Alcohol relapse and its predictors after liver transplantation for alcoholic liver disease: a systematic review and meta-analysis

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Abstract

Background: Alcoholic liver disease (ALD) is the leading cause of liver transplantation (LT). The magnitude and risk factors of post-LT alcohol relapse are not well described. We conducted a meta-analysis to evaluate alcohol relapse rate and its predictors after LT.

Methods: Searches of MEDLINE and SCOPUS identified eligible published studies of alcohol relapse after LT published up to 31 March 2018. Alcohol relapse was defined as any alcohol consumption post-LT, and heavy alcohol relapse was defined as a relapse of alcohol consumption that was associated with a significant harm. Data for the proportion of alcohol relapse was pooled using a meta-analysis for pooling proportion. An odds ratio (OR) of the predictor of alcohol relapse was extracted and pooled using meta-analysis for the pooling risk factor. Data were analyzed using a random effect model if heterogeneity was presented; otherwise, a fixed effect model was applied. The study was registered at PROSPERO (CRD42017052659).

Results: Ninety-two studies with over 8000 cases were recruited for pooling proportion of alcohol relapse. The alcohol relapse rate and heavy alcohol relapse rate after LT during the mean follow-up time of 48.4 ± 24.7 months were 22% (95% confidence interval (CI): 19–25%) and 14% (95%CI: 12–16%). Psychiatric comorbidities (odds ratio (OR) 3.46, 95%CI: 1.87–6.39), pre-transplant abstinence of less than 6 months (OR 2.76, 95%CI: 2.10–3.61), unmarried status (OR 1.84, 95%CI: 1.39–2.43), and smoking (OR 1.72, 95%CI: 1.21–2.46) were associated with alcohol relapse after LT. However, we noticed publication bias of unpublished negative studies and high heterogeneity of results.

Conclusions: Post-transplant alcohol relapse occurred in about one-fifth of patients who underwent alcohol-related LT. Psychiatric comorbidities represented the strongest predictor of alcohol relapse. Psychiatric comorbidities monitoring and pre-LT alcohol abstinence for at least 6 months may decrease alcohol relapse after LT.

Keywords: Liver transplantation, Alcohol, Relapse, Recidivism, Psychiatric comorbidity

Background

Chronic and excessive alcohol consumption is a major cause of death around the world. Regular alcohol consumption can lead to steatosis, steatohepatitis, liver cirrhosis, and hepatocellular carcinoma [1–3]. Liver transplantation (LT) is an extended treatment for end-stage liver diseases; alcoholic liver cirrhosis is the second most frequent cause for LT in the United States and in Europe [4]. Previous studies demonstrated that LT in ALD patients offers an equal survival rate as that in other causes of end-stage liver disease [5]. Furthermore, LT for severe alcoholic hepatitis has a favorable outcome and better survival than medical therapy, but non-surgical therapy remains the standard of care for patients with severe alcoholic hepatitis [6, 7].

The issues of recidivism and disease recurrence remain a concern in LT for alcoholic liver disease. Alcohol relapse negatively impacts outcomes including graft rejection and graft loss from poor medical compliance, post-transplant malignancy, cardiovascular diseases, alcoholic cirrhosis, and decreased long-term survival [8–11]. An abstinence period of at least 6 months before
LT is a mandatory selection criterion in most liver transplant centers, but the benefit of such pre-transplant 6 month abstinence remains unclear [8, 12, 13]. Furthermore, there are subsequent reports indicating that an abstinence period of 6 months is not a significant predictive factor for recidivism [14–16]. Careful evaluation of patients with alcoholic liver disease prior to liver transplantation can identify patients with a high risk of alcohol relapse. Modifying the negative factors before LT can prevent alcohol relapse and improve post-transplant survival.

Most of these studies on alcohol recidivism after LT were done in single centers and were reported as descriptive data [16–24]. A previously published meta-analysis study of alcohol relapse after liver transplantation by Dew et al. in 2008 only included published reports on this topic up to 2004 [25]. Several predictive factors have been reported in the last decade [8, 14, 15, 25, 26]. Thus, we performed a systematic review and meta-analysis from the published literature with the following objectives: First, to pool prevalence of alcohol relapse after LT; second, to explore factors associated with alcohol relapse and pool their magnitude of effects in alcoholic liver disease patients with LT.

Methods
This meta-analysis was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, and the review protocol was registered at PROSPERO (CRD42017052659).

Search strategy
Two investigators (L.C. and A.S.) independently conducted a search of databases via MEDLINE and SCOPUS via PubMed and Scopus search engines to identify relevant studies published up to 31 March 2018. The search terms were constructed by domains of patients, intervention/exposure, and outcome. The search strategy is outlined in Table 1. The investigators supplemented the manual reviews of article reference lists to identify studies that had not been included from the initial database search and also performed manual reviews of the relevant studies.

Study selection
Two investigators (L.C. and A.S.) determined the eligibility of each article for inclusion by screening for relevance on titles and abstracts in parallel. If an eligibility of the study was indeterminable from abstracts, then the full articles were retrieved. The kappa statistic was used to estimate the agreement between the two reviewers [27]. Discordant decisions between the two investigators were advanced to full-text review and resolved by consensus with the third investigator (A.T.).

