

Meta-Analysis

Risk factors for recurrent primary biliary cirrhosis after liver transplantation: A systematic review and meta-analysis

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ABSTRACT

Background: Recurrent primary biliary cirrhosis (PBC) is frequently observed in patients with PBC after liver transplantation (LT). We performed a meta-analysis to evaluate the risk factors for PBC recurrence.**Methods:** We searched the EMBASE, PubMed and the Cochrane Library databases for studies published before August 2020. Studies that identified the risk factors of PBC recurrence were eligible for inclusion. We extracted the hazard ratio (HR) data with 95% confidence intervals (CI) for the risk factors.**Results:** Our meta-analysis included 6 studies, which comprised 3184 patients (88.5% females) who underwent liver transplantation from 1982 to 2017, and of these patients, 935 (29.4%) developed PBC recurrence. The use of tacrolimus (HR = 2.62, 95% CI = 1.35, 5.09) and preventive ursodeoxycholic acid (UDCA) (HR = 0.40, 95% CI = 0.28, 0.57) were significantly associated with the risk of PBC recurrence based on the pooled analysis of the results obtained from the multivariate analysis.**Conclusions:** The use of tacrolimus is associated with an increased risk of PBC recurrence. Preventive UDCA after LT for PBC can help to prevent disease recurrence.

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1. Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic autoimmune-mediated liver disease that is characterized by progressive destruction of the intrahepatic bile ducts, leading to fibrosis and further resulting in cirrhosis, portal hypertension and liver failure [1]. The main clinical manifestations of PBC include jaundice, fatigue and pruritus. The reported incidence and prevalence of PBC varies widely within different regions [2]. A systematic review has revealed an incidence of 0.33 to 5.8 per 100,000 persons and prevalence of 1.91 to 40.20 per 100,000 persons [3]. Compared with males, the disease has greater influence on middle-aged females with a male to female ratio of 1:10 [4].

Liver transplantation (LT) is the only life-saving option for patients with terminal stage PBC [5]. If patients are diagnosed early enough, drug treatment can significantly enhance the prognosis of PBC and improve the quality of life. Unfortunately, recurrent PBC (rPBC), which requires retransplantation and increases the risk of death, occurs in 17–46% of patients who have undergone LT

[6–10]. Given the scarcity of donor livers, it is extremely important to maximize the use of available grafts. Recurrence of PBC is a risk factor that affects the survival of recipients and grafts [11]. The etiology of rPBC is still unclear, but identification of potential risk factors for recurrence may help to discover new methods for reducing the incidence of relapses.

Several potential risk factors for rPBC have been identified in previous studies [11–17], including some baseline characteristics of patients, biochemical indicators and use of immunosuppressive medications. However, the results of these previous studies are contradictory. Therefore, the purpose of the present systematic review and meta-analysis was to identify risk factors for rPBC after LT by summarizing all available data.

2. Methods

2.1. Search strategy

We designed and performed a systematic literature search with the assistance of two researchers. To identify relevant available articles irrespective of language, the EMBASE, PubMed and Cochrane Library electronic databases were rigorously searched from their establishment to January 2020. The search terms

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included “transplantation”, “transplantations”, “transplant”, “transplants”, “liver cirrhosis, biliary”, “biliary cirrhosis”, “biliary cirrhoses”, and “cholestatic cirrhosis”. The search strategies for the electronic databases are detailed in Supplementary Table S1. In addition, we screened all references in relevant studies and reviews to attain additional eligible studies.

Two researchers (Xiaocheng Li and Huapeng Lin) individually evaluated the titles and abstracts of identified articles, and they selected full-text articles according to the predefined selection criteria. Discrepancies between the researchers were resolved through discussion, and a third author (Renbin OuYang) was consulted if no consensus was reached.

2.2. Inclusion criteria for meta-analysis

2.2.1. Types of participants

We included any individual with a diagnosis of PBC who underwent liver transplantation for their condition. Occurrence of recurrent PBC was evaluated by protocol liver biopsies.

2.2.2. Types of interventions

We included studies evaluating the risk factors for PBC recurrence after liver transplantation. Each study had to provide clinical data and information regarding risk factors for developing rPBC as well as characteristics of patients at transplantation.

2.2.3. Types of outcome measures

The primary outcome was the rate of PBC recurrence. Hazard ratio (HRs) with 95% confidence intervals (CIs) for the risk of the PBC recurrence were extracted or calculated for further analysis.

2.2.4. Types of studies

Original clinical research of randomized controlled trials (RCTs) or non-randomized controlled trials (non-RCTs) were included.

