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Meta-analysis: Prevalence and impact of alcohol abstinence in alcohol-associated cirrhosis

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CONFLICT OF INTEREST STATEMENT

Cheng Han Ng: CHN serves as a consultant to Boxer Capital. Brian P Lee: BPL receives Siemens Healthineers Consulting fees from GlaxoSmithKline. Philippe Mathurin: PM serves as a consultant for Abbvie, Advanz Pharma Services, Agomab Therapeutics, Astra Zenneca, Bayer Healthcare, Eisai, Evive Biotech, Gilead Sciences, GlaxoSmithKline, Iddi, Intercept, Ipsen, Novo Nordisk, Pfizer, Resolution Therapeutics, Roche, Surrozen. Rohit Loomba: RL serves as a consultant to Aardvark Therapeutics, Altimmune, Arrowhead Pharmaceuticals, AstraZeneca, Cascade Pharmaceuticals, Eli Lilly, Gilead, Glympse bio, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Lipidio, Madrigal, Neurobo, Novo Nordisk, Merck, Pfizer, Sagimet, 89 bio, Takeda, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institution received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc. Daniel Q. Huang: DQH has served as a consultant for Gilead Sciences.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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Summary

Background: Although alcohol abstinence may be an effective intervention for alcohol-associated cirrhosis, its association with prognosis has not been systematically assessed or quantified.

Aims: To determine the prevalence of alcohol abstinence, factors associated with alcohol abstinence and the impact of abstinence on morbidity and overall survival in people with alcohol-associated cirrhosis.

Methods: We searched Medline and Embase from inception to 15 April 2023 for prospective and retrospective cohort studies describing alcohol abstinence in people with known alcohol-associated cirrhosis. Meta-analysis of proportions for pooled estimates was performed. The method of inverse variance, employing a random-effects & model, was used to pool the hazard ratio (HR) comparing outcomes of abstinent against non-abstinent individuals with alcohol-associated cirrhosis.

Results: We included 19 studies involving 18,833 people with alcohol-associated cirrhosis. The prevalence of alcohol abstinence was 53.8% (CI: 44.6%–62.7%). Over a mean follow-up duration of 48.6 months, individuals who continued to consume alcohol had significantly lower overall survival compared to those who were abstinent (HR: 0.611, 95% CI: 0.506–0.738). These findings remained consistent in sensitivity/subgroup analysis for the presence of decompensation, study design and studies that assessed abstinence throughout follow-up. Alcohol abstinence was associated with a significantly lower risk of hepatic decompensation (HR: 0.612, 95% CI: 0.473–0.792).

Conclusions: Alcohol abstinence is associated with substantial improvement in overall survival in alcohol-associated cirrhosis. However, only half of the individuals with known alcohol-associated cirrhosis are abstinent.

1 | INTRODUCTION

Alcohol-associated liver disease is a significant contributor to preventable morbidity and mortality worldwide, encompassing a range of conditions from steatosis to advanced fibrosis, cirrhosis and hepatocellular carcinoma (HCC).[1-4] Alcohol-associated cirrhosis is a leading cause of liver disease and accounts for a quarter of global cirrhosis deaths.[5-8] People with alcohol-associated cirrhosis have a 5-year mortality rate exceeding 70%.[9]

Specific therapies for alcohol-associated cirrhosis are lacking, hence the cornerstone of management is the achievement and maintenance of alcohol abstinence.[10-14] In a previous meta-analysis,[15] achieving alcohol abstinence has been linked to a significant survival benefit and an improved outcome. However, it is unclear what proportion of people with alcohol-associated cirrhosis are able to achieve alcohol abstinence, with emerging data suggesting that this ranges from 50% to 70%.[16,17] In addition, there remains a paucity of data on the factors that predict alcohol abstinence. The impact of alcohol cessation on overall survival, hepatic decompensation and the development of HCC among people with alcohol-associated cirrhosis has not been recently evaluated systematically. A meta-analysis that was conducted nearly a decade ago was limited by a modest sample size and several large cohort studies have been recently published.[17-20] In light of these considerations, we aimed to assess the proportion of people with known alcohol-associated cirrhosis who were abstinent from alcohol, the factors associated with alcohol abstinence and the impact of alcohol abstinence on morbidity and overall survival.

2 | MATERIALS AND METHODS

2.1 | Search strategy

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21] Medline and Embase databases were searched for articles reporting on alcohol abstinence in people with alcohol-associated cirrhosis from inception to 15 April 2023. Key search terms included but were not limited to synonyms of ‘alcohol abstinence’ and ‘alcohol cirrhosis’ in the titles and abstracts. The full search strategy is included in Data S1. All references were imported into Endnote X9 for removal of duplicates. To ensure a comprehensive search, the bibliographies of included articles and previous meta-analyses were reviewed by two independent authors.