Inclusion criteria
Studies were eligible if they met all of the following criteria

- The study was an observational design including cohort, cross-sectional, or case-control study published as an original article.
- The work studied adult patients aged over 18 years with alcoholic liver disease who underwent any type of LT.
- Reporting any of the following outcomes: alcohol relapse or alcohol recurrence.
- The study assessed association between alcohol relapse and any risk factor including seven domains as follows: demographic data, psychiatric conditions, socioeconomic status, family support, alcohol abstinence, rehabilitation program, and high-risk alcohol relapse (HRAR) scale [28].

Exclusion criteria
Studies were excluded if they met one of the below criteria:

- Non-English articles that cannot be translated.
- Studies with multi-organ transplantation.
- Insufficient data for extraction.

Outcome of interest
The outcome of interest was alcohol relapse and heavy alcohol relapse in patients who underwent LT for alcoholic liver disease. We selected papers on the occurrence of alcohol relapse based on the original authors’ definition of alcohol relapse and heavy relapse and used several methods of relapse assessment such as self-reporting and collateral reporting except for biochemical testing and indirect measures. In general, alcohol relapse was defined as any alcohol consumption post-transplantation, and heavy alcohol relapse was defined as a relapse of alcohol consumption associated with significant medical or social harm [29].

Data extraction
Data obtained from each study was independently extracted by two reviewers (L.C. and A.S.) using a standardized extraction form. Study design, details of the publication, the number of subjects, and baseline characteristics of study populations were extracted including patients with alcohol relapse and predictive factors of alcohol relapse after LT.
| Domain          | Search term                                      | Search strategy |
|-----------------|--------------------------------------------------|-----------------|
| P-Patient       | “Alcoholic hepatitis”                            | #1              |
|                 | “Alcoholic liver disease”                         | #2              |
|                 | “Alcoholic cirrhosis”                             | #3              |
|                 | “Liver transplantation”                           | #4              |
|                 | “Hepatic transplantation”                         | #5              |
|                 | #6 #1 OR #2 OR #3 AND #4 OR #5                    |                 |
| All P           | #7 #9 OR #10 OR #13 OR #17 OR #18 OR #24 OR #25 OR #31 OR #32 OR #35 |                 |
| E-Exposure      | Gender                                           | #7              |
|                 | Sex                                              | #8              |
|                 | Age                                              | #10             |
|                 | “Marital status”                                 | #11             |
|                 | Divorced                                         | #12             |
|                 | #13 #11 OR #12                                   |                 |
|                 | “Socioeconomic status”                            | #14             |
|                 | Income                                           | #15             |
|                 | Education                                        | #16             |
|                 | #17 #14 OR #15 OR #16                             |                 |
|                 | “Alcohol dependence”                             | #18             |
|                 | Depression                                       | #19             |
|                 | “Drug use”                                       | #20             |
|                 | “Substance use”                                  | #21             |
|                 | “Substance abuse”                                | #22             |
|                 | substance                                        | #23             |
|                 | #24 #20 OR #21 OR #22 OR #23                      |                 |
|                 | Family history of alcohol                        | #25             |
|                 | Alcohol abstinence                               | #26             |
|                 | Alcohol cessation                                 | #27             |
|                 | Alcohol quit                                     | #28             |
|                 | Alcohol stop                                     | #29             |
|                 | Alcohol sobriety                                 | #30             |
|                 | #31 #26 OR #27 OR #28 OR #29 OR #30               |                 |
|                 | Rehabilitation                                   | #32             |
|                 | High Risk Alcoholism Relapse                     | #33             |
|                 | HRAR                                             | #34             |
|                 | #35 #33 OR #34                                   |                 |
| All E           | #36 #9 OR #10 OR #13 OR #17 OR #18 OR #19 OR #24 OR #25 OR #31 OR #32 OR #35 |                 |
| O-Outcome       | Alcohol relapse                                  | #37             |
|                 | Alcohol recurrence                               | #38             |
|                 | Recidivism                                       | #39             |
| All O           | #40 #37 OR #38 OR #39                            |                 |
| Overall         | #6 AND #36 AND #40                               |                 |
Quality and risk of bias assessment
All selected studies were independently reviewed by two investigators (L.C. and A.S.). Disagreements between the two reviewers were resolved by consensus with the third investigator (A.T.). Quality was assessed using a Newcastle-Ottawa Scale for eligible studies including selection, exposure, and comparability of studies on the basis of the design or analysis and assessment of the outcomes (Table 2).

Statistical analysis
The rate of alcohol relapse after LT was estimated along with its 95% confidence interval (CI) for each study. The rate was then pooled across studies using a meta-analysis for pooling proportion [102]. The random effect model was applied if there was heterogeneity between studies; otherwise, a fixed-effect model was applied. An odds ratio (OR) along with 95% CI of risk factor associated with alcohol relapse after LT was estimated for each study. Heterogeneity was assessed using the Cochrane Q test and the I² statistic. Heterogeneity was present when the Q test was significant \( p < 0.1 \) or \( I^2 \geq 25\% \). The sources of heterogeneity were then explored using a meta-regression if the data of the co-variables were available. Subgroup analysis by age, region of study, definition of alcohol relapse, and follow-up time was then performed accordingly. Publication bias was assessed by Egger’s test and a funnel plot. If there was asymmetry suggested from either a funnel plot or Egger’s test, then a contour-enhanced funnel plot was used to explore whether the asymmetry was due to publication bias or heterogeneity. All analyses were performed using STATA software version 14.1. \( P \)-values < 0.05 and < 0.10 were considered statistically significant for a two-sided test and one-sided test, respectively.