2.3. Exclusion criteria for meta-analysis

The exclusion criteria were as follows: (1) studies that only included children, pregnant women and patients infected with human immunodeficiency virus (HIV) or other immunodeficiency diseases; (2) publication type was correspondence, case reports or review articles; and (3) studies in which there was unavailable or insufficient data for analysis. When there were several duplicated studies from the same population, the latest and complete study was included.

2.4. Data extraction

Two independent researchers (Xiaocheng Li and Huapeng Lin) used a data extraction form to extract information and specified data. The following variables were extracted from the included studies: first author, country of origin, publication year, study period, study design, patient baseline characteristics, median time to recurrence and immunosuppression regimens as well as corresponding HRs, risk ratios, odds ratios, 95% CIs and p-values for univariate and multivariate analyses.

2.5. Risk of bias and quality assessment

The quality of RCTs was evaluated based on the Jadad scale. For the observational studies (such as case-control studies or cohort studies), the quality was evaluated by the Newcastle–Ottawa Scale (NOS), which scores the aspects of population selection, comparability and outcome. The NOS scores range from 1 to 9 points (low to high quality). If the meta-analysis included more than 10 studies, the risk of publication bias for each risk factor would be assessed using funnel plots [18].

2.6. Statistical analysis

The meta-analysis was performed by RevMan software (version 5.3; The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). The summary statistic was evaluated by adopting standard meta-analysis methods, and the HR was an effective measure to assess risk factors for PBC recurrence. When the number of events and recurrence proportions in groups were obtained from included studies, the HR could be calculated [19]. If none of this information was available, relative risks and odds ratios were considered good estimates of HR. Pooled HR estimates and 95% CIs were calculated from a random effects model. Forest plots were drawn to display the pooled HR estimates with 95% CIs. Statistical significance was established based on two-sided *P*-values < 0.05. Heterogeneity of results across studies was qualitatively tested using the Cochran's *Q*-test and quantified using *I*² statistics. The *I*² statistics of 25%, 50% and 75% represent the low, moderate and high categories of heterogeneity, respectively [20].

2.7. Statistical consultation

All statistical analysis in this study were conducted in consultation with Professor Chengdong Yu from Peking Union Medical College Hospital, and the statistical methods of this study were reviewed by Professor Chengdong Yu.

3. Results

3.1. Search results and study characteristics

The search yielded 415 studies from EMBASE, 302 studies from PubMed and 54 studies from the Cochrane Library. After identifying and excluding overlapping articles, 609 articles remained for further screening. We excluded case reports, systematic reviews, comments and irrelevant studies based on the title, abstract or full text. The detailed process of literature retrieval is illustrated in Fig. 1. Finally, six retrospective cohort studies that addressed risk factors for rPBC were included. A total of 3184 patients who underwent LT from 1982 to 2017 were included in this study (88.5% females), and 935 of these patients developed rPBC (29.4%). The characteristics of the studies and patients are shown in Table 1.

Of the six studies in the meta-analysis, all patients underwent protocol or clinically driven liver biopsies after LT. The following risk factors for rPBC were evaluated: (1) donor and recipient factors, including recipient age, donor age, Model of End Stage Liver Disease (MELD) score, gender mismatch, cold ischaemic time, warm ischaemic time and acute cellular rejection; (2) liver biochemistries, including bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and γ -glutamyl transferase (GGT); and (3) immunosuppression medications, including mycophenolate mofetil, azathioprine, antimetabolites at 1 year, tacrolimus, cyclosporine A, preventive ursodeoxycholic acid (UDCA), corticosteroid and steroid.

We combined the data and assessed the risk factors using univariate and multivariate analyses. Some common variables related to the risk of rPBC from the univariate analysis were systematically evaluated in this review. In the multivariate analysis, only the recipient age, gender mismatch, antimetabolites at 1 year and cyclosporine A were evaluated, while the remaining variables were not included due to the lack of supportive data.

3.2. Risk factors of rPBC in univariate analysis

3.2.1. Baseline characteristics of patients

Baseline characteristics of patients were evaluated in three studies [11,13,17]. Among donor and recipient factors, recipient age

Table 1
Characteristics of included trials in the review.