2.2 | Eligibility and selection criteria

Two pairs of authors (WHL and PT, CHN and DJHT) independently conducted the title abstract sieve followed by the full-text review. Discrepancies were resolved by consensus or in consultation with a fifth independent author (DQH). Original articles, including prospective and retrospective cohort studies, in the English language were included whereas systematic reviews, meta-analyses, commentaries, editorials and conference abstracts were excluded. Studies were considered for inclusion if (i) subjects were diagnosed with alcohol-associated cirrhosis, (ii) at least one relevant outcome of subjects who were abstinent from alcohol versus those who continued drinking was reported and (iii) effect estimates were reported in hazard ratios (HR) or sufficient raw data was provided for calculation of HR. We did not include studies focusing on acute alcoholic hepatitis, acute-on-chronic liver failure, or alcohol-associated liver disease unless the authors of the study specified that all patients had alcohol-associated cirrhosis. Additionally, specific interventions for alcohol use disorder that promote abstinence in alcohol-associated cirrhosis were not considered. All animal-related studies, studies conducted in the paediatric population and studies focusing on liver transplant recipients were excluded. Studies inferring results from the same databases were also removed to avoid duplication of the same cohort.

2.3 | Data extraction

Alcohol-associated cirrhosis was diagnosed based on histology, clinical, biochemical and radiological parameters, or based on International Classification of Diseases Codes. Alcohol intake was assessed based on self-reported information, information from relatives, biochemical parameters, as well as the clinical judgement of the managing physician. Two pairs of authors (WHL and PT, CHN and DJHT) independently extracted study-level aggregated data in a blinded fashion. The extracted data included study characteristics (e.g. author, publication year, country, study design, study period, sample size, follow-up period), and clinical characteristics, (e.g. age, sex, smoking status, diabetes, body mass index (BMI), anti-hepatitis C virus (HCV) antibody positivity, alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), platelets, albumin, bilirubin, alpha-fetoprotein (AFP), model of end-stage liver disease (MELD) scores, Child-Pugh scores and class, hepatic encephalopathy, varices and bleeding events). Transformation of values was carried out using pre-existing formulae, in which mean and standard deviations were estimated from the median and range using the widely adopted formula by Wan et al.[22]

2.4 | Objectives

The co-primary objectives were to determine the prevalence of alcohol abstinence, and its association with overall survival in people with alcohol-associated cirrhosis. Overall survival was defined as the duration from the date of inclusion to the date of death by any cause. The secondary objectives were to determine factors associated with alcohol abstinence, the association of alcohol abstinence with decompensation and the development of HCC. Hepatic decompensation was defined as variceal bleeding, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy. Co-variate adjusted hazard ratios (HR) and 95% confidence intervals (CIs) of outcomes in abstinent versus non-abstinent people with alcohol-associated cirrhosis were recorded. In cases where HR was not reported, unadjusted effect estimates were obtained through extraction of individual patient survival data via reconstruction of reported Kaplan-Meier curves using the formula detailed by Guyot et al.[23]

2.5 | Statistical analysis

To calculate the proportion of alcohol abstinence among people with alcohol-associated cirrhosis, a single-arm analysis of binary events in pooled proportions was performed using a generalised linear mixed model with Clopper-Pearson intervals.[24,25] To explore potential sources of heterogeneity, sensitivity analysis was conducted for studies that reported abstinence throughout follow-up and for decompensated patients. Multiple subgroup analyses were also conducted to stratify prevalence by geographical region (Europe, America, or Asia), mean follow-up duration (1-5 years vs more than 5 years),[26] as well as study design (retrospective vs prospective). To explore the determinants of alcohol abstinence, a meta-regression analysis was performed. This involved utilising a generalised linear model within the binomial family with a logit link and incorporating inverse variance weightage.[27] The meta-regression analysis employed the proportion of abstinence in each study as the dependent variable, with study-level covariates serving as independent variables. The resulting coefficient was subsequently exponentiated to derive the odds ratio (OR) and its associated 95% confidence intervals (95% CI). For continuous variables,

the OR obtained describes how the outcome variable changes with a unit increase in the explanatory variable. To assess the impact of alcohol abstinence on overall survival, decompensation and the development of HCC, the method of inverse variance, employing a random-effects model,[28,29] was used to pool the HR comparing abstinent against non-abstinent individuals with alcohol-associated cirrhosis. Pre-specific sensitivity/subgroup analyses, as mentioned previously, were conducted when sufficient studies were available. All analyses were conducted in RStudio (Version 1.3.1093). A $p \leq 0.05$ was considered as the threshold for statistical significance. Statistical heterogeneity was assessed via I^2 and Cochran's Q test values, where an I^2 value of 25% represented a low degree of heterogeneity, 50% represented a moderate degree and 75% represented a high degree while a Cochran Q-test with a $p \leq 0.10$ was considered significant for heterogeneity.[30] Random-effects model was employed in all analyses irrespective of all measures of heterogeneity based on evidence indicating that random-effects models yield more reliable effect estimates compared to fixed-effect models.[31,32]

