

The prognostic impact of psychiatric intervention on alcohol-associated liver disease : the UK Biobank cohort study

(Running title: Efficacy of psychiatric intervention in ALD)

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List of Abbreviations

ALD, alcohol-associated liver disease; AST, aspartate transaminase; ATE, average treatment effect; AUD, alcohol use disorder; BMI, body mass index; GGT, gamma-glutamyl transferase; HR, hazard ratio; LC, liver cirrhosis; PSM, propensity score matching

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ABSTRACT

Background/Aims: Alcohol-associated liver disease (ALD) is a public health concern. ALD patients often have psychiatric comorbidities, but the effects of psychiatric interventions on ALD are not well-established. This study explores the prognostic impact of psychiatric intervention on ALD within UK Biobank cohort.

Methods: This population-based study included 2,417 ALD patients from the UK Biobank cohort. Psychiatric intervention was defined by a consultation with psychiatrists during hospitalization or a history of medication related to alcohol use disorder and psychiatric comorbidities. Survival analysis was conducted, incorporating propensity score matching (PSM), to precisely assess the impact of psychiatric intervention.

Results: Among 2,417 ALD patients, those with F10 (mental disorders due to alcohol) codes had poorer survival outcomes. Psychiatric intervention significantly improved the outcomes of both all-cause and liver-related mortality and reduced the incidence of liver cirrhosis. In subgroup or 2-year landmark analyses, psychiatric intervention consistently showed a survival benefit in ALD patients. In the multivariate analysis, psychiatric intervention was identified as a favorable prognostic factor (hazard ratio, 0.780; $P = 0.002$ after PSM).

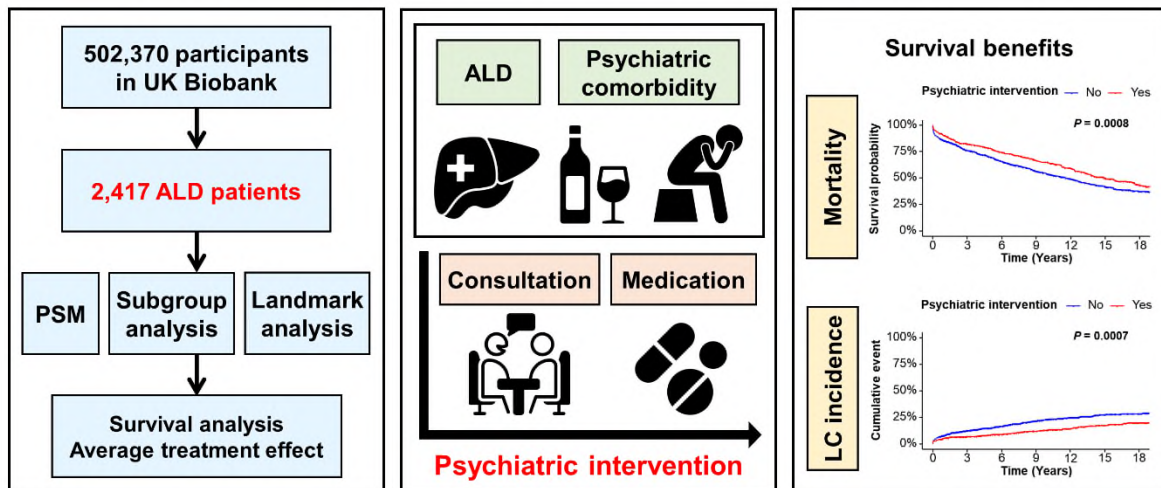
Conclusions: This study demonstrates the favorable effect of psychiatric intervention in ALD patients with psychiatric comorbidities. These findings emphasize the importance of integrated management for ALD patients to address both their medical and psychiatric aspects. Therefore, we suggest the potential benefits of early psychiatric interventions in improving survival outcomes in ALD.

Keywords: Alcohol-associated liver disease; Psychiatric comorbidities; Psychiatric medication; Psychiatric consultation.

Highlights

- Psychiatric intervention improved all-cause and liver-related mortality in ALD patients.
- Reduced mortality is associated with a decreased incidence of liver cirrhosis, attributable to psychiatric intervention.
- The study emphasizes the importance of integrated management for ALD patients, addressing both their medical and psychiatric aspects.

The prognostic impact of psychiatric intervention on alcohol-associated liver disease: the UK Biobank cohort study



1. INTRODUCTION

Alcohol-associated liver disease (ALD) is a complicated health concern with high morbidity and mortality rates.^{1,2} The disease appears in various forms, ranging from alcohol-associated fatty liver to the more severe phenomenon of alcoholic hepatitis and liver cirrhosis (LC).²⁻⁴ The treatment of ALD should involve a comprehensive approach targeting the reduction of alcohol consumption, managing complications of liver disease, and addressing the risk factors associated with the disease progression.^{5,6} In particular, a reduction in alcohol consumption is associated with significant improvements among patients with alcohol use disorder (AUD).^{7,8} Therefore, the recent practice guidelines for ALD emphasize that abstinence is the most crucial factor in determining the prognosis for patients.^{5,6}

Various psychosocial, behavioral, and pharmacological interventions have been explored as strategies in the comprehensive management of AUD.⁹ Disulfiram (an aldehyde dehydrogenase inhibitor), acamprosate (a glutamate system modulator), and naltrexone (an opioid receptor antagonist) are drugs approved by the U.S. Food and Drug Administration to reduce cravings for alcohol.¹⁰⁻¹² Recently, other off-label medications, such as topiramate and gabapentin, have been trialed in AUD patients to regulate the release of neurotransmitters in the central nervous system.^{13,14} However, due to the side effects and limited efficacy, it is recommended that ALD patients receive individual psychosocial interventions, such as motivational interviewing or psychiatric consultations, alongside psychiatric medications.^{5,11,15} Unfortunately, for ALD patients who primarily require management for physical symptoms, it is difficult for patients to be exposed early to psychiatric intervention in real-world clinical settings.

The prevalence of psychiatric comorbidities in AUD patients—which include mood disorders (30%), anxiety disorders (19%), substance use disorders (47%), attention-deficit hyperactivity disorder (24%), and psychotic disorder (4%) that are often exacerbated by the medical stress associated with ALD¹⁶—is a significant concern. Therefore, when ALD is initially diagnosed, it is essential not only to screen patients for psychiatric comorbidities but also to ensure that their psychosocial status is clearly assessed through early psychiatric consultation.^{6,17} In fact, the presence of any psychiatric illness in patients with LC exacerbates the all-cause mortality rate.¹⁸ Otherwise, major depressive disorder is the most common co-occurring mental disorder in patients with AUD, though the effectiveness of antidepressants is still uncertain in terms of patients' prognosis.¹⁹ Based on the information above, we propose a hypothesis that the implementation of psychiatric interventions

could improve the survival outcomes for patients with ALD.

Here, we first analyzed the impact of psychiatric intervention on the survival prognosis of patients diagnosed with ALD in the UK Biobank cohort. Furthermore, we investigated the influence of psychiatric intervention on the incidence of LC among patients with ALD and aimed to minimize statistical bias by performing various subgroup analyses. We also used methodological techniques like propensity score matching (PSM) to precisely estimate the effects of psychiatric intervention.