Source	Study design	Period	Women, No. (%)	Median age at diagnosis (years)	Median age at LT (years)	Type of LT	Initial immunosuppression, N (%)	Median follow-up (months)	Liver biopsies	Median time to recurrence (months)	Recurrence (%)
Corpechot et al., 2020 [21]	Retrospective study	1983–2017	694(89%)	NR	54.0 ± 9.0	LDLT or DDLT	TAC, 515(66%) CyA, 242 (31%) Steroid, 647(83%) MMF or AZA, 468(60%) UDCA, 190(24%)	128.4(55.2–195.6)	Protocol or Clinically driven	NR	233(30%)
Neuberger et al., 2004 [17]	Retrospective study	1982–2002	427(88%)	NR	55(33–74)	LDLT or DDLT	TAC, 136(28%) CyA, 266(54.8%) AZA, 298 (64.1%)	79	Protocol	NR	114(23%)
Montano-Loza et al., 2018 [11]	Retrospective study	1983–2016	696(89%)	47 ± 1	54 ± 1	LDLT or DDLT	TAC, 527(67%) CyA, 220(28%) Steroid, 15(2%) Sirolimus, 631(80%) MMF, 267(34%) AZA, 265(34%)	82.8(73.2–94.8)	Protocol or Clinically driven	52.8(40.8–61.2)	240(31%)
Bosch et al., 2015 [13]	Retrospective study	1988–2010	77(85.6%)	45.7 ± 9.9	54.3 ± 8.3	LDLT or DDLT	TAC, 61(67.8%) CyA, 28(31.1%) Steroid, 56(62.2%) AZA, 14(15.6%) MMF, 38(42.2%) UDCA, 19(21.1%)	140.4(18–307.2)	Protocol or Clinically driven	76.8(12–259.2)	48(53%)
Corpechot et al., 2019 [14]	Retrospective study	NR	828(88%)	NR	54	NR	UDCA, 211(22%)	116.4 ± 92.4	Protocol or Clinically driven	NR	264(28%)
Manousou et al., 2010 [16]	Retrospective study	1988–2008	95(92%)	NR	53.3	NR	TAC, 62(60.2%) CyA, 41(39.8%) AZA, 70(68%) Steroid, 7(6.8%)	108.5(10–239)	Protocol	44(10–200)	36(35%)

Abbreviations: LT, liver transplantation; LDLT, living-donor liver transplantation; DDLT, deceased-donor liver transplantation; NR, not reported; TAC, tacrolimus; CyA, cyclosporine A; AZA, azathioprine; MMF, mycophenolate mofetil; UDCA, ursodeoxycholic acid.

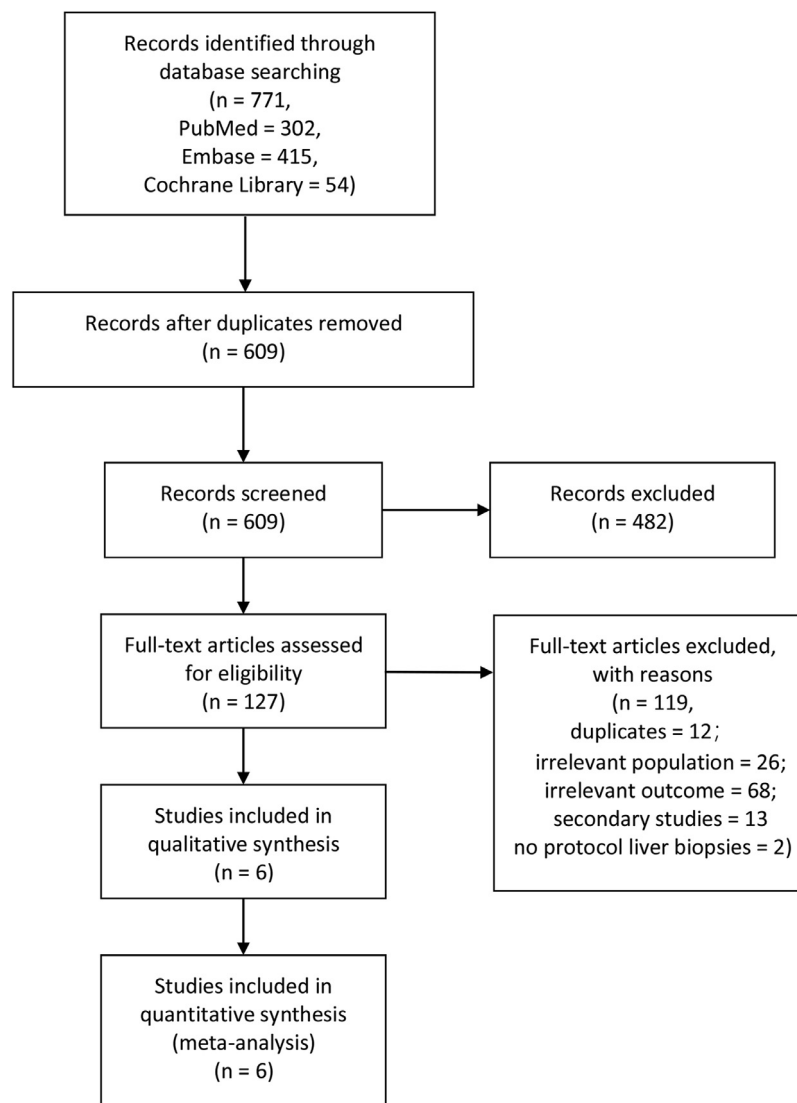


Fig. 1. Flowchart of study selection.