Results
Search result
A total of 291 studies were identified from PubMed and Scopus databases plus 30 additional studies from the reference lists (Fig. 1). The title and abstracts were reviewed for 321 studies; 123 duplicated studies, 1 meta-analysis, and 4 systematic reviews were removed [25, 103–106]. The remaining 193 studies were reviewed in full text excluding 101 studies. Of the remaining studies, 90 reported the proportion of alcohol relapse, and 37 studies assessed risk factors of alcohol relapse. The kappa index between the two reviewers (L.C. and A.S.) was 0.96 for data extraction, which indicated very good inter-observer agreement.

Study characteristics
Of the 90 studies reporting alcohol relapse, 86 were cohort studies (72 retrospective and 14 prospective cohorts), 2 were cross-sectional studies, and 2 were case-control studies (Table 3). Data for the 86 cohort studies were used for pooling in the incidence of alcohol relapse. Of these, 45 cohorts (40 retrospective and 5 prospective cohorts) were pooled for the proportion of heavy alcohol relapse; 37 studies (43.0%) were from North America, 40 studies (46.5%) were from Europe, 8 studies (9.3%) were from Asia-Pacific, and 1 study (0.1%) was from Brazil.

The incidence of alcohol relapse
The characteristics of the studies and the data on alcohol relapse rates are detailed in Table 3. A total of 86 cohort studies with 8061 patients reported incidences of alcohol relapse at any time after LT. The mean age of patients ranged from 35 to 60 years, and the mean follow-up time was 10 to 112 months. The alcohol relapse rate varied across studies with a range of 4 to 95% with an \( I^2 \) of 90.7%. A random effect model was applied and yielded the pooled alcohol relapse rate of 22% (95% CI: 19–25%) during the mean follow-up time of 48.4 ± 24.7 months. The rate of heavy alcohol relapse varied markedly across studies with an \( I^2 \) of 85% and pooled rate of 14% (95%CI: 12–16%).

Pooled risk factors of alcohol relapse
The effects of all of the risk factors on alcohol relapse after LT that were classified by demographic, risk behavior, social, and comorbidity factors; these were pooled in 37 cohort studies (Table 4). The results of pooling these effects are summarized in Table 5. The results showed that psychiatric comorbidities, pre-transplant abstinence less than 6 months, being unmarried, and smoking were significantly associated with alcohol relapse after LT with corresponding pooled ORs of 3.46 (95% CI: 1.87–6.39), 2.76 (95%CI: 2.10–3.61), 1.84 (95%CI: 1.39–2.43), and 1.72 (95%CI: 1.21–2.46), respectively. In addition, the \( I^2 \) ranged from 0 to 40.6%, with the highest \( I^2 \) in psychiatric comorbidities.

Subgroup analysis
Subgroup analysis by age (≤ 50 years or > 50 years), regions of studies (Europe, North America, Asia Pacific, and Brazil), definition of alcohol relapse (only report or report combining with biochemical testing), and follow-up time (≤ 4 years or > 4 years) was performed to explore the potential cause of heterogeneity of pooled rates of alcohol relapse and heavy alcohol relapse. Likewise, the subgroup analysis was performed with psychiatric comorbidities to identify the factor associated with alcohol relapse with the highest risk and heterogeneity. Subgroup analyses showed no significant difference in all analyses of alcohol relapse and heavy alcohol relapse rates except for one analysis of psychiatric comorbidities.
### Table 2
Newcastle-Ottawa quality assessment scale of each included studies

| Author          | Year | S1 | S2 | S3 | S4 | C | O1 | O2 | O3 |
|-----------------|------|----|----|----|----|---|----|----|----|
| Starzl TE       | 1988 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Bird GLA        | 1990 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Kumar S         | 1990 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Doffoel M       | 1992 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Knechtle SJ     | 1992 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Lucey MR        | 1992 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Berlakovich GA  | 1994 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Howard L        | 1994 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Osorio RW       | 1994 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Gerhardt TC     | 1996 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Tringali RA     | 1996 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Tripp LE        | 1996 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Zibari GB       | 1996 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Anand AC        | 1997 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Coffman KL      | 1997 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Everson G       | 1997 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Foster PF       | 1997 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Lucey MR        | 1997 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Reeck UH        | 1997 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Shakil AO       | 1997 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Stefanini GF    | 1997 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| DiMartini A     | 1998 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Fabrega E       | 1998 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Heinemann A     | 1998 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Tang H          | 1998 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Conjeevaram HS  | 1999 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Gledhill J      | 1999 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Newton SE       | 1999 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Pageaux GP      | 1999 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Romano DR       | 1999 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Abosh D         | 2000 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Berlakovich GA  | 2000 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Burra P         | 2000 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| DiMartini A     | 2000 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Jain A          | 2001 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Pereira SP      | 2001 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Platz KP        | 2001 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Bellamy CO      | 2001 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| DiMartini A     | 2001 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Gish RG         | 2001 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Karman JF       | 2001 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Mackie J        | 2001 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |
| Tome S          | 2002 | ✷  | ✷  | ✷  | ✷  | ✷ |    |    |    |

(Continued)
Patients with psychiatric comorbidities who had longer follow-up time (>4 years) had an increased risk of alcohol relapse versus those with a shorter follow-up time (≤4 years) (Fig. 2).