2.6 | Quality assessment and risk of bias

The included articles underwent quality assessment using the Joanna Briggs Institute (JBI) Critical Appraisal Tool for prevalence studies.[33] This tool evaluates the risk of bias in cohort studies based on several criteria, including the appropriateness of the sample frame, sampling method, adequacy of sample size, data analysis, methods for identifying and measuring relevant conditions, statistical analysis and adequacy of response rate. Studies were characterised as having a high (JBI checklist score 1–3), moderate (4–6), or low (7–9) risk of bias. Publication bias was evaluated via visual examination of funnel plots for analyses involving more than 10 studies to assess whether there was an asymmetrical distribution of data points along the vertical axis representing the intervention effect.[34]

3 | RESULTS

3.1 | Summary of included articles

The initial search from Medline and Embase yielded 1959 articles. After the removal of 484 duplicates and the exclusion of 1423 studies based on the study title and abstract, 52 reports were selected for full-text review, of which 20 reports from 19 studies were included in this meta-analysis (Figure 1). In total, there were 11 prospective studies and eight retrospective cohort studies. Four studies each originated from the United States[18,19,35,36] and Spain,[17,37-39] two from France,[40,41] and one from the United Kingdom,[42] Argentina,[43] Belgium,[44] Iceland,[45] Norway,[9] Austria,[20] Sri Lanka,[46] and Japan[47] respectively. In addition, there were two reports on different outcomes from one multi-centre study which included study sites from both France and Belgium.[16,48] A total of 18,833 people with alcohol-associated cirrhosis were included in this study, including 9745 individuals who were abstinent from alcohol. The mean age was 54.6 years old while the proportion of men ranged from 61% to 98%. Table 1 summarises the key characteristics and quality assessment of the included studies. The definitions of alcohol abstinence in the various studies can be found in Table S1. All studies were assessed to have a low risk of bias based on the JBI appraisal tool.

3.2 | Prevalence of alcohol abstinence in people with known alcohol-associated cirrhosis

In a pooled analysis of 19 studies involving 18,663 individuals with alcohol-associated cirrhosis and with available data for the status of alcohol consumption, the prevalence of abstinence was 53.8% (CI: 44.6%–62.7%, p<0.01) (Figure S1 and Table 2). There was no evidence of publication bias on visual inspection of the funnel plot (Figure S2).

3.3 | By studies that reported abstinence throughout the study follow-up

The prevalence of sustained alcohol abstinence throughout the study follow-up was 52.2% (CI: 40.9%–63.2%, $p < 0.01$).

3.4 | By the presence of hepatic decompensation

Sensitivity analysis determined that the prevalence of alcohol abstinence in decompensated alcohol-associated cirrhosis was 52.7% (CI: 32.7%–71.8%, $p < 0.01$).

3.5 | By follow-up duration

The pooled prevalence of alcohol abstinence in people with alcohol-associated cirrhosis was similar in studies with a mean follow-up duration of five or less years (54.8%, CI: 44.9%–64.3%, $p < 0.01$) and studies with a mean follow-up duration of more than 5 years (45.3%, CI: 26.1%–65.9%, $p < 0.01$), with no significant subgroup difference ($p = 0.42$).

3.6 | By geographical region

Alcohol abstinence in alcohol-associated cirrhosis was similar between geographical regions ($p = 0.97$) when comparing Europe (53.4%, CI: 41.4%–64.9%, $p < 0.01$), America (55.2%, CI: 42.6%–67.2%, $p < 0.01$) and Asia (51.1%, CI: 18.1%–83.2%, $p < 0.01$).

3.7 | By study design

The pooled prevalence of alcohol abstinence among people with alcohol-associated cirrhosis was similar ($p = 0.62$) in prospective versus retrospective studies (55.7%, CI: 44.9%–66.0%, $p < 0.01$ vs. 50.8%, CI: 35.3%–66.2%, $p < 0.01$).

