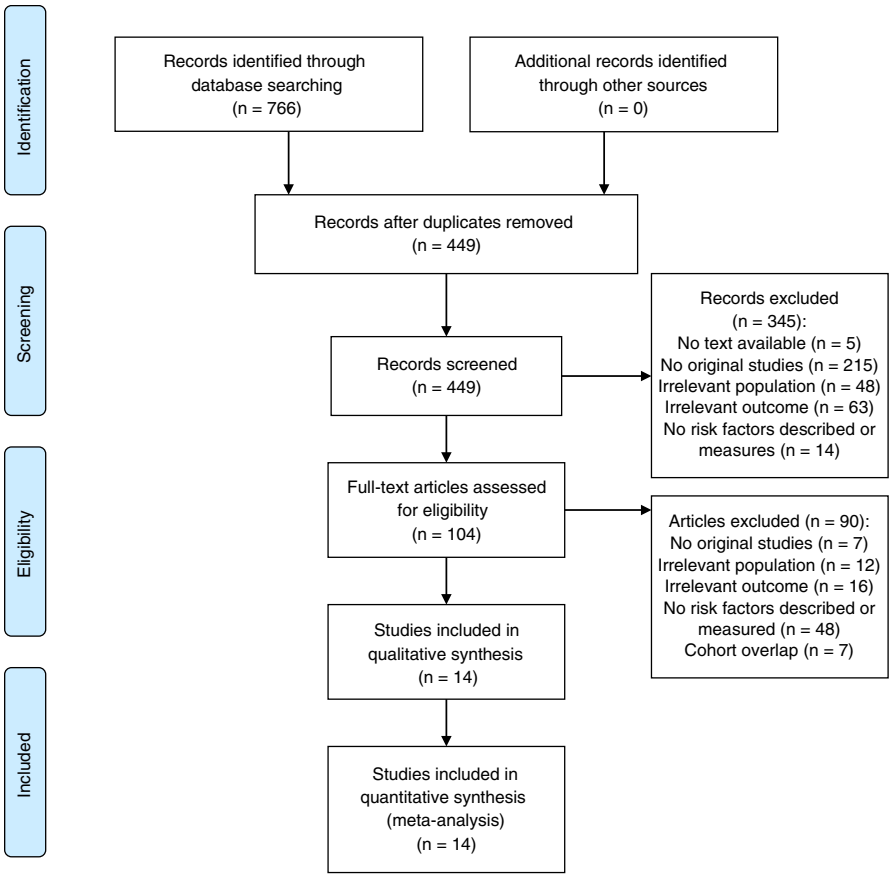

FIGURE 1 Inclusion process

factors: the hazard ratio was used as effect measure in the meta-analysis. When recurrence proportions in groups and number of events were available, hazard ratios could be calculated.[14] If such information was not provided, OR and relative risks were taken as good estimates of hazard ratios. When studies reported hazard ratios for different cut-off points comparing to a reference class, risks were transformed into continuous scale.[15]

Statistical analysis was performed using Cochrane Review Manager (Revman 5.3) and R. Hazard ratios were pooled using random-effects inverse variance models using 95% confidence intervals. Pooled risks were further explained with forest plots. Heterogeneity between studies was measured using I^2, assigning categories low, moderate and high with I^2 of respectively 25%, 50% and 75%.[16,17]

3 | RESULTS

The electronic database search yielded 449 results. All abstracts and titles were reviewed, and 21 studies were identified that addressed risk factors for rPSC after liver transplantation. Seven were excluded due to cohort overlap and addressing the same risk factors as larger studies of the same cohort.[5,18–23] In total, 14 retrospective cohort studies met the inclusion criteria for the review (Table 1).

Of studies included in the review, suspicion of overlapping cohorts was found in three studies from the United Kingdom,[6,24,25] two studies including patients from Colorado, United States[22,26] and two studies using patient data from Norway.[27,28] When studies using overlapping cohort addressed the same risk factors, the study with the largest cohort was included in the meta-analysis per risk factor.