**Publication bias**
The Egger test showed no evidence of publication bias among the studies, and the shape of the funnel plots was symmetrical in all analyses except for psychiatric comorbidities (Fig. 3) and abstinence less than 6 months (Fig. 4). The studies that reported less than 6 months of abstinence were both non-significant and significant leading to a contour-enhanced funnel plot; thus, asymmetry may not be due to either publication bias or heterogeneity. The studies with negative effect of psychiatric co-morbidities and abstinence less than 6 months were not reported.

**Discussion**
Alcohol relapse after LT remains an ethical issue in LT for alcoholic liver disease due to its harmful and negative impacts on liver grafts. One meta-analysis and four systemic reviews of alcoholic liver disease in LT patient were published earlier [25, 103–106]. The well-designed meta-analysis of rate and risk factors of alcohol relapse by Dew et al. in 2008 included 54 studies published between 1983 and 2005 [25]. A systematic review by Rustard et al. in 2015 selected only articles of the risk factors of alcohol relapse [103]. A systematic review by McCallum et al. in 2006 included only studies that were associated with psychosocial criteria [106]. Bravata et al. performed a systematic review of alcohol relapse and evaluated only the association between employment aspect and alcohol relapse [105]. One systematic review focused on neither alcohol relapse rate nor risk factor [104]. Our study is a systematic review and meta-analysis of all published studies up to 2018, which aimed to estimate post-LT alcohol relapse rate and its predictive factors. To date, the current study is the most extensive meta-analysis of alcohol relapse in LT patients.
| Author          | Year | Type of study   | Region of study | Mean age (years) | Number of population | Number of any relapse | Number of heavy relapse | Follow-up time (months) |
|-----------------|------|-----------------|-----------------|------------------|---------------------|-----------------------|-------------------------|-------------------------|
| Starzl TE [30]  | 1988 | Retrospective   | US-Canada       | -                | 35                  | 2                     | -                       | 24                      |
| Bird GL [12]    | 1990 | Retrospective   | Europe          | -                | 18                  | 4                     | -                       | -                       |
| Kumar S [31]    | 1990 | Retrospective   | US-Canada       | 48.2             | 52                  | 6                     | 2                       | 25                      |
| Doffoel M [32]  | 1992 | Retrospective   | Europe          | -                | 57                  | 19                    | -                       | -                       |
| Knechtle SJ [33]| 1992 | Case-control    | US-Canada       | 51               | 32                  | 4                     | -                       | -                       |
| Lucey MR [34]   | 1992 | Retrospective   | US-Canada       | 44               | 45                  | 5                     | 2                       | 15                      |
| Berlakovich GA  | 1994 | Retrospective   | Europe          | 47.6             | 44                  | 14                    | 7                       | 33                      |
| Howard L [36]   | 1994 | Retrospective   | Europe          | 50               | 20                  | 19                    | 16                      | 34                      |
| Osorio RW [37]  | 1994 | Prospective     | US-Canada       | 47               | 37                  | 7                     | 3                       | 21                      |
| Gerhardt TC [38]| 1996 | Retrospective   | US-Canada       | 49               | 41                  | 20                    | 2                       | 47                      |
| Tringali RA [39]| 1996 | Retrospective   | US-Canada       | 47.4             | 58                  | 12                    | 10                      | 28                      |
| Tripp LE [40]   | 1996 | Retrospective   | US-Canada       | 49               | 68                  | 9                     | 5                       | -                       |
| Zibari GB [41]  | 1996 | Retrospective   | US-Canada       | 47               | 29                  | 2                     | -                       | -                       |
| Anand AC [42]   | 1997 | Retrospective   | Europe          | 47.5             | 39                  | 5                     | -                       | 25                      |
| Coffman KL [43] | 1997 | Prospective     | US-Canada       | -                | 91                  | 18                    | -                       | -                       |
| Everson G [44]  | 1997 | Retrospective   | US-Canada       | 53               | 62                  | 11                    | 6                       | 12                      |
| Foster PF [24]  | 1997 | Retrospective   | US-Canada       | 48.6             | 63                  | 13                    | -                       | 49.3                    |
| Lucey MR [45]   | 1997 | Retrospective   | US-Canada       | 46               | 50                  | 17                    | -                       | 63                      |
| Reeck UH [46]   | 1997 | Retrospective   | Europe          | -                | 52                  | 6                     | -                       | -                       |
| Shakil AO [47]  | 1997 | Retrospective   | US-Canada       | 41               | 8                   | 3                     | -                       | -                       |
| Stefanini GF [48]| 1997 | Retrospective   | Europe          | 47               | 11                  | 3                     | 1                       | 48                      |
| DiMartini A [49]| 1998 | Retrospective   | US-Canada       | 49.5             | 63                  | 15                    | -                       | -                       |
| Fabrega E [50]  | 1998 | Retrospective   | Europe          | 49               | 44                  | 8                     | -                       | 37.8                    |
| Heinemann A [51]| 1998 | Retrospective   | Europe          | 45.6             | 13                  | 4                     | -                       | -                       |
| Tang H [52]     | 1998 | Retrospective   | Europe          | 48               | 56                  | 28                    | 9                       | 24                      |
| Conjeevaram HS  | 1999 | Retrospective   | US-Canada       | 47               | 68                  | 8                     | 8                       | -                       |
| Gledhill J [54] | 1999 | Retrospective   | Europe          | 48               | 31                  | 7                     | -                       | 13.5                    |
Table 3: Main characteristics of the studies included in the meta-analysis (Continued)