3.8 | Factors associated with alcohol abstinence in alcohol-associated cirrhosis

The factors associated with alcohol abstinence in alcohol-associated cirrhosis are summarised in Table 3. Regression analysis of study-level data determined that increased ALT (OR: 0.977, 95% CI: 0.966–0.988, $p = 0.01$), AST (OR: 0.993, 95% CI: 0.990–0.996, $p = 0.01$) and GGT (OR: 0.997, 95% CI: 0.996–0.998, $p < 0.01$) were associated with continued consumption of alcohol.

3.9 | Impact of alcohol abstinence on overall survival

A summary of the impact of alcohol abstinence on overall survival can be found in Table 4. In a pooled analysis of 17 studies involving 18,076 people with known alcohol-associated cirrhosis, individuals who continued to consume alcohol had significantly lower overall survival compared to those who were abstinent (HR: 0.611, 95% CI: 0.506–0.738, $p < 0.01$, I^2: 77.4%) over a mean follow-up duration of 48.6 months (Figure 2). Publication bias was

present in the analysis of overall survival based on visual inspection of funnel plots (Figure S3).

3.10 | By studies that reported abstinence throughout study follow-up

Sustained alcohol abstinence throughout follow-up was associated with improved survival in people with alcohol-associated cirrhosis (HR: 0.560, 95% CI: 0.437–0.717, $p = 0.003$, I^2: 51.2%).

3.11 | By the presence of decompensation

Alcohol abstinence was associated with improved survival in people with decompensated cirrhosis (HR: 0.416, 95% CI: 0.245–0.706, $p = 0.01$, I^2: 49.4%) and compensated cirrhosis (HR: 0.636, 95% CI:0 485–0.833, $p < 0.01$, I^2: 0.00%).

3.12 | By study design

Alcohol abstinence was associated with improvement in overall survival in both prospective (HR: 0.511, 95% CI: 0.406–0.644, $p < 0.01$, I^2: 36.7%) and retrospective studies (HR: 0.787, 95% CI: 0.612–1.01, $p = 0.04$, I^2: 70.4%).

3.13 | Impact of alcohol abstinence on hepatic decompensation and HCC

Alcohol abstinence was associated with a lower risk of hepatic decompensation (HR: 0.612, 95% CI: 0.473–0.792, $p = 0.002$, I^2: 73.0%) in people with alcohol-associated cirrhosis (7 studies, $n = 15{,}627$ individuals, Figure S4A). However, abstinence was not associated with a reduction in the development of HCC (HR: 0.860, 95% CI: 0.618–1.20, $p = 0.28$, I^2: 46.3%), but data were limited (4 studies, $n = 16{,}060$ individuals, Figure S4B). A summary of the findings can be found in Table S2.

4 | DISCUSSION

4.1 | Main findings

In this systematic review and meta-analysis of 19 studies and 18,833 individuals, we demonstrated that approximately one in two people with known alcohol-associated cirrhosis abstained from alcohol. These findings remained consistent in subgroup/sensitivity analyses for the presence of decompensation, geographical region, follow-up and study design.

Alcohol abstinence in people with alcohol-associated cirrhosis was associated with an approximately 40% improvement in overall survival and a similar reduced risk of hepatic decompensation, over a mean follow-up of 4 years. The survival benefits of alcohol abstinence persisted in subgroup analyses for the presence of decompensation and study design.

4.2 | In context with current literature

The current study builds upon a previous meta-analysis that was published a decade ago[15] and provides new data for the prevalence of alcohol abstinence with the inclusion of several large new studies,[16-20] as well as updated estimates on the impact of alcohol abstinence on overall survival. The previous meta-analysis determined that a minimum of 1.5 years of

alcohol abstinence was required before a statistically significant improvement in survival could be discerned.[15] Although sensitivity analysis by the duration of follow-up could not be carried out in the present study due to insufficient sample size, alcohol abstinence was associated with survival benefits in studies with a mean follow-up of up to 5 years, with preliminary data suggesting that such effect sustains after 5 years. However, there were limited studies with more than 5-years follow-up and additional studies with long-term follow-up are required. Additionally, recent meta-analyses reporting on alcohol abstinence as a primary outcome were primarily focused on interventions for alcohol use disorder in patients with alcohol-associated cirrhosis and hepatitis.[49,50] In contrast, the current review aims to study the prevalence of abstinence, irrespective of the specific intervention received.