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2. PATIENTS AND METHODS

2.1 Study design and participants

The UK Biobank is a population-based, prospective cohort study that has enrolled 502,370 participants to date (with a response rate of 5.5%) all aged 40–69 years and residing in the United Kingdom.²⁰ This study has been ongoing since 2006 and operates from 22 assessment centers across Scotland, England, and Wales (<http://www.ukbiobank.ac.uk>). During the baseline assessment from 2006–2010, all participants completed a questionnaire to provide detailed information about their lifestyles using an electronic device with a touchscreen. Additionally, they regularly provided biological samples, such as blood, urine, and saliva.²⁰ Among these, 2,417 inpatients diagnosed with ALD were included in this study (Figure 1). ALD was defined as a condition in participants who had the International Classification of Diseases, 10th Revision (ICD-10), code K70 (for alcoholic liver disease), as acquired from the dataset. The development of LC was defined based on the first report of the ICD-10 code K74, which indicates cirrhosis of the liver. We excluded patients with extrahepatic malignancies and those with a history of LC prior to the diagnosis of ALD. The presence of ICD-10 code F10 (for mental and behavioral disorders due to the use of alcohol) for AUD was also extracted.

2.2 Ethical approval of the UK Biobank cohort

The UK Biobank study received approval from the North West Multi-Centre Research Ethics Committee, and all participants provided signed written informed consent forms (<http://www.ukbiobank.ac.uk>). This research was performed using the UK Biobank dataset under application number 85156.

2.3 Definitions of psychiatric intervention

Psychiatric intervention was defined as either consulting with a psychiatrist during hospitalization or having a history of medication use for AUD and associated psychiatric comorbidities. Supplementary Table 1 includes detailed information of psychiatric medications based on the recent AUD guideline.¹¹ Among the 497 patients who underwent psychiatric intervention, 345 (69.4%) received psychiatric medication, and the medications were categorized into anti-craving drugs (10.1%), antidepressants (54.5%), and anxiolytics (10.5%). Among the anti-craving drugs, naltrexone was not listed in the UK Biobank medication codes and was therefore

excluded from the analysis. The codes for psychiatric consultations in the UK Biobank used in this study are summarized in Supplementary Table 2.

2.4 Statistical analysis

The significance of continuous factors (mean, \pm standard deviation values) was analyzed using Wilcoxon rank-sum tests, while Pearson's chi-squared or Fisher's exact tests were applied for categorical variables (number, %) to evaluate their significance. Overall survival and liver-related survival were analyzed from the time of ALD diagnosis to all-cause death and liver-related death, respectively. The log-rank test was used in survival analyses to identify significant differences in outcomes between various patient groups. Cox regression analyses were used for univariate and multivariate assessments to study the effects of various factors on patient survival, accounting for potential confounders. PSM was conducted using the nearest-neighbor method with a 1:2 matching ratio ensuring a balanced comparison between the groups. Time zero for the survival and landmark analyses was defined as the date of diagnosis of ALD, identified using the ICD-10 code K70. To address significant differences in baseline demographic and clinical characteristics, we included variables such as age, sex, presence of F10, aspartate transaminase (AST), gamma-glutamyl transferase (GGT), creatinine, alcohol intake frequency, and physical activity frequency in the propensity score estimation. R (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) was the primary tool used for statistical analyses.

3. RESULTS

3.1 Baseline demographic and clinical characteristics of patients

Table 1 outlines the baseline demographic and clinical characteristics of ALD patients before PSM. Our cohort consisted of 2,417 patients diagnosed with ALD, divided into two groups of 1,920 patients who did not receive psychiatric intervention and 497 who did, respectively. The mean age was 56.78 ± 7.51 years, with those receiving psychiatric care being slightly younger ($P < 0.001$). Out of 2,417 patients, 1,630 (67.4%) had ICD-10 code F10, with a significantly higher prevalence (82.9%) of this code in those receiving psychiatric intervention ($P < 0.001$). In terms of liver function test results, the intervention group had lower mean AST and GGT levels. Alcohol consumption was a daily habit for 48.2% of the total cohort, with significant variations between the two groups ($P < 0.001$). Regular physical activity was reported by 45.6% of patients, with a statistically significant difference in frequency observed between the groups ($P = 0.028$). In the psychiatric intervention group, 69.4% of patients were administered psychiatric medications and 44.5% had undergone consultations.

3.2 Impact of psychiatric intervention in ALD

The presence of alcohol-related psychiatric illness is verified by identifying the F10 code in their medical records. Therefore, we first analyzed the impact of this code on ALD patients' survival, as its presence is associated with longer hospital stays and increased mortality rates.²¹ As expected, ALD patients with the F10 code experienced a remarkably higher rate of all-cause and liver-related mortality (Supplementary Figure 1A and S1B). Interestingly, there has been a noticeable increase in the incidence of LC among patients with the F10 disease code, and it can be inferred that this is associated with a worsening mortality rate (Supplementary Figure 1C). The finding that alcohol-related psychiatric problems have a decisive impact on the prognosis of ALD patients has led us to propose the hypothesis that psychiatric intervention could improve the survival of these patients. In Figure 2A–C, patients who received psychiatric intervention experienced a notable reduction in all-cause mortality ($P < 0.0001$) (Figure 2A), liver-related mortality ($P = 0.0003$) (Figure 2B), and the incidence of LC ($P = 0.0005$) (Figure 2C). In the univariate analysis, psychiatric intervention was associated with improved survival (HR, 0.700; 95% CI, 0.607–0.808; $P < 0.001$). In the multivariate analysis, psychiatric intervention

remained a significant factor, with an HR of 0.727 (95% CI, 0.618–0.856; $P < 0.001$), indicating a 27% reduction in the risk of death for patients receiving psychiatric care (Supplementary Table 3).

3.3 Survival outcomes after PSM

PSM was utilized due to notable imbalances in baseline characteristics between two groups, aiming to ensure a balanced comparison and enhance the study's accuracy (Table 2). All clinical parameters were not significantly different, indicating that PSM effectively balanced these characteristics. After PSM, the presence of the ICD-10 code F10 significantly impacted the prognosis negatively (Supplementary Figure 2). The Kaplan–Meier curves consistently demonstrate the existence of significant improvements in all-cause mortality ($P = 0.0008$), liver-related mortality ($P = 0.0008$), and the incidence of LC ($P = 0.0007$) for patients who received psychiatric intervention (Figure 2D–F). Age, presence of F10, AST, GGT, albumin levels, reduced alcohol consumption, and psychiatric intervention were the significant factors for overall survival in the multivariate analysis (Table 3). The median survival time of the psychiatric intervention group in Table 4 remained significant after PSM except for consultation only group: consultation only (12.60 years for the control and 13.95 years for the intervention group; $P = 0.193$), medication only (12.02 years for the control and 17.26 years for the intervention group; $P < 0.001$) or both (11.55 years for the control and 15.00 years for the intervention group; $P = 0.001$).