| Author            | Year  | Type of study   | Region of study | Mean age (years) | Number of population | Number of any relapse | Number of heavy relapse | Follow-up time (months) |
|-------------------|-------|-----------------|-----------------|-----------------|----------------------|-----------------------|-------------------------|-------------------------|
| Newton SE         | 1999  | Retrospective Cohort | US-Canada       | 47              | 122                  | 33                    | -                       | 62                      |
| Pageaux GP        | 1999  | Retrospective Cohort | Europe          | 48.8            | 47                   | 15                    | 5                      | 42.1                    |
| Romano DR         | 1999  | Case-control     | Europe          | 47.6            | 152                  | 7                     | -                       | -                      |
| Abosh D           | 2000  | Retrospective Cohort | US-Canada       | 50              | 10                   | 5                     | 5                      | 10                      |
| Berlakovitch GA   | 2000  | Retrospective Cohort | Europe          | -               | 118                  | 15                    | -                       | 53.7                    |
| Burra P           | 2000  | Prospective Cohort | Asia Pacific    | 48              | 34                   | 11                    | 4                      | 40.1                    |
| DiMartini A       | 2000  | Retrospective Cohort | Europe          | 50              | 72                   | 4                     | 1                      | -                       |
| Jain A            | 2000  | Retrospective Cohort | US-Canada       | 50.8            | 185                  | 37                    | 1                      | 94                      |
| Pereira SP        | 2000  | Retrospective Cohort | Europe          | 51              | 56                   | 28                    | 15                     | 30                      |
| Platz KP          | 2000  | Retrospective Cohort | Europe          | -               | 117                  | 30                    | -                      | -                       |
| Bellamy CO        | 2001  | Retrospective Cohort | US-Canada       | 53              | 123                  | 13                    | -                      | 84                      |
| DiMartini A       | 2001  | Prospective Cohort | US-Canada       | -               | 36                   | 8                     | -                      | -                       |
| Gish RG           | 2001  | Prospective Cohort | US-Canada       | 47              | 61                   | 12                    | -                      | 82.8                    |
| Karman JF         | 2001  | Retrospective Cohort | US-Canada       | 49              | 19                   | 4                     | -                      | 36                      |
| Mackie J          | 2001  | Retrospective Cohort | Europe          | 51              | 46                   | 21                    | 3                      | 25                      |
| Torre S           | 2002  | Prospective Cohort | Europe          | 51              | 68                   | 7                     | 2                      | 38                      |
| Berlakovitch GA   | 2004  | Case-control     | Europe          | 51.5            | 44                   | 3                     | -                      | 43.5                    |
| Jauhar S          | 2004  | Retrospective Cohort | US-Canada       | 51              | 11                   | 17                    | 15                     | 44.1                    |
| Miguert M         | 2004  | Prospective Cohort | Europe          | 48.7            | 51                   | 13                    | 9                      | 35.7                    |
| Björnsson E       | 2005  | Retrospective Cohort | Europe          | 53              | 93                   | 32                    | 7                      | 31                      |
| Cuadrado A        | 2005  | Retrospective Cohort | Europe          | 48.9            | 54                   | 14                    | 14                     | 99.2                    |
| DiMartini A       | 2006  | Prospective Cohort | US-Canada       | 49.7            | 167                  | 70                    | 43                     | -                       |
| Hwang S           | 2006  | Prospective Cohort | US-Canada       | 50              | 15                   | 3                     | -                      | 41                      |
| Kelly M           | 2006  | Retrospective Cohort | Asia Pacific    | 50.1            | 90                   | 28                    | 18                     | 67                      |
| De Gottardi A     | 2007  | Retrospective Cohort | Europe          | 51.3            | 387                  | 46                    | 46                     | 61.2                    |
| Dumortier J       | 2007  | Retrospective Cohort | Europe          | 50              | 305                  | 37                    | 37                     | 63                      |
| Newton SE         | 2007  | Cross sectional  | US-Canada       | -               | 18                   | 4                     | -                      | -                       |
| Author       | Year | Type of study | Region of study | Mean age (years) | Number of population | Number of any relapse | Number of heavy relapse | Follow-up time (months) |