4.3 | Strengths and limitations

The current study is the largest and most comprehensive study to date evaluating the prevalence and impact of alcohol cessation in people with known alcohol-associated cirrhosis. However, there are several limitations. Data from the included studies were heterogenous, as evidenced by significantly large I^2 in several analyses. This may be attributable to heterogeneous definitions of alcohol abstinence and differences in methodology or population characteristics. To address this, multiple sensitivity and subgroup analyses were conducted to test for the robustness of associations. While these findings require cautious interpretation, it should be noted that large sample sizes often inflate heterogeneity estimates.[51,52] This is evident in several previous meta-analyses which yielded substantial $I^2 > 90\%$,[53,54] suggesting a lack of appropriate tools for accurate assessments of heterogeneity in single-arm analyses.[55,56] Second, this study was unable to analyse the effect of reduction of alcohol consumption as the amount of alcohol consumption and pattern of drinking were not quantified in many studies. This highlights the need to develop uniform criteria to better characterise alcohol consumption which may inform clinical trial designs regarding alcohol cessation at different risk levels of drinking among people with alcohol-associated cirrhosis.[57] All included studies were observational, and hence subject to confounding and bias. Additionally, publication bias was observed in the analysis of overall survival. Misclassification of abstinence also cannot be ruled out, although the majority of studies reported close surveillance and the use of multiple parameters to evaluate abstinence throughout the follow-up period. Importantly, individuals may have underreported alcohol consumption and consequently, the reported abstinence rates may be overestimated. Moreover, none of the included studies employed direct alcohol metabolites to confirm alcohol abstinence and biochemical parameters may be inaccurate in the setting of cirrhosis. Additionally, disease awareness in alcohol-associated liver disease is poor, hence these data are only reflective of people who have been diagnosed with cirrhosis, and it is likely that the true prevalence of alcohol abstinence among people with alcohol-associated cirrhosis in the community is lower. The paucity of data on concomitant metabolic dysfunction, that is, Met-ALD also precluded further analysis to assess the impact of abstinence on these patients. Finally, there were insufficient data regarding psychosocial history such as other substance use disorders, ongoing treatment for alcohol use disorder, depression, anxiety, insurance, occupation, income level, family support and marital status to assess the interplay between these factors and alcohol abstinence.

4.4 | Implications for clinical care and research

These data provide important information for care providers to counsel people with alcohol-associated cirrhosis.[58] The fact that only half of the patients with alcohol-associated cirrhosis are abstinent is concerning and highlights the potential importance of a multidisciplinary approach to achieving this goal.[59-61] In addition, these data call for greater training and awareness among care providers in the available treatments for alcohol use disorder, including behavioural and pharmacological therapies, which are underutilized.[62-64] These findings underscore the urgent need for the implementation of multidisciplinary strategies that effectively engage and address the needs of this special population and support them in achieving sustained alcohol abstinence.[65,66] These data should be validated in large, prospective studies that account for the time-varying nature of alcohol use with long-term follow-up. Although alcohol abstinence was not associated with a reduction in the development of HCC, this may be related to the limited number of studies available, and more studies are required.

5 | CONCLUSION

This updated meta-analysis determined that alcohol abstinence is associated with substantial improvement in overall survival in people with known alcohol-associated cirrhosis, but only half are abstinent. These findings call for urgent measures to improve the rates of alcohol abstinence through multidisciplinary collaboration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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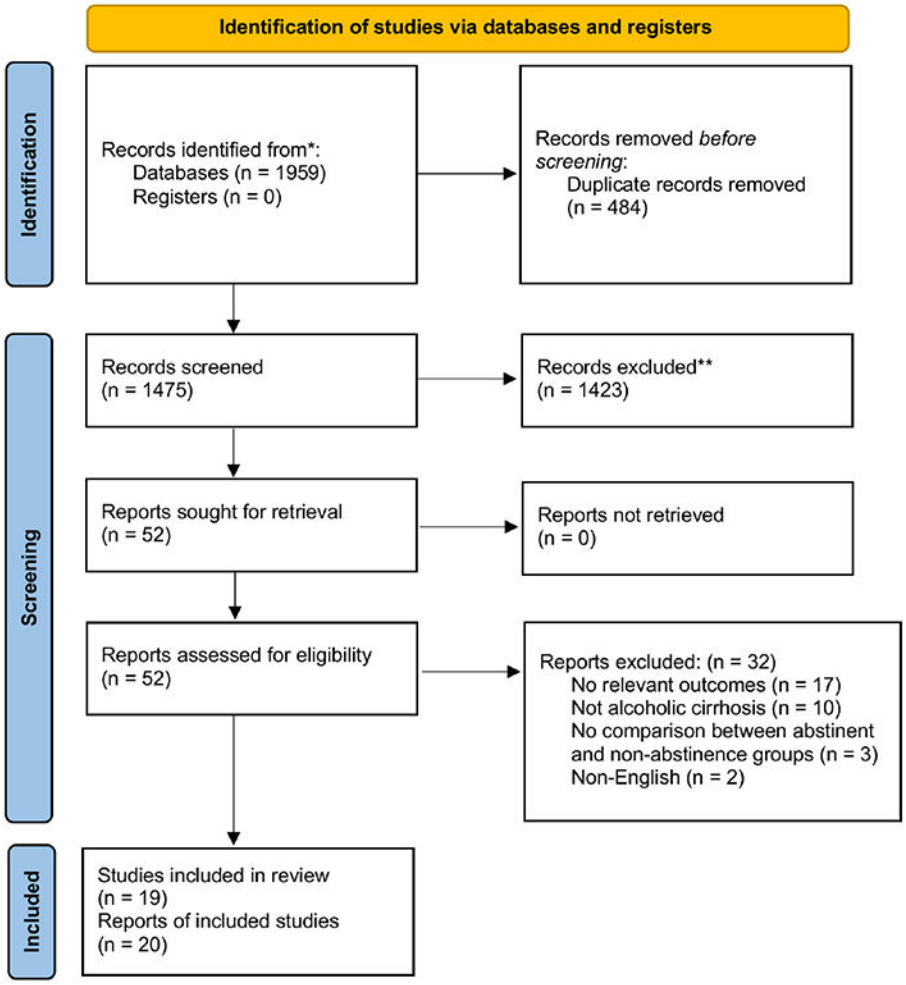