3.4 Subgroup analysis of patients with mental and behavioral disorders due to use of alcohol

Next, we conducted a subgroup analysis of ALD patients with the F10 code in their medical records. The survival analysis conducted on patients with F10 code revealed a marked reduction in all-cause mortality, liver-related mortality, and the incidence of LC for those who underwent psychiatric intervention (Supplementary Figure 3). This finding was corroborated by the univariate and multivariate analysis, where psychiatric intervention remained a strong predictor of enhanced survival, with an HR of 0.709 ($P < 0.001$) (Supplementary Table 4). To reduce the lead time bias where psychiatric illness is diagnosed before ALD, leading to prior exposure to psychiatric medication or consultation, we re-analyzed the patients who had the F10 code entered in their medical records after a diagnosis of ALD. As a result, we observed a remarkable decrease in mortality among patients receiving psychiatric intervention (Figure 3A–C). In the multivariate analysis,

psychiatric intervention, along with reduced alcohol consumption and higher albumin levels, were still identified as significant factors (Supplementary Table 5). To make the evidence more concrete, we conducted the same analysis after performing PSM on the cohort used in Figure 3A–C, and psychiatric intervention showed a similar effect on survival outcomes (Figure 3D–F and Supplementary Table 6). In the median survival time analysis (Table 4), all ALD patients with the F10 code showed significantly longer survival time when treated with consultation only, medication only, or both (all $P < 0.001$). Additionally, patients diagnosed with ALD and subsequently diagnosed with F10 had significantly longer survival times both before and after PSM only when treated with a combined psychiatric intervention of consultation and medication.

3.5 Two-year landmark analysis

Next, a 2-year landmark analysis was conducted to account for the dynamic nature of patient characteristics and other covariates over time, similar to as was done in other prospective research of UK Biobank cohorts.^{22,23} This approach allowed for a focused examination of patient outcomes at a specific time point, mitigating the potential confounding effects of time-varying factors. As such, this approach ensured an unbiased estimation of the psychiatric intervention's impact and minimized the effects of reverse causality on ALD patients. The results were consistent with previous subgroup analyses, showing that psychiatric treatment significantly reduced mortality and the incidence LC, while maintaining a significant protective effect in multivariate analysis (Supplementary Figure 4, Supplementary Table 7, and Table 4). The prognostic effect of psychiatric intervention on liver-related mortality and the incidence of LC in the cohorts used for all the above analyses is summarized in Supplementary Tables 8 and 9.

3.6 Other subgroup analysis

We conducted additional subgroup analyses focusing on the impact of different psychiatric medications, as well as the influence of gender on prognosis. The analysis indicated that the use of antidepressants effectively improved overall survival in the total cohort both before and after PSM (Supplementary Table 10). Anxiolytic drugs did not show a significant impact on survival due to the small sample size, showing only a trend towards significance. Gender-specific analysis revealed that psychiatric intervention was associated with a significant reduction in mortality in males before and after PSM

(Supplementary Table 11). In females, the intervention improved survival significantly before PSM, but did not show significance after PSM. The effect of psychiatric intervention was relatively less in females compared to males and was only significant in some cohorts. These analyses confirm that the prognostic benefits of psychiatric interventions vary by gender, highlighting the importance of gender-specific approaches in treatment.

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4. DISCUSSION

Despite ongoing multifaceted efforts to reduce the social and economic burdens caused by ALD, the mortality rate from ALD has continued to rise recently, highlighting an urgent need for therapeutic interventions using novel approaches.²⁴ In the present study, we unveiled a significant impact of psychiatric intervention that led to improved survival outcomes of patients with ALD. Our findings, derived from a comprehensive investigation of a UK Biobank cohort, underscore a marked reduction in all-cause and liver-related mortality as well as a decreased incidence of LC among ALD patients receiving psychiatric care. The statistical rigor of our research is anchored in PSM, DR estimation, various subgroup analyses, and a 2-year landmark analysis, ensuring a balanced and precise evaluation of psychiatric intervention effects. To the best of our knowledge, this is the first study to explore the impact of psychiatric management on ALD patients using UK Biobank cohort data, unveiling new insights into ALD management.

Abstinence from alcohol emerges as the cornerstone of therapy, playing a pivotal role in mitigating disease progression and reducing mortality.^{25,26} Even modest alcohol intake is associated with increased mortality among individuals with elevated alanine transaminase levels, underscoring the imperative of complete abstinence.²⁷ Consistent with this finding, a significant benefit of alcohol abstinence is a reduced risk of hepatocellular carcinoma among patients with alcohol-related LC.²⁸ These findings proved that abstinence not only prevents liver damage but also reduces the risk of life-threatening complications such as cancer. A German cohort study demonstrated that healthy alcohol abstainers without risk factors do not exhibit greater mortality, cautioning against generalized recommendations for alcohol consumption.²⁹ Therefore, psychiatric interventions, customized to the individual's unique psychological and behavioral profile, can target the underlying aspects of alcohol dependence, creating a comprehensive and enduring pathway to abstinence.

Several previous studies have investigated the role and impact of AUD medication on prognosis among ALD patients. Patients with both AUD and LC exhibit a significant reduction in hepatic decompensation when undergoing behavioral and pharmacological treatments, highlighting the essential role of comprehensive AUD therapy in enhancing clinical outcomes.³⁰ A recent study has identified that medical addiction therapy for AUD is significantly associated with a lower risk of developing ALD and a reduced incidence of hepatic decompensation.³¹ On the other hand, maintaining alcohol abstinence showed remarkable benefits for patients with alcohol-related LC at every stage of portal hypertension, thereby improving their overall prognosis.³²

Compared to the above reports, the present study incorporates a more comprehensive approach by integrating the concept of psychiatric consultation during hospitalization and assessing the detailed effect of other psychiatric medications in ALD patients. The inclusion of antidepressants and anxiolytics, alongside conventional AUD medications, allows us to explore the broader effects of psychiatric intervention on prognostic outcomes. Moreover, the longitudinal design of our study enables a thorough analysis of the long-term effects of combined psychiatric and pharmacological interventions on the incidence of LC. These findings contribute to a more nuanced understanding of the complex characteristics of psychiatric interventions, proposing an integrated approach for enhanced patient outcomes.

Considering the nature of AUD, the presence of various psychiatric comorbidities, including mood and anxiety disorders, is inevitable. Particularly, mood disorders are the most common psychiatric disorders among people with AUD, and their co-occurrence is associated with greater severity and worse prognosis for both disorders.¹⁶ In fact, more than 30% of people in treatment for AUD met criteria for major depressive disorder, and depression interacts significantly with heavy alcohol consumption, leading to an increased risk of all-cause mortality.^{16,33} Furthermore, the manifestation of alcohol-induced psychotic disorder and delirium has been associated with poor outcomes in patients, serving as another compelling piece of evidence supporting the need for psychiatric intervention in ALD patients.³⁴ The robust results from our study consistently identified the crucial role of medications in managing psychiatric comorbidities, demonstrating a significant improvement in both all-cause and liver-related mortality rates as well as the incidence of LC. This evidence emphasizes the need to prioritize psychiatric care during the early stages of ALD management, aiming to improve patient outcomes and their quality of life.