|--------------|------|---------------|-----------------|------------------|----------------------|----------------------|------------------------|--------------------------|
| Nickels M    | 2007 | Retrospective Cohort | US-Canada | 48.8              | 27                   | 8                    | -                      | 23.4                     |
| Pfitzmann R  | 2007 | Retrospective Cohort | Europe   | 51.2              | 290                  | 56                   | 23                     | 89                       |
| Vieira A     | 2007 | Retrospective Cohort | Other(Brazil)| 47                | 17                   | 2                    | -                      | 29.6                     |
| Wells JT     | 2007 | Retrospective Cohort | Europe   | 50.3              | 148                  | 24                   | 20                     | 90.5                     |
| Gedaly R     | 2008 | Retrospective Cohort | US-Canada | 52                | 142                  | 27                   | -                      | 41.2                     |
| Immordino G  | 2009 | Retrospective Cohort | US-Canada | 53.2              | 110                  | 13                   | -                      | -                        |
| Tandon P     | 2009 | Retrospective Cohort | US-Canada | 52                | 171                  | 41                   | 22                     | 64.8                     |
| Biselli M    | 2010 | Retrospective Cohort | Europe   | 48                | 49                   | 13                   | 3                      | 58                       |
| Chen GH      | 2010 | Retrospective Cohort | Asia Pacific | 52.8            | 16                   | 1                    | -                      | 32.4                     |
| DiMartini A  | 2010 | Prospective Cohort | US-Canada | 52                | 208                  | 95                   | -                      | -                        |
| Karim Z      | 2010 | Retrospective Cohort | US-Canada | 50.5              | 80                   | 8                    | 8                      | -                        |
| Hartl J      | 2011 | Retrospective Cohort | Europe   | 52.5              | 109                  | 17                   | -                      | 31                       |
| Mathurin P   | 2011 | Prospective Cohort | Europe   | 47.4              | 26                   | 3                    | 2                      | 20                       |
| Schmeding M  | 2011 | Retrospective Cohort | Europe   | 48.9              | 271                  | 73                   | 73                     | -                        |
| Staufer K    | 2011 | Prospective Cohort | Europe   | 53.5              | 141                  | 28                   | -                      | -                        |
| Faure S      | 2012 | Retrospective Cohort | Europe   | 51                | 206                  | 90                   | 50                     | 81.7                     |
| Addolorato G | 2013 | Retrospective Cohort | Europe   | 49.4              | 92                   | 22                   | -                      | -                        |
| Deruytter E  | 2013 | Retrospective Cohort | Europe   | 56                | 108                  | 31                   | 17                     | 55                       |
| Kawaguchi Y  | 2013 | Retrospective Cohort | Asia Pacific | 52            | 13                   | 1                    | -                      | 38                       |
| Park YH      | 2013 | Retrospective Cohort | Asia Pacific | 52            | 18                   | 3                    | 2                      | 57                       |
| Rice JP      | 2013 | Retrospective Cohort | US-Canada | 49.3              | 300                  | 48                   | 16                     | 82                       |
| Rodrigue JR  | 2013 | Retrospective Cohort | US-Canada | 55                | 118                  | 40                   | 12                     | 55                       |
| Egawa H      | 2014 | Retrospective Cohort | Asia Pacific | 35            | 140                  | 32                   | 21                     | 44                       |
| Gràt M       | 2014 | Retrospective Cohort | Europe   | 46                | 66                   | 22                   | -                      | 88.8                     |
| Piano S      | 2014 | Prospective Cohort | Europe   | 60                | 23                   | 5                    | -                      | -                        |
| Dumortier J  | 2015 | Retrospective Cohort | Europe   | 47.2              | 712                  | 128                  | 128                    | 63                       |
| Hasanin M    | 2015 | Cross-sectional | US-Canada | -                | 45                   | 8                    | -                      | -                        |
Our study demonstrated that any alcohol relapse and heavy alcohol relapse rates were as high as 22 and 14% during the mean follow-up time of 48.4 ± 24.7 months, respectively. The literature on alcohol relapse post-transplantation has reported a wide range of alcohol relapse rates, which might be due to different definitions of alcohol relapse. Dew et al. reported that the average rate for alcohol relapse after LT was 5.6 cases per 100 patients per year for any alcohol relapse and 2.5 cases per 100 patients per year for heavy alcohol relapse [25]. The authors suggested that a significant proportion of patients who returned to any alcohol drinking then became heavy drinkers, which led to a significant harm to LT recipients [25].