FIGURE 1.
PRISMA flow diagram.

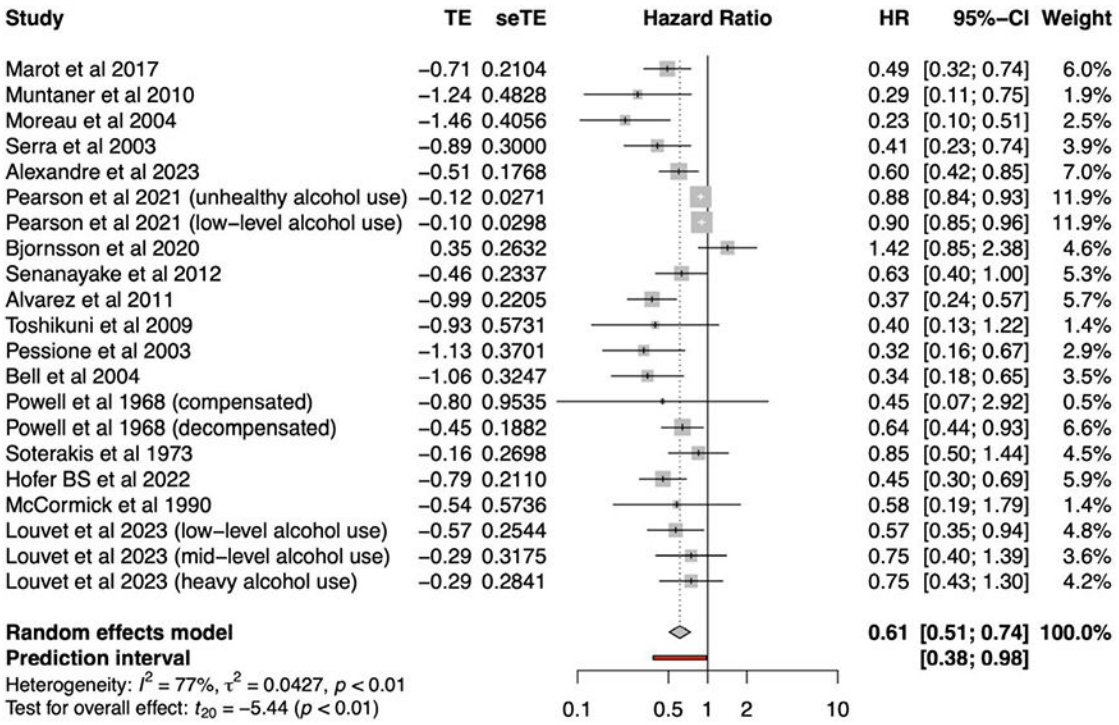

FIGURE 2.

Pooled overall survival of non-abstinent vs abstinent individuals with known alcohol-associated cirrhosis. Pooled hazard ratio (95% CI): 0.61 [0.51–0.74], Using random-effects model. I^2: 77.4%.

TABLE 1

Summary of included articles.