Generally, medications for AUD or psychiatric comorbidities are often prescribed by psychiatrists rather than primary care physicians, so we included the psychiatric consultation during hospitalization as a variable for survival analyses. In a recent study, inpatient psychiatric consultation for addiction played a pivotal role during the hospitalization period and was associated with a reduction in 90-day all-cause mortality among patients with ALD.³⁵ Moreover, early psychiatric intervention through integrated management is crucial for ALD patients, as it helps stabilize their mental health, manage alcohol use, and support long-term recovery.³⁶ Integrated care of ALD involves a combination of laboratory assessments, pharmacological and behavioral therapies, and follow-up care by specialists.³⁷ In our study, patients who received at least one psychiatric

consultation, medication related to AUD, or medication associated with psychiatric comorbidities during the observation period were included in the psychiatric intervention group. Therefore, there is a high likelihood that these individuals received care from psychiatric specialists, leading to improved survival outcomes.

However, it is important to note that in clinical settings, clinicians sometimes hesitate to prescribe AUD-related medications to ALD patients due to concerns about potential side effects. These side effects can include hepatotoxicity, gastrointestinal disturbances, and neurological symptoms, which may complicate the management of ALD patients already at risk of liver dysfunction.^{10,11} This hesitancy is particularly pronounced when dealing with medications like disulfiram, which can cause severe adverse reactions if alcohol is consumed concurrently.¹⁰ The potential for these adverse effects underscores the necessity for careful patient selection and monitoring when implementing pharmacotherapy for AUD in ALD patients. This reality highlights the critical role of psychiatric consultations and individualized treatment plans that weigh the benefits of psychiatric interventions against potential risks. It also underscores the importance of further research to develop safer and more effective therapeutic options for this vulnerable population.

One critical challenge of our study is the potential for immortal time bias, which occurs when patients who die before receiving psychiatric intervention are classified into the no intervention group, potentially overestimating the effect size. To address this, we re-analyzed patients with the F10 code (mental and behavioral disorders due to alcohol use) entered after their ALD diagnosis, ensuring psychiatric intervention occurred post-ALD diagnosis. This approach demonstrated improved survival outcomes both before and after PSM (Figure 3). Additionally, we employed a two-year landmark analysis, defining time zero as the ALD diagnosis date (ICD-10 code K70), to capture the majority of psychiatric interventions and robustly assess their impact on survival. This method aligns with other similar UK Biobank studies and mitigates confounding effects of time-varying factors.^{22,23} Our results remained consistent across different landmark points (1, 2, and 3 years; data not shown), confirming the robustness of our findings and demonstrating that psychiatric treatment significantly reduced mortality and the incidence of LC. Future research should aim to collect more precise data on the timing and duration of psychiatric interventions to further minimize time bias.

There are several limitations to discuss in this study. First, the psychiatric intervention group included patients exposed to at least one consultation or medication during the observational period, but specific dosages, start dates, and durations of the medications remain unclear. Additionally, the specific psychiatric assessments

conducted by specialists during the consultations of ALD patients remain unidentified. The inclusion of antidepressants and anxiolytic drugs in the psychiatric medication category raises another concern, as it is uncertain which specific psychiatric comorbidities were being treated with these medications. Our results suggest a potential reduction in alcohol consumption among ALD patients receiving psychiatric intervention, inferred from the decreased incidence of LC and mortality rates. However, there is a lack of concrete data on the actual changes in alcohol-consumption patterns following the intervention. Therefore, we have emphasized the importance of future research using more detailed longitudinal data to capture the frequency, duration, and adherence to psychiatric interventions. Such studies would provide a more comprehensive understanding of how these factors influence the prognosis of ALD and help validate our findings.

Incorporating the insights from this study, we conclude with an emphasis on the tangible benefits of psychiatric intervention in the management of ALD. The reduction in both all-cause and liver-related mortality underscores the pivotal role of psychiatric care in enhancing survival outcomes. The individualized approach, adapting to each patient's distinct mental health status, is not just a recommendation but a necessity, reflecting the complexity and multifaceted nature of ALD treatment. In conclusion, our findings support a shift in ALD management, emphasizing the early integration of psychiatric care as a core component to address both physical and mental health in patients with ALD.

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Table 1. Baseline demographic and clinical characteristics before propensity score matching

Characteristic	Overall, N = 2,417 ¹	Psychiatric intervention		P value ²	SMD
		No, N = 1,920 ¹	Yes, N = 497 ¹		
Age at recruitment	56.78 ± 7.51	57.41 ± 7.43	54.35 ± 7.33	< 0.001	0.41
Sex (Male)	1,859 (76.9%)	1,497 (78.0%)	362 (72.8%)	0.016	0.12
Presence of F10	1,630 (67.4%)	1,218 (63.4%)	412 (82.9%)	< 0.001	-0.45
Body mass index (kg/m ²)	28.73 ± 5.38	28.83 ± 5.32	28.36 ± 5.57	0.057	0.09
Protein (g/L)	73.89 ± 4.96	74.00 ± 4.93	73.49 ± 4.70	0.034	0.11
Albumin (g/L)	44.41 ± 3.69	44.37 ± 3.74	44.60 ± 3.28	0.508	-0.06
AST (U/L)	49.73 ± 40.67	50.73 ± 40.68	45.36 ± 39.28	< 0.001	0.12
GGT (U/L)	157.58 ± 187.49	160.66 ± 188.05	141.11 ± 178.39	< 0.001	0.08
Cr (μmol/L)	72.42 ± 24.95	73.40 ± 26.69	68.78 ± 15.95	< 0.001	0.21
HbA1c (mmol/mol)	37.95 ± 10.32	37.84 ± 10.21	38.35 ± 10.74	0.375	-0.05
LDL (mmol/L)	3.32 ± 0.98	3.32 ± 0.97	3.31 ± 0.99	0.902	0.01
Coffee intake				0.209	0.06
≥ 3 cups/day	713 (29.5%)	555 (28.9%)	158 (31.8%)		
< 3 cups/day	1,704 (70.5%)	1,365 (71.1%)	339 (68.2%)		
Alcohol intake frequency				< 0.001	-0.27
Daily or almost daily	1,164 (48.2%)	978 (50.9%)	186 (37.4%)		
Less than 3 times a week	1,253 (51.8%)	942 (49.1%)	311 (62.6%)		
Physical activity frequency				0.028	-0.11
≥ 4 times a week	1,103 (45.6%)	898 (46.8%)	205 (41.2%)		
< 4 times a week	1,314 (54.4%)	1,022 (53.2%)	292 (58.8%)		
Psychiatric medication	345 (14.3%)	0 (0.0%)	345 (69.4%)	< 0.001	-2.10
Psychiatric consultation	221 (9.1%)	0 (0.0%)	221 (44.5%)	< 0.001	-1.31

¹Mean ± SD; n (%)

²Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Data are described as mean ± standard deviation or n (%). SMD, standardized mean difference; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; SD, standard deviation.