Twelve of fourteen studies used the Mayo clinic criteria proposed by Graziadei et al for diagnosing rPSC and two studies[29,30] described other criteria (Table S2).

In total, 14 studies were included in the meta-analysis describing possible risk factors for rPSC for 2481 patients (Table 1). One study described recipient age as a possible risk factor for rPSC and used different age cut-off points instead of age as a continuous scale. In this particular case, recipient age in this particular case was changed into a continuous variable.[27] To ascertain the recurrence rate without overlapping cohorts, we included studies with the largest number of patients in the cohort, which resulted in a total cohort of 2159 patients. Of these 2159 patients, with median age ranging from 31 to 49 years, 1486 were male (68.8%) and 369 developed rPSC. Through a pooled proportion analysis using random effects model we found a recurrence rate of 17.66% (95% CI: 14.86-20.86).

The following risk factors were examined: recipient sex, donor sex, donor-recipient sex mismatch, recipient age, donor age, living or deceased donor, cytomegalovirus (CMV) status of recipient, cholangiocarcinoma before liver transplantation, IBD presence (ulcerative colitis or Crohn's disease not specified), Model of End Stage Liver Disease (MELD) score at liver transplantation, type of biliary

TABLE 1 Articles included in the review

No.	First author, publication year	Country	Inclusion period	N	Sex (% men)	IBD presence (Yes/UC/CD/other IBD)	Median age at LT (range), years	Median follow-up (range), months	Recurrence (%)	Median time to recurrence (range), months
1	Alabraba, 2009[24,a]	United Kingdom	1986-2006	230	74	162/146/16/0	47.5 (16.4-72.1)	82.50 (0.04-238.6)	61 (26.5%)	55.20 (6.00-154.8)
2	Alexander, 2008[4,a]	Washington, USA	1990-2003	69	83	59/NR/NR/NR	49.0 (21.0-69.0)	50.00 (1.0-173.0)	7 (10.1%)	68.00 (24.0-134.0)
3	Brandsaeter, 2005[28,a]	Norway	1984-2003	39	62	NR	NR	76.8 (16.8-182.4)	9 (23.1%)	NR
4	Cholongitas, 2008[25,a]	United Kingdom	1989-2004	53	57	NR/36/NR/NR	43.0 (17.0-66.0)	110.0 (12.0-185.0)	7 (13.2%)	60.0 (4.0-120.0)
5	Egawa, 2011[3,a]	Japan	1996-2008	96	50	44/NR/NR/NR	31.0 (1.0-66.0)	42.0 (1.0-153.0)	26 (27.1%)	NR (8.0-79.0)
6	Gelley, 2014[32,a]	Hungary	1995-2011	25	64	19/NR/NR/NR	34.7[b] ± 11.0	NR	6 (24.0%)	NR
7	Gordon, 2016[26,a]	North-America	1998-2013	307	70	212/167/45/0	44.7[b] ± 13.2	60.0 (NR–180)	34 (11.1%)	NR
8	Graziadei, 1999[9,a]	Rochester, USA	1985-1996	120	56	NR/94/NR/NR	45.6[b] ± 10.8	48.39 (3.87-133.55)	24 (20.0%)	NR
9	Hildebrand, 2016[33,a]	Germany	1990-2006	305	68	227/192/27/NR	39.0[b] ± 10.9	98.5[b] ± 59.6	62 (20.3%)	55.2[b] (5.83-171.6)
10	Jeyarajah, 1998[29,a]	Texas, USA	1985-1995	115	63	84/70/10/4	46.7[b] ± 10.4	NR	18 (15.7%)[c]	21[b] ± 7.5
11	Kashyap, 2009[30,a]	Rochester, USA	2002-2006	58	74	NR	NR	45.3[b] ± 28.4	11 (19.0%)[c]	NR
12	Lindstrom, 2018[27,a]	Nordic countries	1984-2000	440	70	354/306/32/16	43.0 (11.0-70.0)	103.2 (0.0-348.0)	85 (19.3%)	81.6[b] (4.8-204.0)
13	Moncrief, 2010[31,a]	Edmonton, Canada	1989-2006	59	78	42/32/8/2	46.0 (37.0-53.0)[d]	68.0 (33.0-106.0)[d]	15 (25.4%)	40.2 (19.5-66.1)
14	Ravikumar, 2015[6,a]	United Kingdom	1990-2010	565	72	347/306/29/12	49.0 (40.0-57.0)[d]	108.0 (60.0-168.0)[d]	81 (14.3%)	NR