Author, year	Country	Study setting	Study period	Study design	Mean follow-up (months)	Total alcohol cirrhosis (*n*)	Abstinent (*n*)	Age (years)	Gender male(%)	Decompensated (*n*)	Compensated (*n*)	Quality assessment	Factors that HR were adjusted for
Rodriguez et al,[1] 2021	Spain	Cohort	1992–2018	Prospective	60.0	727	354	55.0	82.9	480	247	8	Age, gender, anti-hepatitis B core antibody, AST, platelets, Child-Pugh class and AFP
Marot et al,[2] 2017	Belgium	Cohort	1995–2014	Prospective	56.7	529	189	55.7	68.0	–	–	7	Age, gender
Muntaner et al,[3] 2010	Spain	Cohort	2001–2007	Prospective	30.3	67	48	–	–	67	0	8	Child-Pugh score, creatinine, nadolol dose, viral cirrhosis and HCC
Moreau et al,[4] 2004	France	Cohort	1997–1999	Prospective	18.0	61	50	55.7	–	61	0	8	–
Serra et al,[5] 2003	Spain	Cohort	1973–1997	Retrospective	110	213	127	51.0	–	85	128	8	Age, Child-Pugh grade, anti-HCV positivity
Alexandre et al,[6] 2023	USA	Cohort	2014–2020	Retrospective	37.1	436	307	56.0	67.0	–	–	8	Age, HE, HCC
Pearson et al,[7] 2021	USA	Administrative database	2012–2020	Retrospective	56.7	14,385	7491	–	–	–	–	8	History of ascites, history of HE, history of variceal bleeding, history of HCC, Charlson Comorbidity Index, age, sex, race/ethnicity, body mass index, HCV genotype, human immunodeficiency virus infection, HBV, diabetes mellitus, platelet count, serum bilirubin, creatinine, albumin, AST to ALT ratio, international normalised ratio and haemoglobin

Author, year	Country	Study setting	Study period	Study design	Mean follow-up (months)	Total alcohol cirrhosis (*n*)	Abstinent (*n*)	Age (years)	Gender male(%)	Decompensated (*n*)	Compensated (*n*)	Quality assessment	Factors that HR were adjusted for
Bjornsson et al,[8] 2020	Iceland	Cohort	2001–2016	Retrospective	48.0	118	50	57.0	74.7	–	–	8	–
Senanayake et al,[9] 2012	Sri Lanka	Cohort	1995–2010	Retrospective	29.3	306	150	52.5	97.7	–	–	8	Age, sex, body mass index, diabetes mellitus, Child-Pugh Grade at diagnosis
Alvarez et al,[10] 2011	Spain	Cohort	1998–2010	Prospective	55.8	165	99	56.0	82.0	165	0	8	Age, gamma-glutamyl transpeptidase, albumin, Child-Pugh score and MELD, development of HE
Toshikuni et al,[11] 2009	Japan	Cohort	1997–2007	Retrospective	54.9	75	19	55.6	89.3	0	75	8	–
Pessione et al,[12] 2003	France	Cohort	1991	Retrospective	60.0	122	58	52.1	61.5	63	23	7	Age, gender, gastrointestinal/ variceal bleeding, HBs Ag and/or anti-HCV, acute alcoholic hepatitis, smoking status
Bell et al,[13] 2004	Norway	Cohort	1984–2000	Prospective	180	100	25	58.0	65.0	94	6	9	Age, ALP
Powell et al,[14] 1968	USA	Cohort	1951–1963	Prospective	60.0	283	93	51.0	56.5	233	45	7	–
Soterakis et al,[15]1973	USA	Cohort	1973	Prospective	44.8	146	77	–	–	146	0	7	–
Hofer BS et al,[16] 2022	Austria	Cohort	2004–2020	Prospective	43.3	320	241	56.6	75.6	280	40	9	Age, previous decompensation, MELD score, albumin, AST, C-reactive protein, hepatic venous pressure gradient
McCormick et al,[17] 1990	UK	Cohort	1975–1987	Retrospective	51.4	100	15	50.5	75.0	100	0	8	–

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Author, year	Country	Study setting	Study period	Study design	Mean follow-up (months)	Total alcohol cirrhosis (*n*)	Abstinent (*n*)	Age (years)	Gender male(%)	Decompensated (*n*)	Compensated (*n*)	Quality assessment	Factors that HR were adjusted for
J Vorobioff et al,[18] 1996	Argentina	Cohort	1980–1990	Prospective	42.0	30	21	53.0	76.7	–	–	8	–
Ganne-Carrié et al,[19] 2018 (CIRRAL)	France and Belgium	Cohort	2010–2016	Prospective	49.7	650[a]	331[a]	58.0	67.4	0	650	8	Age, platelet count, creatinine, Child Pugh class, glass-years >25
Louvet et al,[20] 2023 (CIRRAL)													

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; HCV, viral hepatitis C; HE, hepatic encephalopathy; HR, hazard ratio; MELD, Model for End-stage Liver Disease.