Table 2. Baseline demographic and clinical characteristics after propensity score matching

Characteristic	Overall, N = 1,491 ¹	Psychiatric intervention		P value ²	SMD
		No, N = 994 ¹	Yes, N = 497 ¹		
Age at recruitment	54.74 ± 7.41	54.93 ± 7.45	54.35 ± 7.33	0.125	0.08
Sex (Male)	1,095 (73.4%)	733 (73.7%)	362 (72.8%)	0.709	-0.09
Presence of F10	1,299 (82.4%)	817 (82.2%)	412 (82.9%)	0.736	-0.02
Body mass index (kg/m ²)	28.37 ± 5.52	28.38 ± 5.49	28.36 ± 5.57	0.945	< 0.01
Protein (g/L)	73.70 ± 4.64	73.81 ± 4.60	73.49 ± 4.70	0.240	0.07
Albumin (g/L)	44.44 ± 3.40	44.36 ± 3.45	44.60 ± 3.28	0.334	-0.07
AST (U/L)	45.87 ± 38.65	46.47 ± 38.34	45.36 ± 39.28	0.250	0.05
GGT (U/L)	142.19 ± 175.11	142.74 ± 173.54	141.11 ± 178.39	0.204	0.01
Cr (μmol/L)	68.97 ± 16.40	69.07 ± 16.62	68.78 ± 15.95	0.609	0.02
HbA1c (mmol/mol)	37.64 ± 10.15	37.29 ± 9.83	38.35 ± 10.74	0.096	-0.10
LDL (mmol/L)	3.34 ± 1.00	3.35 ± 1.00	3.31 ± 0.99	0.544	0.04
Coffee intake				0.525	0.03
≥ 3 cups/day	458 (30.7%)	300 (30.2%)	158 (31.8%)		
< 3 cups/day	1,033 (69.3%)	694 (69.8%)	339 (68.2%)		
Alcohol intake frequency				0.217	-0.06
Daily or almost daily	591 (39.6%)	405 (40.7%)	186 (37.4%)		
Less than 3 times a week	900 (60.4%)	589 (59.3%)	311 (62.6%)		
Physical activity frequency				0.095	-0.09
≥ 4 times a week	667 (44.7%)	462 (46.5%)	205 (41.2%)		
< 4 times a week	824 (55.3%)	532 (53.5%)	292 (58.8%)		
Psychiatric medication	345 (23.1%)	0 (0.0%)	345 (69.4%)	< 0.001	-2.10
Psychiatric consultation	221 (14.8%)	0 (0.0%)	221 (44.5%)	< 0.001	-1.31

¹Mean ± SD; n (%)

²Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Data are described as mean ± standard deviation or n (%). SMD, standardized mean difference; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; SD, standard deviation.

Table 3. Univariate and multivariate analysis for overall survival after propensity score matching

Characteristic	Univariate			Multivariate		
	HR ⁱ	95% CI ⁱ	P value	HR ⁱ	95% CI ⁱ	P value
Age at recruitment	1.022	1.012, 1.033	< 0.001	1.025	1.015, 1.036	< 0.001
Sex (Male)	1.221	1.023, 1.456	0.027	1.097	0.917, 1.312	0.312
Presence of F10	1.612	1.294, 2.007	< 0.001	1.573	1.258, 1.966	< 0.001
Body mass index (kg/m ²)	0.998	0.983, 1.012	0.754			
Protein (g/L)	1.017	1.001, 1.034	0.034	1.011	0.994, 1.028	0.220
Albumin (g/L)	0.948	0.929, 0.967	< 0.001	0.960	0.940, 0.981	< 0.001
AST (U/L)	1.005	1.004, 1.007	< 0.001	1.003	1.001, 1.005	0.001
GGT (U/L)	1.001	1.001, 1.002	< 0.001	1.001	1.000, 1.001	0.003
Cr (μmol/L)	0.998	0.993, 1.002	0.331			
HbA1c (mmol/mol)	1.005	0.998, 1.001	0.171			
LDL (mmol/L)	0.927	0.856, 1.003	0.060			
Coffee intake (< 3 cups/day)	1.004	0.930, 1.083	0.918			
Alcohol intake frequency (Less than 3 times a week)	0.778	0.719, 0.842	< 0.001	0.806	0.688, 0.944	0.007
Physical activity frequency (< 4 times a week)	1.098	0.982, 1.228	0.102			
Psychiatric medication	0.723	0.604, 0.865	< 0.001			
Psychiatric consultation	0.875	0.717, 1.069	0.193			
Psychiatric intervention (Medication or consultation)	0.765	0.654, 0.895	0.001	0.780	0.665, 0.913	0.002
HR = Hazard Ratio, CI = Confidence Interval						

AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein.

Table 4. Median survival time of psychiatric consultation, medication, and both interventions for each group.

	Median survival time, years (95% CI)		P value	
	Control group	Intervention group		
Total cohort before propensity score matching				
Consultation	11.06 (9.86, 12.02)	13.95 (12.19, 17.56)	0.014	
Medication	10.52 (9.63, 11.51)	17.26 (13.70, 20.90)	< 0.001	
Consultation + Medication	10.08 (9.29, 11.29)	15.00 (13.29, 17.56)	< 0.001	
Total cohort after propensity score matching				
Consultation	12.60 (11.47, 13.84)	13.95 (12.19, 17.56)	0.193	
Medication	12.02 (10.69, 13.04)	17.26 (13.70, 20.90)	< 0.001	
Consultation + Medication	11.55 (10.19, 12.96)	15.00 (13.29, 17.56)	0.001	
ALD patients with F10				
Consultation	9.12 (8.46, 10.10)	13.53 (12.05, 17.26)	< 0.001	
Medication	9.19 (8.33, 10.10)	14.84 (12.27, 18.52)	< 0.001	
Consultation + Medication	8.57 (7.78, 9.59)	13.75 (12.31, 17.26)	< 0.001	
F10 patients after diagnosis of ALD before propensity score matching				
Consultation	11.74 (10.43, 12.89)	16.87 (12.70, NA*)	0.077	
Medication	11.41 (9.86, 12.69)	17.42 (13.70, NA*)	0.003	
Consultation + Medication	11.20 (9.53, 12.26)	17.26 (13.53, 25.62)	0.001	
F10 patients after diagnosis of ALD after propensity score matching				
Consultation	14.31 (12.26, 16.45)	16.87 (12.70, NA*)	0.359	
Medication	13.04 (11.74, 15.84)	17.42 (13.70, NA*)	0.055	
Consultation + Medication	12.84 (11.41, 15.84)	17.26 (13.53, 25.62)	0.048	
2-year landmark analyses				
Consultation	15.71 (14.61, 17.42)	17.26 (14.00, 20.90)	0.274	
Medication	14.97 (13.72, 16.04)	20.90 (17.53, NA*)	< 0.001	
Consultation + Medication	14.84 (13.59, 16.04)	18.52 (16.87, 24.41)	< 0.001	

CI, confidence interval; ALD, alcohol-associated liver disease; NA, not available.

The asterisk (*) indicates that the median survival could not be calculated for this subgroup due to the absence of a 50% survival point during the observation period.

Figure Legends

Figure 1. A research flow for statistical analysis.