(HR = 0.97, 95% CI: 0.86–1.09, $P = 0.60$), donor age (HR = 1.01, 95% CI: 0.89–1.13, $P = 0.93$), gender mismatch (HR = 0.75, 95% CI: 0.56–1.00, $P = 0.05$), cold ischaemic time (HR = 1.16, 95% CI: 0.84–1.62, $P = 0.37$) and acute cellular rejection (HR = 1.01, 95% CI: 0.64–1.61, $P = 0.95$) were not significantly associated with the risk of developing rPBC. Heterogeneity of these studies was from low to moderate ($I^2 = 0\%$ –50%). The corresponding forest plots are shown in Fig. 2. MELD score and warm ischaemic time were only evaluated in one study [13,17], which lacked sufficient data to calculate the HR.

3.2.2. Biochemical features

Two studies [11,17] described the influence of liver biochemistries on rPBC. The pooled data of these studies showed that bilirubin (HR = 0.99, 95% CI: 0.97–1.01, $P = 0.23$) was not significantly associated with an increased risk of developing rPBC after LT without heterogeneity ($I^2 = 0\%$). The corresponding forest plots are shown in Fig. 3. AST, ALT, ALP and GGT were only evaluated in one study [11], which lacked sufficient data to calculate the HR.

3.2.3. Immunosuppression medications

Among immunosuppression regimens, only tacrolimus and preventive UDCA were significantly associated with rPBC. Two stud-

ies [11,17] including 1270 patients, evaluated tacrolimus as a risk factor for rPBC. Among those patients who developed rPBC ($n = 354$), use of tacrolimus was associated with higher risk of rPBC (HR = 2.45, 95% CI: 1.93–3.11, $P < 0.001$) without heterogeneity ($I^2 = 0\%$) (Fig. 4C).

Two studies [13,14], including 1031 patients, evaluated preventive UDCA as a risk factor for rPBC. The meta-analysis displayed a pooled HR of 0.41 (95% CI: 0.30–0.56, $P < 0.001$) without heterogeneity ($I^2 = 0\%$) (Fig. 4D). The pooled results in the meta-analysis showed that the use of mycophenolate mofetil, azathioprine, corticosteroid and steroid was not significantly associated with an increased risk of developing rPBC. Heterogeneity of these studies was from moderate to high ($I^2 = 0\%$ –82%). The corresponding forest plots are shown in Fig. 4.

3.3. Risk factors of rPBC in multivariate analysis

When the meta-analysis mainly included HR data from the multivariate analysis, data pooled by meta-analysis identified that the risk of developing rPBC was statistically and significantly associated with two factors (shown in Fig. 5B and C). Among immunosuppression medications, only tacrolimus and preventive UDCA