In our study, the most significant risk factors of relapse were psychiatric comorbidities followed by pre-transplant alcohol abstinence less than 6 months, being unmarried, and smoking. Four of the nine studies reported that psychiatric conditions had a link with alcohol relapse [16, 29, 72, 81]. The finding was consistent with the previous meta-analysis [25]. The study identified 3 of the 12 psychosocial variables associated with any alcohol relapse: < 6 months abstinence prior to transplant, poor social support, and a family history of alcohol abuse or dependence [25]. We found that 9 of the 20 studies revealed that alcohol abstinence less than 6 months was associated with alcohol relapse [8, 18, 29, 37, 81, 82, 95, 107, 108]. Our study confirms the validity of using the 6-month rule of alcohol abstinence as a criterion for pre-transplant selection in patients with ALD; this is consistent with the previous meta-analysis study [25].

A systematic review of large prospective studies focusing on risk factors for alcohol relapse following LT has also suggested that a shorter length of pre-transplant sobriety was a significant predictor of alcohol relapse [103]. However, the 6-month rule cannot be applied in LT for patients with severe acute alcoholic hepatitis whose condition is not allowed to wait until 6 months. LT in this group of patients remains a controversial issue in many transplant centers. The current data do not suggest that LT in patients with severe alcoholic hepatitis leads to more alcohol relapse [109]. Therefore, 6 months of alcohol abstinence may not reliably predict post-LT alcohol relapse. Other risk factors were psychiatric comorbidities, a high score on the HRAR scale, and a diagnosis of alcohol dependence [103]. Scoring systems to predict alcohol relapse after LT such as HRAR and the ARRA were proposed for use, but they have never been validated by well-designed studies.

In this study, psychiatric co-morbidities and pre-transplant abstinence less than 6 months were strong predictive factors of alcohol relapse with some publication bias against negative studies. Psychiatric comorbidities were the strongest risk factor in this study but with high heterogeneity. Interestingly, subsequent subgroup analysis showed that longer follow-up times led to an increased impact.

| Author       | Year | Type of study | Region of study | Mean age (years) | Number of population | Number of any relapse | Number of heavy relapse | Follow-up time (months) |
|--------------|------|---------------|-----------------|-----------------|----------------------|-----------------------|------------------------|------------------------|
| Satapathy SK [94] | 2015 | Retrospective Cohort | US-Canada | 54 | 148 | 16 | 16 | 112.8 |
| Zhou M [28] | 2015 | Retrospective Cohort | US-Canada | 54.2 | 35 | 6 | - | - |
| Askgaard G [95] | 2016 | Retrospective Cohort | Europe | 54 | 156 | 35 | 35 | - |
| Hajifathalian K [96] | 2016 | Prospective Cohort | Europe | 56 | 19 | 4 | - | 40.8 |
| Im GY [97] | 2016 | Retrospective Cohort | US-Canada | 41 | 9 | 2 | 1 | 24.5 |
| Kollmann D [98] | 2016 | Retrospective Cohort | Europe | - | 382 | 16 | - | 73 |
| Lee BP [99] | 2017 | Retrospective Cohort | US-Canada | 51.4 | 31 | 11 | 7 | 19.2 |
| Onishi Y [100] | 2017 | Retrospective Cohort | Asia Pacific | 46 | 7 | 1 | - | 60 |
| Wigg AJ [101] | 2017 | Retrospective Cohort | Asia Pacific | 50 | 87 | 18 | 14 | 52 |
Table 4 Summary of the included studies reported risk factors in the meta-analysis

| Author          | Year | Demographic factors        | Risk behavior factors | Social factors                  | Comorbidity |
|-----------------|------|---------------------------|-----------------------|---------------------------------|-------------|
| Kumar S [31]    | 1990 | -                         | Abstinence < 6months  | -                               | -           |
| Osoio RW [37]   | 1994 | Male Unmarried Unemployed | Substance use         | Abstinence < 6months Rehabilitation | Psychiatric disease |
| Gerhardt TC [38] | 1996 | -                         | -                     | Abstinence < 6months             | -           |
| Tringali RA [39]| 1996 | -                         | -                     | Abstinence < 6months             | -           |
| Foster PF [24]  | 1997 | Family history of alcohol use | Substance use       | Abstinence < 6months Rehabilitation | -           |
| Lucey MR [45]   | 1997 | Male                      | -                     | Abstinence < 6months             | -           |
| Shakil AO [47]  | 1997 | Male                      | -                     | -                               | -           |
| Tang H [52]     | 1998 | Male                      | -                     | -                               | -           |
| Conjeevaram HS [53]| 1999 | Male                      | -                     | -                               | -           |
| Newton SE [55]  | 1999 | Male Unmarried Unemployed | Substance use         | -                               | -           |
| Burra P [59]    | 2000 | Unmarried Family history of alcohol use | Substance use       | Rehabilitation                  | -           |
| Jain A [61]     | 2000 | -                         | -                     | Abstinence < 6months Rehabilitation | -           |
| Mackie J [15]   | 2001 | Male Unmarried Lack of social support Low SES Family history of alcohol use Smoking | - | Abstinence < 6months |
| Jauhar S [14]   | 2004 | Male Unmarried Unemployed | Substance use         | Abstinence < 6months Rehabilitation | Psychiatric disease |
| Björnsson E [20]| 2005 | -                         | -                     | Rehabilitation                  | -           |
| Cuadrado A [10]| 2005 | Male                      | -                     | -                               | -           |
| Hwang S [71]    | 2006 | -                         | -                     | Abstinence < 6months             | -           |
| Kelly M [72]    | 2006 | Unmarried Lack of social support Unemployed | Substance use       | Abstinence < 6months Depression | -           |
| De Gottardi A [29]| 2007 | Age < 50 years Male Unmarried Low SES Unemployed | High HRAR            | Abstinence < 6months Depression |
| Nickels M [75]  | 2007 | Age < 50 years Male       | Alcohol dependence    | -                               | Depression |
| Pfiztmann R [8] | 2007 | Age < 50 years Male Unmarried | -                     | Abstinence < 6months             | -           |
| Karim Z [81]    | 2010 | Age < 50 years Male Unmarried Low SES Unemployed Smoking Substance use | Abstinence < 6months Rehabilitation | Psychiatric disease |
| Hartl J [82]    | 2011 | -                         | Smoking               | Abstinence < 6months Rehabilitation | -           |
| Addolorato G [85]| 2013 | -                         | -                     | Rehabilitation                  | -           |
| Deruytter E [86]| 2013 | Age < 50 years Male Unmarried Unemployed Family history of alcohol use Smoking Alcohol dependence | - | Psychiatric disease |
| Kawaguchi Y [87]| 2013 | Male                      | High HRAR             | -                               | -           |
| Park YH [19]    | 2013 | Male                      | -                     | Abstinence < 6months             | -           |
| Rice JP [88]    | 2013 | Male                      | -                     | -                               | -           |
of psychiatric comorbidities on any alcohol relapse. The psychiatric comorbidities defined in enrolled studies included all psychiatric conditions that could cause impaired daily functioning, i.e. anxiety, schizophrenia, and personality disorders. In this study, we analyzed three cohort studies that reported depression separately because depression is a known risk factor associated with alcoholic drinking. We found that depression was not a significant factor in alcohol relapse (OR = 3; 95%CI 0.49–9.25).