Figure 1

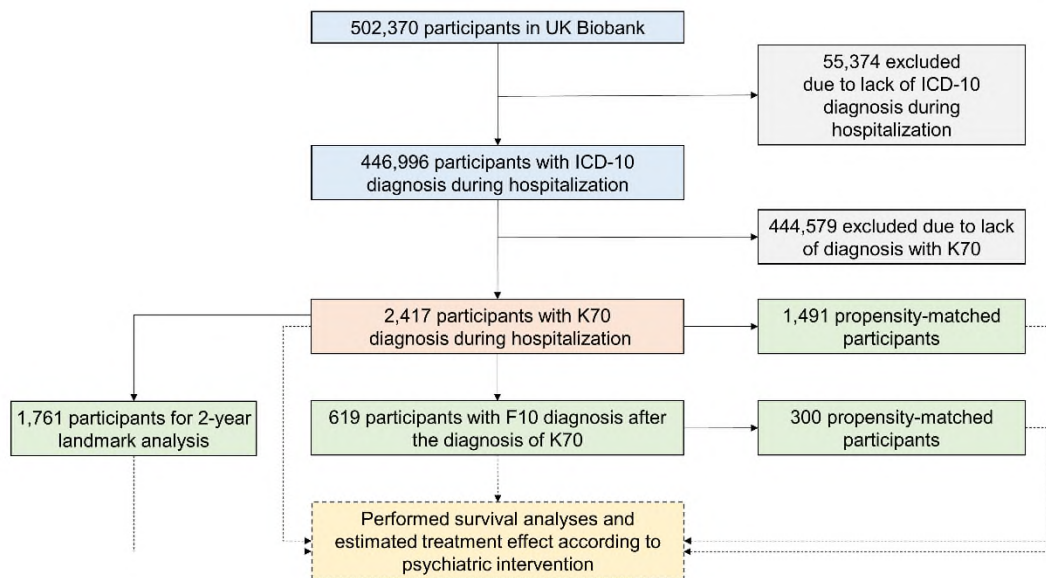


Figure 2. Kaplan–Meier curves present the overall survival rates and the incidence rate of liver cirrhosis in the total cohort. Before PSM: (A) The impact of psychiatric intervention on all-cause mortality ($P < 0.0001$), (B) liver-related mortality ($P = 0.0003$), and (C) the incidence of liver cirrhosis ($P = 0.0005$). After PSM: (D) The effect of psychiatric intervention on all-cause mortality ($P = 0.0008$), (E) liver-related mortality ($P = 0.0008$), and (F) incidence of liver cirrhosis ($P = 0.0007$).

Figure 2

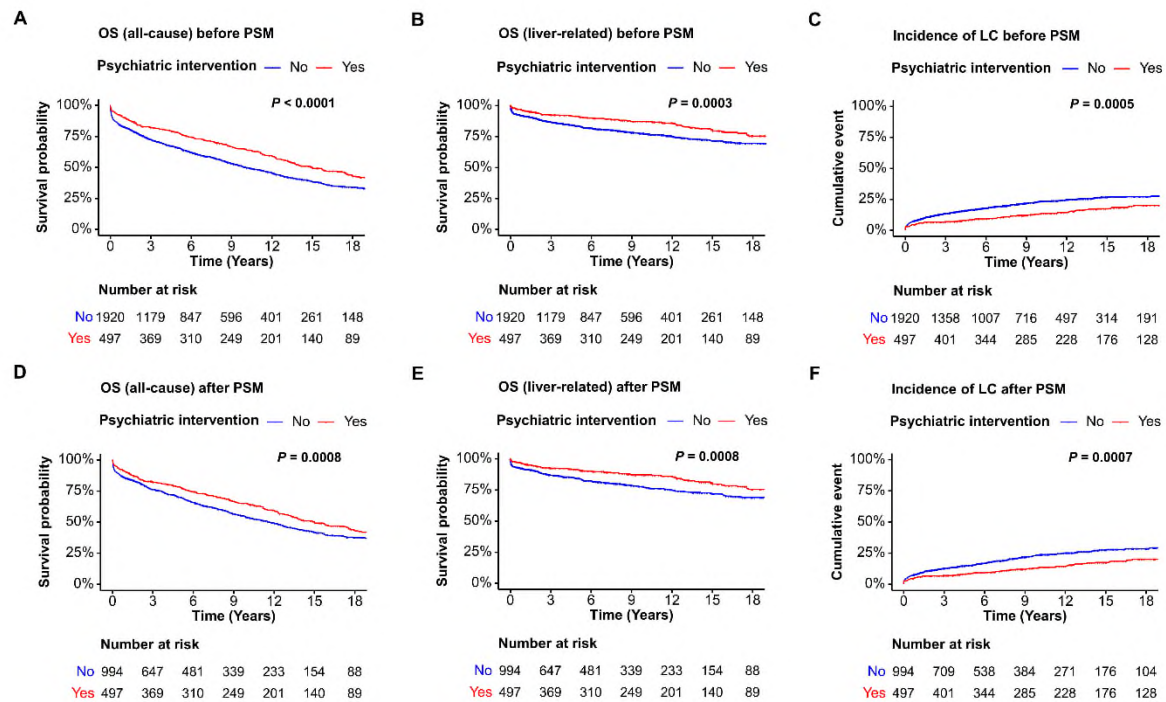
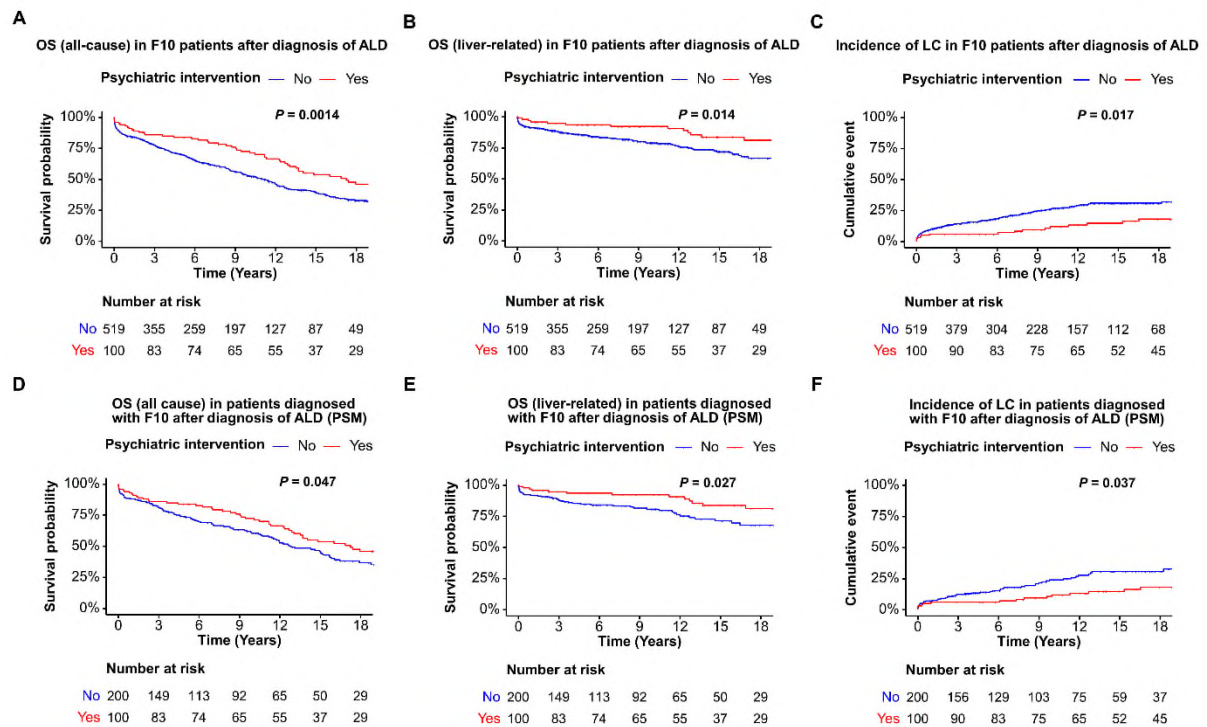