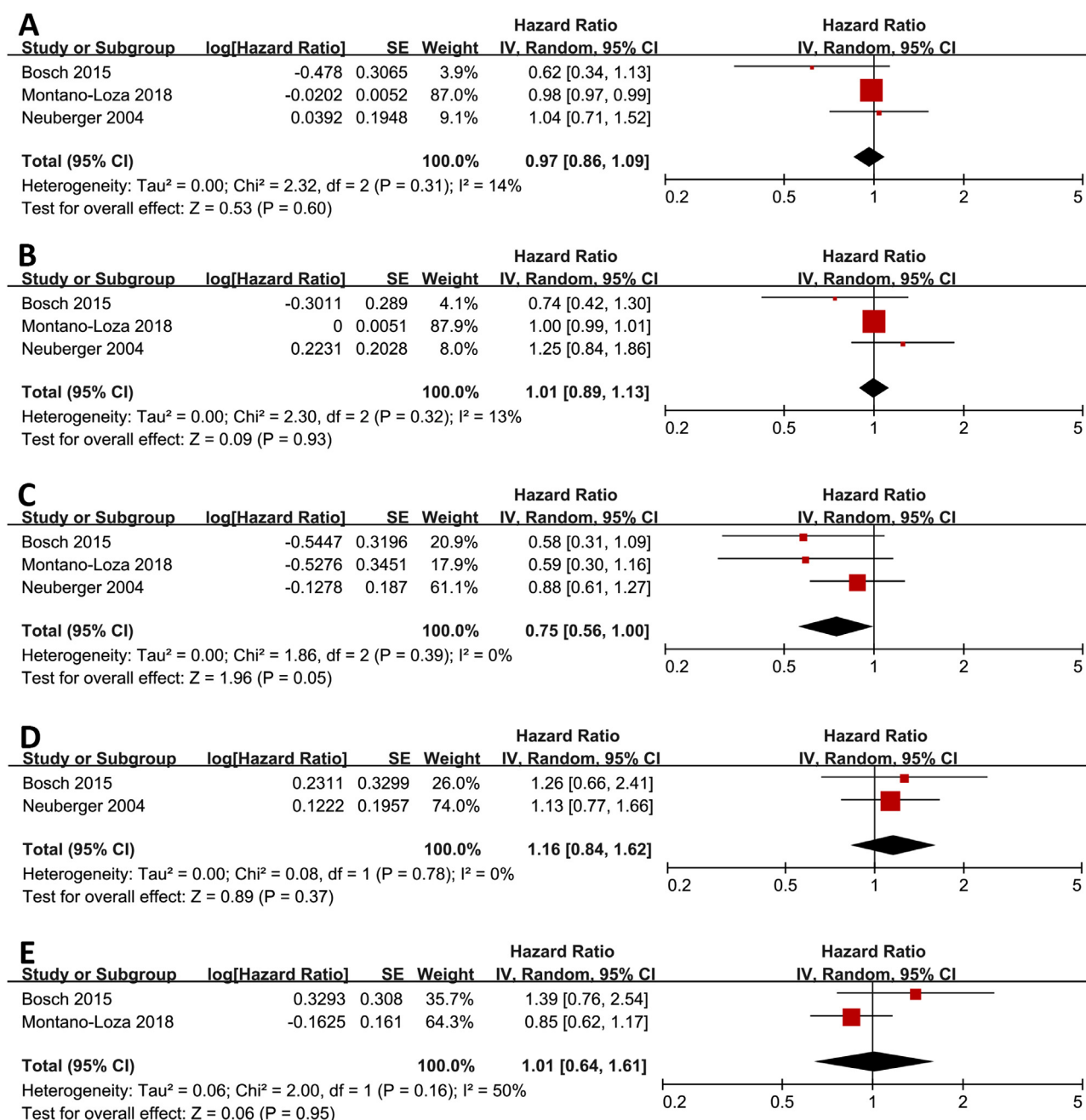


Fig. 2. Forest plots of association between the patient baseline characteristics and recurrence of primary biliary cirrhosis in the univariate analysis. (A) Recipient age; (B) Donor age; (C) Gender mismatch; (D) Cold ischaemic time; and (E) Acute cellular rejection.

were significantly associated with the risk of rPBC. Two studies [11,21], including 1656 patients, evaluated tacrolimus as a risk factor for rPBC. The meta-analysis displayed a pooled HR of 2.62 (95% CI: 1.35–5.09, $P = 0.004$) with moderate heterogeneity ($I^2 = 54\%$) (Fig. 5B).

Five studies [12–15,21] described the influence of preventive UDCA on rPBC. Among these studies, three [12,14,15] could not be included in the meta-analysis due to lack of sufficient information. Two studies, including 870 patients, evaluated preventive UDCA as a risk factor for rPBC. The pooled results in the meta-analysis found that the use of preventive UDCA was significantly associated with reduced risk of PBC recurrence. The meta-analysis displayed a pooled HR of 0.40 (95% CI: 0.28–0.57, $P < 0.001$) without heterogeneity ($I^2 = 0\%$) (Fig. 5C).

3.4. Additional analyses

There is little research on the risk factors of rPBC after LT, and some variables have not been analysed by multivariate analysis. Therefore, an additional analysis was performed to obtain enough data for multivariate analysis. We pooled the data of certain variables from both univariate and multivariate analyses to assess the impact of this variable on increased rPBC risk. The pooled results in the meta-analysis showed that gender mismatch (HR = 0.76, 95% CI: 0.57–1.01, $P = 0.06$), use of mycophenolate mofetil (HR = 1.04, 95% CI: 0.52–2.08, $P = 0.92$) and use of azathioprine (HR = 0.56, 95% CI: 0.28–1.11, $P = 0.10$) were not adverse factors associated with an increased risk of developing rPBC. Heterogeneity of these studies was from low to high ($I^2 = 0$ –83%). The corresponding forest plots

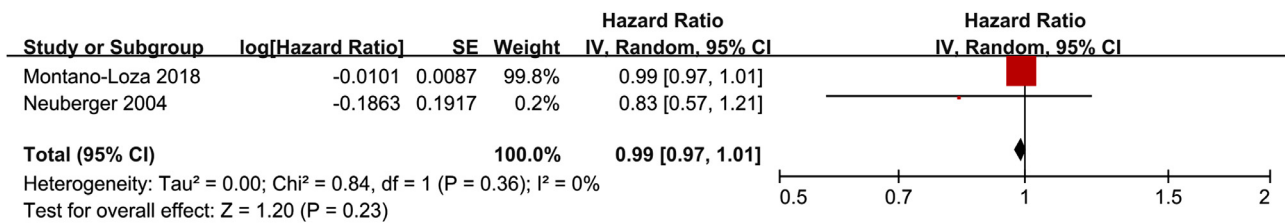


Fig. 3. Forest plots of association between bilirubin and recurrence of primary biliary cirrhosis in the univariate analysis.