CD, Crohn's disease; IBD, inflammatory bowel disease; LT, liver transplantation; N, sample size; NR, not reported; UC, ulcerative colitis.
[a]Study was included in the meta-analysis.
[b]Mean ± standard deviation.
[c]Study diagnosed recurrent primary sclerosing cholangitis by other criteria than Mayo Clinic criteria.
[d]Interquartile range.

anastomosis at liver transplantation, any episode of acute cellular rejection and primary immunosuppressive regimen.

We found that colectomy before liver transplantation, presence of IBD, cholangiocarcinoma before liver transplantation, donor age (per 10 years), any episode of acute cellular rejection after liver transplantation, multiple episodes of acute cellular rejection and laboratory MELD score per point were associated with the risk of rPSC (Figure 2).

3.1 | Colectomy before liver transplantation

Eight studies described colectomy before liver transplantation.[4,6,24–27,31,32] Among these studies, two could not be evaluated due to overlapping cohorts.[24,25] Among the six studies left, meta-analysis showed a pooled HR of 0.65 (95% CI: 0.42-0.99), I^2 = 0%, which indicates that colectomy before liver transplantation may reduce the risk for developing rPSC (Figure 2A).

3.2 | IBD presence

IBD presence (ulcerative colitis and Crohn's disease) was evaluated in eight studies,[3,4,24,26,28,29,32,33] of which two[28,29] studies did not provide enough information to calculate the HR. Among the six remaining studies, Hildebrand et al found IBD presence to be a significant risk factor for rPSC with HR of 1.15 (95% CI: 1.15-4.75).[33] Meta-analysis describing a total cohort of 1079 patients showed a pooled HR of 1.73 (95% CI: 1.17-2.54), I^2 = 21% (Figure 2B).

3.3 | Cholangiocarcinoma

Six studies described the influence of cholangiocarcinoma on rPSC.[3,6,22,24,26,29] Among these, two had to be excluded due to overlapping cohorts.[22,24] Meta-analysis of four remaining studies including a total cohort of 1083 patients, showed cholangiocarcinoma to