Figure 3. Survival analysis in patients with mental and behavioral disorders due to the use of alcohol (F10) following the diagnosis of alcohol-associated liver disease. Before PSM: (A) All-cause mortality ($P = 0.0014$), (B) liver-related mortality ($P = 0.014$), and (C) the incidence of liver cirrhosis ($P = 0.017$). After PSM: (D) All-cause mortality ($P = 0.047$), (E) liver-related mortality ($P = 0.027$), and (F) incidence of liver cirrhosis ($P = 0.037$) according to the psychiatric intervention.

Figure 3



Supplementary Information

The prognostic impact of psychiatric intervention on alcohol-associated liver disease: the UK Biobank cohort study

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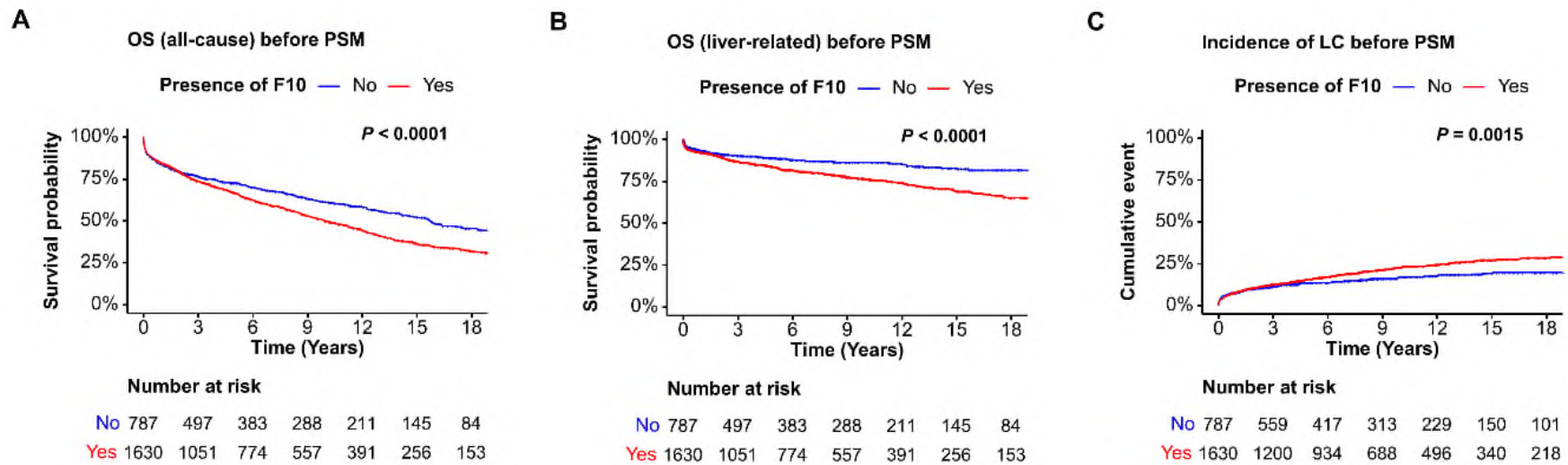
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Supplementary Figures

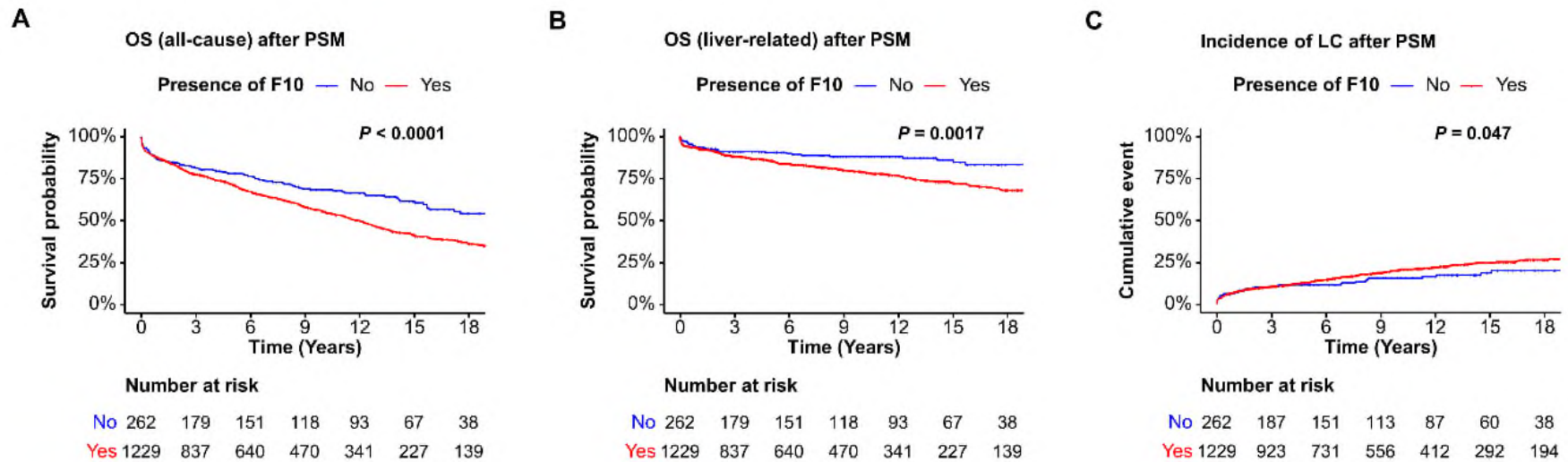
- **Supplementary Figure 1.** Kaplan-Meier curves present the overall survival rates and incidence of liver cirrhosis in the total cohort ($n = 2,417$) before propensity score matching.
- **Supplementary Figure 2.** Kaplan-Meier curves show the overall survivals and occurrence of liver cirrhosis among 1,491 patients with alcohol-associated liver disease after propensity score matching.
- **Supplementary Figure 3.** Survival analysis in patients with mental and behavioral disorders due to use of alcohol (F10) ($n = 1,630$).
- **Supplementary Figure 4.** 2-year landmark analyses investigate the overall survivals and incidence of liver cirrhosis using Kaplan-Meier curves.

Supplementary Figure 1



Supplementary Figure 1. Kaplan-Meier curves present the overall survival rates and incidence of liver cirrhosis in the total cohort ($n = 2,417$) before propensity score matching. (A) The impact of mental and behavioral disorders due to use of alcohol (F10) on all-cause mortality ($P < 0.0001$), (B) liver-related mortality ($P < 0.0001$), and (C) incidence of liver cirrhosis ($P = 0.0015$).