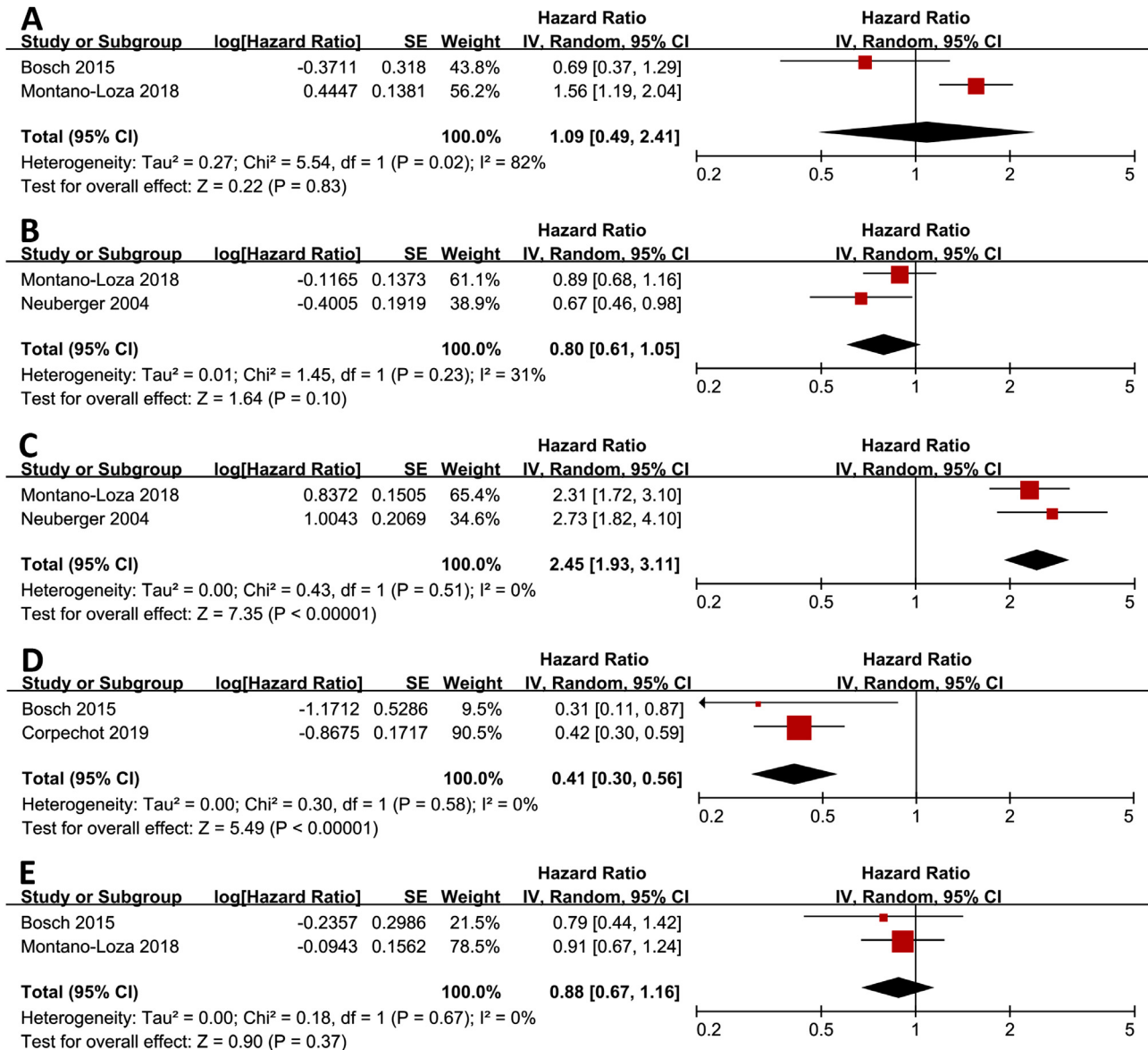


Fig. 4. Forest plots of association between immunosuppression regimens and recurrence of primary biliary cirrhosis in the univariate analysis. (A) Mycophenolate mofetil; (B) Azathioprine; (C) Tacrolimus; (D) Preventive ursodeoxycholic acid; and (E) Corticosteroid and steroid.

as well as the pooled data from the univariate and multivariate analyses are shown in the supplemental materials (Fig. S1).