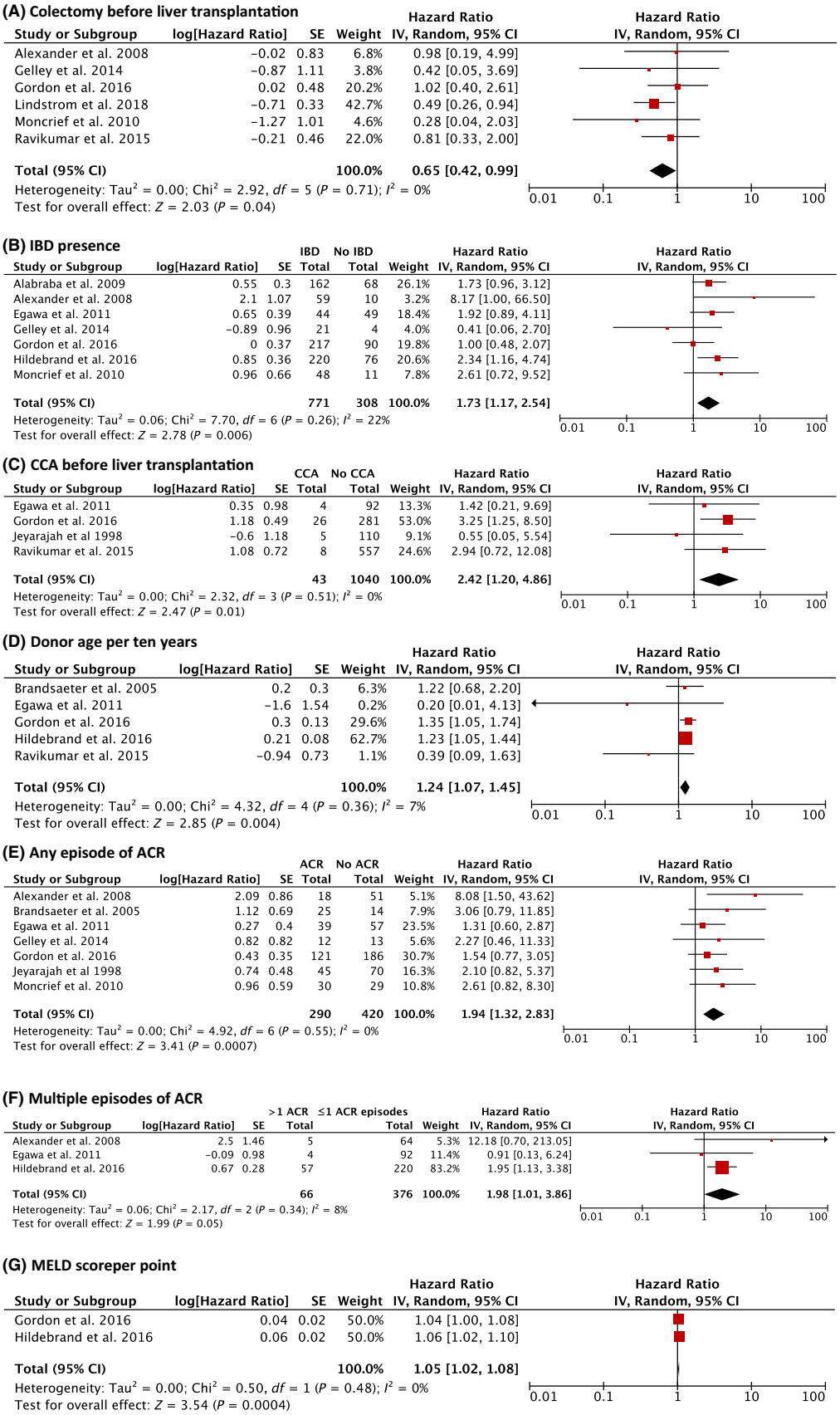

FIGURE 2 Potential risk factors for recurrent primary sclerosing cholangitis: (A) Colectomy before liver transplantation (B) IBD (Inflammatory bowel disease) presence (C) CCA (cholangiocarcinoma) before liver transplantation (D) Donor age per 10 y. (E) Any episode of ACR (acute cellular rejection) (F) Multiple episodes of ACR (G) MELD (Model of End Stage Liver Disease) score per point

be a significant risk factor for rPSC with a pooled HR of 2.42 (95% CI: 1.20-4.86), I^2 = 0% (Figure 2C).

3.4 | Donor age

Donor age was evaluated in five studies.[3,6,26,28,33] Hildebrand et al found an advanced donor age to be a significant risk factor for rPSC with HR of 1.02 (1.01-1.04).[26,33] Meta-analysis in a total cohort of 1310 patients showed a pooled HR of 1.24 (95% CI: 1.07-1.45) per 10 advancing years, I^2 = 7% (Figure 2D).