[a]Prevalence of abstinence, overall survival and decompensation outcomes were reported by Louvet et al while the development of hepatocellular carcinoma was reported by Ganne-Carrié et al.

TABLE 2

Proportion of alcohol abstinence in people with alcohol-associated cirrhosis.

	No. of studies	Total sample size	Events	Pooled proportion (95% CI)	Cochran-*Q*	I^2(%)	Subgroup difference
Overall	19	18,663	9745	53.8(44.6–62.7)	<0.01	95.3	
Sensitivity analysis							
Studies that reported abstinence throughout follow-up	12	3183	1711	52.2(40.9–63.2)	<0.01	95.4	
Decompensated patients only	6	1106	554	52.7(32.7–71.8)	<0.01	94.9	
Geographical region							
Europe	12	3115	1587	53.4(41.4–64.9)	<0.01	95.1	0.97
America	5	15,275	7989	55.2(42.6–67.2)	<0.01	95.8	
Asia	2	273	169	51.1 (18.1–83.2)	<0.01	98.0	
Mean follow-up duration							
≤5 years	17	18,368	9593	54.8(44.9–64.3)	<0.01	95.6	0.42
>5 years	2	295	152	45.3(26.1–65.9)	<0.01	94.8	
Study design							
Prospective	11	3055	1528	55.7(44.9–66.0)	<0.01	95.0	0.62
Retrospective	8	15,608	8217	50.8(35.3–66.2)	<0.01	95.9	

TABLE 3

Factors associated with alcohol abstinence in people with alcohol-associated cirrhosis.

Factors	No. of studies	Sample size	Odds ratio (95% CI)	*p*-value
Age	16	4235	1.03 (0.916–1.15)	0.70
Male gender (%)	14	3791	1.02 (0.992–1.04)	0.25
Current smoker (%)	5	2428	0.984 (0.952–1.02)	0.35
Diabetes (%)	6	2240	0.992(0.933–1.05)	0.78
BMI (kg/m^2)	4	2226	0.938 (0.400–2.20)	0.84
Anti-HCV positive (%)	4	553	1.02 (0.967–1.08)	0.39
ALT (IU/L)	4	2019	0.977(0.966–0.988)	**0.01** *
AST (IU/L)	6	2019	0.993(0.990–0.996)	**0.01** *
GGT (IU/L)	6	2019	0.997(0.996–0.998)	**<0.01** *
Platelets (×10^3/mm^3)	7	2548	0.983(0.968–0.998)	0.07
Albumin (g/L)	10	2804	1.01 (0.975–1.05)	0.54
Bilirubin (mg/dL)	9	2837	1.01 (0.984–1.04)	0.42
MELD score	5	1779	1.18 (0.963–1.44)	0.15
Child Pugh score	7	1475	1.31(0.881–1.93)	0.23
Child-Pugh A (%)	11	3002	1.00 (0.999–1.001)	0.94
Hepatic encephalopathy (%)	5	1466	1.01 (0.986–1.04)	0.38
Ascites (%)	8	2146	1.04 (0.996–1.08)	0.13
Varices (%)	8	2584	1.02 (0.996–1.04)	0.16
Bleeding (%)	6	1756	1.01 (0.997–1.03)	0.15
Previous HCC (%)	11	3661	1.04 (0.996–1.09)	0.13

Abbreviations: AFP, alpha-feto protein; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease.

*Bolded $p \leq 0.05$ denotes statistical significance.

TABLE 4

Association of alcohol abstinence with overall survival, in people with alcohol-associated cirrhosis.

	No of studies	Sample size	Hazard ratio (95% CI)	*p*-value	I^2 (%)	Cochran Q	Subgroup difference
Overall survival	17	18,076	0.611(0.506–0.738)	**<0.01** *	77.4	<0.001	
Studies that reported abstinence throughout follow-up	10	2452	0.560 (0.437–0.717)	**0.003** *	51.2	0.02	
Presence of decompensation							
Compensated	3	770	0.636 (0.485–0.833)	**<0.01** *	0.00	0.81	0.05
Decompensated	5	626	0.416 (0.245–0.706)	**0.01** *	49.4	0.10	
Study design							
Prospective	9	2321	0.511 (0.406–0.644)	**<0.01** *	36.7	0.10	0.004
Retrospective	8	15,755	0.787(0.612–1.01)	**0.04** *	70.4	<0.01	

* Bolded $p \leq 0.05$ denotes statistical significance.

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