3.5. Assessment of bias in included studies

The average NOS score of the included studies was 7.67 (range 7–8), suggesting that the quality of eligible studies was good. Further details are provided in Supplementary Table S2. The meta-analysis for each risk factor did not contain more than 10 studies.

Because the number of studies was too small, it was difficult to distinguish the chance from the actual asymmetry by the funnel plots [18]. Thus, the risk assessment of publication bias was not conducted in this analysis.

4. Discussion

The recurrence of PBC is a frequent adverse outcome after LT in PBC patients, and even several patients have progressed

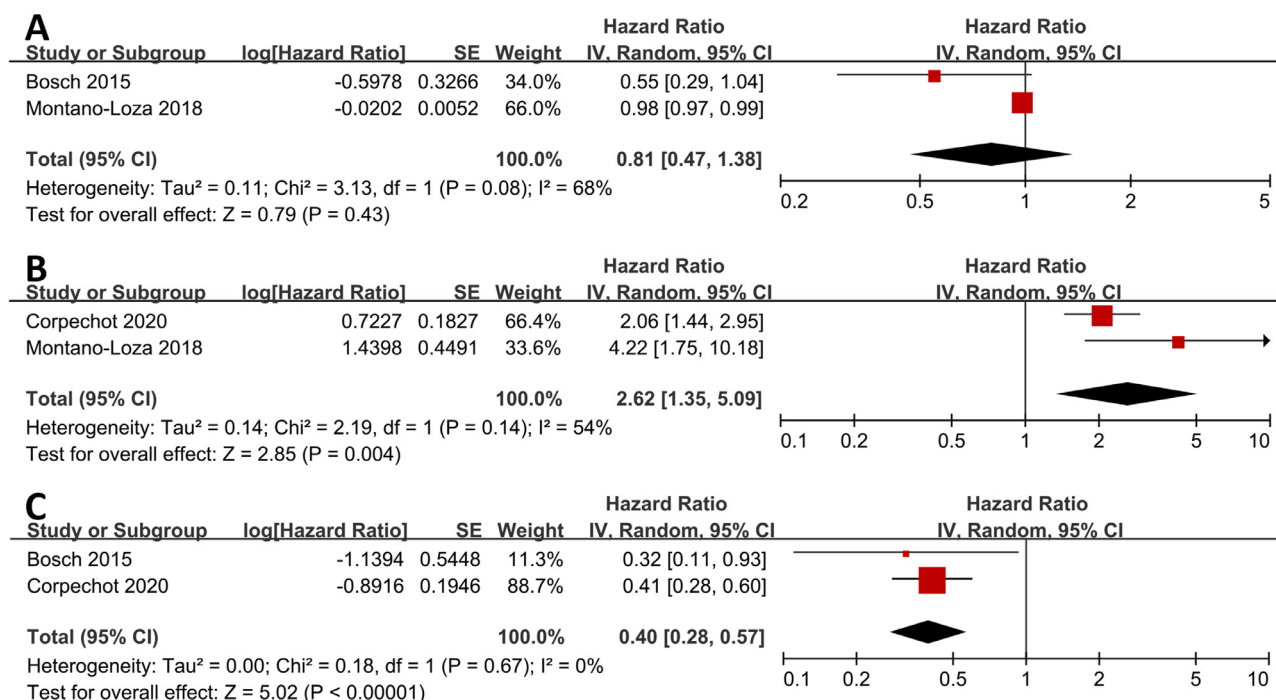


Fig. 5. Forest plots of association between potential risk factors and recurrence of primary biliary cirrhosis in the multivariate analysis. (A) Recipient age; (B) Tacrolimus; and (C) Preventive ursodeoxycholic acid.

irreversible end-stage liver disease requiring liver retransplantation or leading to death. A recent large cohort study has found that patients with rPBC show worse graft and patient survival rates than those without recurrence [11]. Early intervention to prevent rPBC might effectively prolong the survival of grafts and patients. The mechanism of PBC recurrence is currently unclear. Therefore, our attention should be focused on recognizing the associated risk factors for rPBC so that efficient treatment and prevention strategies can be determined. The investigation of such risk factors for rPBC may also help to better understand the pathophysiologic mechanism of PBC in the liver [22].

The present meta-analysis evaluated the preoperative and operative risk factors associated with rPBC by analysing six retrospective studies, which involved a total of 318,4 patients undergoing LT during the years 1982–2017. According to the univariate and multivariate analyses, tacrolimus and preventive UDCA were significantly associated with the risk of rPBC.