3.5 | Acute cellular rejection

Acute cellular rejection was evaluated in seven studies.[3,4,26,28,29,31,32] Meta-analysis showed a pooled HR of 1.94 (95% CI: 1.32-2.83), I^2 = 18% (Figure 2E).

3.6 | Multiple episodes of acute cellular rejection

Having multiple episodes of acute cellular rejection was evaluated in three studies.[3,4,33] Meta-analysis showed a pooled HR of 1.98 (95% CI: 1.01-3.86), I^2 = 8% (Figure 2F).

3.7 | MELD score

Two studies[26,33] were included in the meta-analysis in which MELD score was a significant risk factor with a calculated pooled HR of 1.05 (95% CI: 1.02-1.08), I^2 = 0% (Figure 2G).

Recipient or donor sex, donor-recipient sex mismatch, recipient age, living or deceased donor, CMV status of recipient, CMV disease, type of biliary anastomosis and type of primary immunosuppression were not significantly associated with the risk of developing rPSC. Corresponding forest plots can be found in the supplemental data (Figure S1).

The heterogeneity of the studies included in the meta-analysis showing significant risk factors was low (I^2 = 0%-22%). Heterogeneity of the studies of which we did not find a significant risk factor in the pooled data analysis was moderate to high (I^2 = 0%-64%).

3.8 | Risk of bias in included studies

None of the analyses per risk factor included more than 10 studies. These numbers were too low to obtain sufficient power to distinguish chance from real asymmetry in funnel plots.[13] Therefore, funnel plots were not assessed to calculate risk of bias. The Newcastle Ottawa Scale was used for quality assessment of the studies; studies scored 5-9 points with a median of 8 points. Further details can be found in the Table S3.

4 | DISCUSSION

PSC is a rare disease associated with considerable morbidity and mortality. Medical treatment does not improve disease progression and liver transplantation remains to date the only curative option.[34] In the era of donor scarcity, efficient usage of donor livers is essential. Recurrence of primary disease such as PSC (rPSC) has deleterious consequences, resulting in frequent endoscopic retrograde cholangiography or retransplantation in 37.6%-45.9% of cases.[6,27] Therefore, identifying potential risk factors is essential to categorise and possibly develop interventions to reduce the chances of recurrent disease.

The included studies without possible overlapping cohorts revealed 369 (17.7%) cases of rPSC after liver transplantation. We found that cholangiocarcinoma before liver transplantation, acute cellular rejection after transplantation and IBD presence were risk factors for rPSC. Colectomy before liver transplantation was analysed in 1465 patients, in which the pooled analysis showed a significant risk reduction. Furthermore, the presence of IBD, which occurs in up to 70% of patients with PSC, was a significant risk factor for rPSC after liver transplantation.

One theory for the protective nature of performing a colectomy derives from the strong association between PSC and IBD, suggesting that damage to the biliary tract might result from aberrant lymphocyte trafficking from the intestinal mucosa to the liver.[35] The association between colectomy and PSC was also investigated in a recent study by Nordenvall et al, which showed colectomy prior to PSC diagnosis to be protective against a progressive PSC disease course, although the study did not inform on disease severity and colectomy indication.[36] A recent study by Trivedi et al revealed a colectomy with end-ileostomy to have a more favourable outcome on graft survival and a protective effect on recurrence of biliary strictures as opposed to ileal pouch-anal anastomosis or no colectomy.[37] Moreover Joshi et al identified active IBD as a significant predictor for graft failure after liver transplantation.[38] However, performing a colectomy before transplantation is not routine practice and a colectomy is usually reserved for IBD patients with ongoing inflammation and subsequent high-grade dysplasia found in biopsies during colonoscopy.[39] Based on the current data we may adopt a lower threshold for colectomy in PSC-IBD patients with persistent intestinal inflammation and progressive liver disease that are likely to need a liver transplantation.