Table 5 Pooled risk factors of alcohol relapse

| Factors                      | N  | OR     | 95%CI          | Pooling method | I²  | Egger test (P-value) |
|------------------------------|----|--------|----------------|----------------|-----|----------------------|
| Demographic factors          |    |        |                |                |     |                      |
| Age < 50 years               | 6  | 1.16   | 0.43–3.15      | Random effect  | 75.2| 0.55                 |
| Sex (male)                   | 23 | 0.89   | 0.69–1.11      | Fixed effect   | 21.7| 0.43                 |
| Unmarried                    | 14 | 1.84   | 1.39–2.43      | Fixed effect   | 14.6| 0.57                 |
| Lack of social support       | 5  | 1.78   | 0.72–4.38      | Random effect  | 49.5| 0.18                 |
| Low SES                      | 3  | 0.99   | 0.15–6.50      | Random effect  | 86.3| 0.02                 |
| Unemployed                   | 10 | 1.33   | 0.93–1.89      | Fixed effect   | 7.7 | 0.74                 |
| Family history of alcohol use| 7  | 1.49   | 0.94–2.36      | Fixed effect   | 23.0| 0.50                 |
| Risk behavior factors        |    |        |                |                |     |                      |
| Smoking                      | 9  | 1.72   | 1.21–2.46      | Fixed effect   | 0   | 0.69                 |
| Substance use                | 8  | 1.06   | 0.48–2.34      | Random effect  | 58.5| 0.71                 |
| Alcohol dependence           | 4  | 1.22   | 0.43–3.40      | Random effect  | 61.8| 0.15                 |
| High HRAR                    | 4  | 2.93   | 0.30–28.64     | Random effect  | 79.6| 0.18                 |
| Social factors               |    |        |                |                |     |                      |
| Abstinence < 6 months        | 20 | 2.76   | 2.10–3.61      | Fixed effect   | 18.1| 0.02                 |
| Rehabilitation program       | 11 | 1.10   | 0.59–2.04      | Random effect  | 67  | 0.71                 |
| Comorbidity                  |    |        |                |                |     |                      |
| Psychiatric disease          | 9  | 3.46   | 1.87–6.39      | Random effect  | 40.6| 0.02                 |
| Depression                   | 3  | 2.13   | 0.49–9.25      | Random effect  | 54.4| 0.60                 |

N Number, OR Odds ratio, CI Confidence interval, I² I² statistics, SES Socioeconomic status, HRAR High-risk alcohol relapse scale
Clinical practice has changed considerably since the first studies that recruited in 1988. The differences in the definition of alcohol relapse and heavy relapse as well as a lack of objective means of documenting alcohol use in these studies are limitations. Furthermore, heavy alcohol relapse was defined only in some studies (Table 2). Including unpublished studies may solve this problem. The absence of negative studies of psychiatric co-morbidities and abstinence less than 6 months likely caused publication bias. However, this attempt cannot guarantee a reasonably low heterogeneity after including unpublished studies.

**Conclusions**

We demonstrated the pooled rates of any alcohol relapse and heavy alcohol relapse post-LT. Furthermore, we identified predictive factors of alcohol relapse after LT to be used during the selection process of LT candidates. With respect to the prevention of alcohol relapse post-LT, alcohol abstinence of at least 6 months, appropriate screening and
care of psychiatric co-morbidities, and smoking cessation should be incorporated in pre-transplant selection and management periods. Careful selection of LT candidates and modifying pre-transplant risk factors of alcohol relapse has the potential to reduce alcohol relapse after LT.

**Abbreviations**

ALD: Alcoholic liver disease; CI: Confidence interval; HRAR: High-Risk Alcohol Relapse; LT: Liver transplantation; OR: Odds ratio

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**Authors’ contributions**

LC participated in the design of the study, interpreted the data and wrote the manuscript. NY performed in the design of the study, interpreted the data and reviewed the manuscript. AT participated in the design of the study, statistical analysis, interpretation of the data and reviewed of the manuscript. AS participated in the design of the study, interpreted the data and wrote and edited the manuscript. All authors read and approved the final manuscript.

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**Competing interests**

The authors declare that they have no competing interests.

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