Several investigations have extensively evaluated the impact of immunosuppressive medications on the recurrence of PBC, and they have mainly focused on antimetabolite drugs and calcineurin inhibitors [12,16]. At present, there is still controversy among different investigators regarding the role of immunosuppression [10,23–25]. The current meta-analysis showed that patients receiving tacrolimus have a higher risk of rPBC, which is consistent with previous retrospective studies [11,17,21]. Compared to tacrolimus-based regimens, the use of cyclosporine A is not significantly associated with rPBC. Nevertheless, several other studies have reached opposite conclusions [12,15] as they found that the use of cyclosporine A independently increases the risk of rPBC and that tacrolimus reduces the risk of rPBC. Manousou et al. concluded that the use of tacrolimus or cyclosporine alone has no significant effect on the recurrence of PBC but that the combined use of cyclosporine and azathioprine is protective against rPBC [16]. Although tacrolimus and cyclosporine A are both calcineurin inhibitors, there are distinct differences in the pharmacological action [17,26], which may provide clues to the pathogenesis of PBC.

This meta-analysis also showed that administration of antimetabolites after LT is not a significant risk factor for rPBC. Azathioprine and mycophenolate mofetil are antimetabolites that inhibit the proliferation of B lymphocytes [27]. Prior studies have noted that the comparison of recurrence rates between patients receiving mycophenolate mofetil and azathioprine fail to show any statistically significant difference [28]. A Japanese multicenter study conducted by Kogiso et al. has revealed that the effect of initial treatment of antimetabolites is not significantly different in patients with and without rPBC but that long-term use of antimetabolites after LT increases the incidence of rPBC [12]. The relationship between the use of corticosteroid and developing rPBC remains uncertain. It has been shown that the absence of corticosteroid facilitates PBC recurrence [23,29]. Kogiso et al. also noticed that the long-term use of corticosteroids is associated with reducing the risk of rPBC [12]. Thus, antimetabolites and corticosteroids may exert opposite impacts on rPBC. In addition, Kogiso et al. found that an increased serum immunoglobulin M level, human leukocyte antigen mismatches and donor sex mismatch may be associated with rPBC. Due to the lack of relevant data from other studies, these potential risk factors were not discussed in the present meta-analysis.

UDCA is now considered as the first-line choice for PBC patients [21,30–32]. The use of UDCA may improve liver steatosis and markedly improve serum liver biochemistries [33,34]. In 2015, Bosch et al. described preventive UDCA as a protective factor for preventing rPBC [13]. A recent report has also suggested that preventive administration of UDCA may prevent the recurrence of PBC and prolong graft survival [14,21]. Moreover, the present meta-analysis achieved similar results, indicating that preventive UDCA may be considered a protective factor of rPBC.

Most studies have reported that the average age of PBC patients undergoing LT ranges from 50 to 55 years old. The effect of recipient age on recurrence of PBC remains a controversial issue. Some reports have shown that younger recipients have higher risk of rPBC [11,12,14,15], while other studies have indicated an association between older recipients and a higher risk of rPBC [35,36]. In

the present study, pooled data analysis showed that recipient and donor age had no effect on the recurrence of PBC.

Several limitations of this meta-analysis should not be ignored. First, all six articles included in the meta-analysis are retrospective studies, which have their inherent limitations. Therefore, it is necessary to conduct a prospective study to evaluate which immunosuppression regimen can reduce the risk of rPBC. Second, the number of included studies for evaluating each risk factor was too small to permit sensitivity analysis and quantitatively assess publication bias. Nevertheless, this is the largest meta-analysis on the risk of rPBC published to date. Third, several included studies lacked a standard liver biopsy protocol, which made it difficult for patients with normal biochemical liver tests to be diagnosed with rPBC. Thus, the actual prevalence of rPBC may be underestimated. The histologic assessment based on protocol biopsy is necessary for all PBC patients after LT to evaluate the actual frequency and risk factors associated with rPBC. Finally, the high degree of heterogeneity across studies was the main limitation to this review, indicating that a large prospective study with a standard liver biopsy protocol is needed to properly evaluate the potential risk factors for PBC recurrence.

In conclusion, this study examined the relationship between the potential risk factors and rPBC. Our results revealed that the use of tacrolimus was associated with an increased risk of rPBC and that the use of preventive UDCA reduced the risk of PBC recurrence. By identifying the high risk of rPBC after LT in advance and formulating appropriate prevention strategies, it is possible to reduce the recurrence rate and treatment cost of PBC. Further research is needed to better understand the complex association between the identified risk factors and recurrence of PBC.

Author contributions

Conception and design: XCL, HPL, JP. Data collection and drafting: XCL, HPL, RBOY. Statistical analysis: XCL, YWY, CDY. Manuscript writing: XCL, HPL. Final approval of manuscript: All authors.

Conflict of Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.dld.2020.12.005](https://doi.org/10.1016/j.dld.2020.12.005).

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