Cholangiocarcinoma has deleterious consequences with a high mortality rate in a non-transplant setting up to 80% in 1 year.[40] The current meta-analysis showed pre-transplant cholangiocarcinoma to be a significant risk factor for rPSC. Gordon et al explained this finding by the therapy for cholangiocarcinoma rather than the cholangiocarcinoma itself. The chemotherapy may induce changes in the native hepatic artery, resulting in secondary sclerosing cholangitis after liver transplantation, which makes it difficult to differentiate from recurrent PSC. However, this finding is not fully explained by chemotherapy: it is unknown how many patients in the meta-analysis received treatment for cholangiocarcinoma, especially because cholangiocarcinoma is a contraindication for liver transplantation in most countries. Cholangiocarcinoma is often diagnosed in the explant after liver transplantation.[41]

This meta-analysis also showed acute cellular rejection to be a risk factor for rPSC. Acute cellular rejection results in injury of biliary epithelium, which could lead to increased autoimmune epitopes and therefore immune-mediated ductal damage.[29] It has also been postulated that there might be a predisposition in these patients for rPSC as well as acute cellular rejection. Others suggest that the treatment of acute cellular rejection might predispose developing rPSC.[4] Cholongitas et al found the need for maintenance steroids, for longer than 3 months after transplantation, to be a significant risk factor for rPSC.[25] Prolonged steroid use is debated to influence the development rPSC by altering the immune response but may also reflect more severe IBD activity.[24,42]

Higher pre-transplant laboratory MELD score was a significant risk factor for developing rPSC. Although only two studies were included, 612 patients were analysed and found an increased risk for rPSC per MELD point. MELD score assesses severity of liver disease to determine priorities in allocating organs for liver transplantation. It also predicts survival in patients with cirrhosis.[43] However, patients with PSC have a relative low MELD score and can be assigned additional MELD points when at least two spontaneously septic episodes occur within 6 months.[44] Thus, high MELD scores may reflect ongoing inflammation with corresponding septic episodes in PSC patients, indicating that a more severe disease course pre-LT predicts chances on rPSC post-LT.

In 2011, Egawa et al identified CMV infection as a potential risk factor for developing rPSC.[3] However, studies included in the meta-analysis, which described CMV status, were scarce and the definition of "CMV infection" was not similarly noted.[3,25,26] Therefore, in this meta-analysis CMV infection could not be identified as a potential risk factor (Supplemental data).

A limitation of the current meta-analysis may be the size of the included studies. PSC is a rare disease and rPSC occurs in the lesser proportion of patients after transplantation. Nevertheless, this is the largest meta-analysis regarding this topic to date. Another limitation is the definition of rPSC. Although the criteria for rPSC described by Graziadei et al[9] are the current gold standard, the gold standard was not used to define rPSC in all studies and it remains challenging to discriminate between rPSC and other biliary diseases such as ITBL or (ductopenic) chronic rejection.[45] Taking into account the variable length of studies and the lack of screening methods for rPSC, the prevalence of rPSC may be higher than stated in the included studies. Future studies should focus on finding a non-invasive measure to discriminate between rPSC and ITBL and until then include the use of the standardised criteria for diagnosing rPSC as stated by Graziadei et al.

In conclusion, this meta-analysis revealed several risk factors for rPSC. Colectomy before or during liver transplantation is protective of rPSC and should be considered in the severe diseased, for example, high colonic activity. Furthermore, this meta-analysis showed cholangiocarcinoma, presence of IBD as well as donor age and acute cellular rejection to be risk factors for developing rPSC. The association between the found risk factors and recurrence of PSC need to be confirmed in future studies.

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AUTHORSHIP

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Author contributions: ICS and KSK performed literature search, data extraction and wrote the manuscript; AI, MGR and BvH contributed to the design of the study; BvH, MGR and PJT contributed to interpreting the data; BvH and PJT critically reviewed the manuscript; PWJM designed the study, contributed to interpreting the data, critically reviewed the manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

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

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