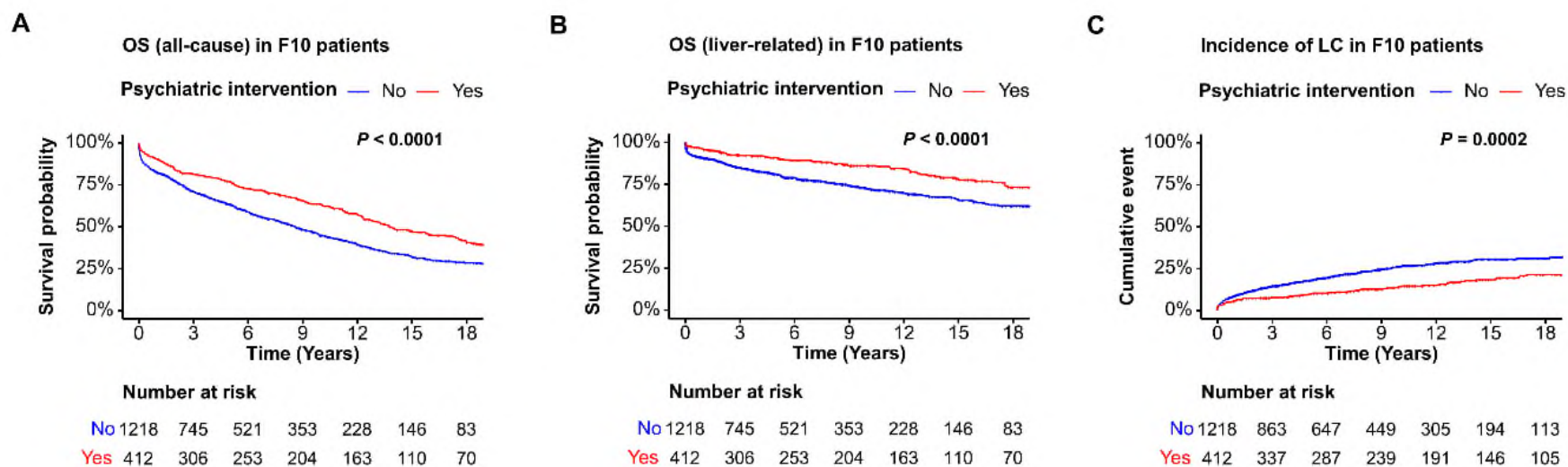
Supplementary Figure 2



Supplementary Figure 2. Kaplan-Meier curves show the overall survivals and occurrence of liver cirrhosis among 1,491 patients with alcohol-associated liver

disease after propensity score matching. (A) The effect of mental and behavioral disorders due to use of alcohol (F10) on all-cause mortality ($P < 0.0001$), (B) liver-related mortality ($P = 0.0017$), and (C) incidence of liver cirrhosis ($P = 0.047$).

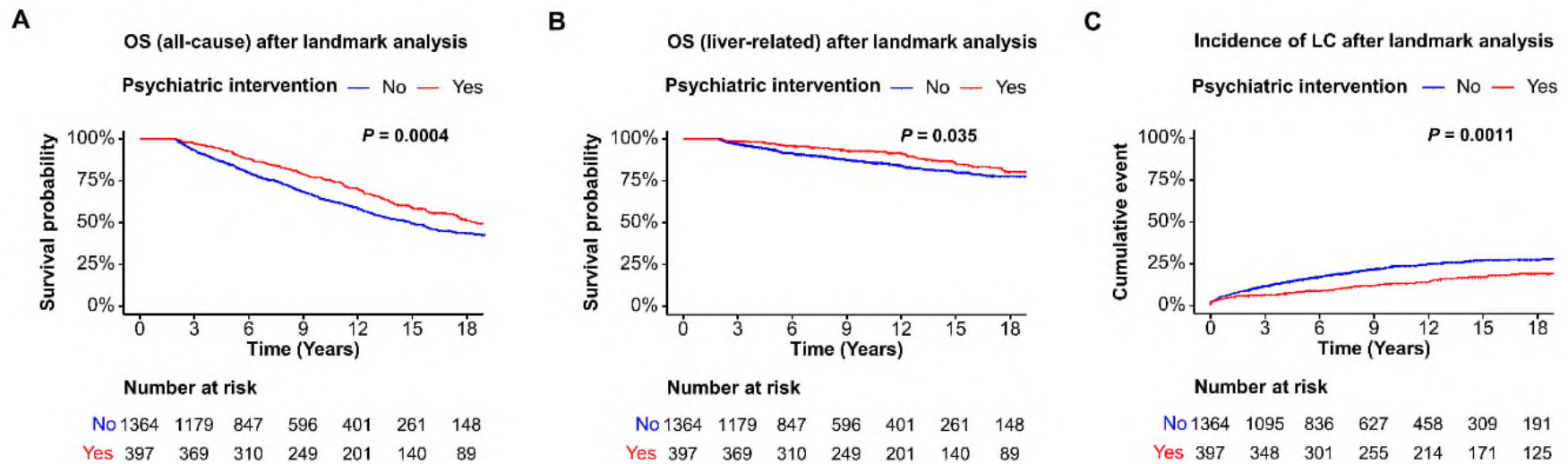
Supplementary Figure 3



Supplementary Figure 3. Survival analysis in patients with mental and behavioral disorders due to use of alcohol (F10) (n = 1,630). (A) All-cause mortality ($P < 0.0001$), (B) liver-related mortality ($P < 0.0001$), and (C) incidence of liver cirrhosis ($P = 0.0002$) according to the psychiatric intervention.

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Supplementary Figure 4



Supplementary Figure 4. 2-year landmark analyses investigate the overall survivals and incidence of liver cirrhosis using Kaplan-Meier curves. (A) The impact of psychiatric intervention on all-cause mortality ($P = 0.0004$), (B) liver-related mortality ($P = 0.035$), and (C) incidence of liver cirrhosis ($P = 0.0011$).

Supplementary Tables

- **Supplementary Table 1.** Detailed information of psychiatric medication in alcohol-associated liver disease
- **Supplementary Table 2.** Used data codes for psychiatric consultation in UK Biobank
- **Supplementary Table 3.** Univariate and multivariate analysis for overall survival before propensity score matching
- **Supplementary Table 4.** Univariate and multivariate analysis for overall survival in patients with F10
- **Supplementary Table 5.** Univariate and multivariate analysis for overall survival in patients with F10 after diagnosis of ALD
- **Supplementary Table 6.** Univariate analysis and multivariate for overall survival in patients with F10 after diagnosis of ALD (PSM)
- **Supplementary Table 7.** Univariate and multivariate analysis for overall survival after 2-year landmark analysis
- **Supplementary Table 8.** Prognostic effect of psychiatric intervention on the liver-related mortality
- **Supplementary Table 9.** Prognostic effect of psychiatric intervention on the incidence of liver cirrhosis
- **Supplementary Table 10.** Subgroup analysis on the impact of different AUD-related medications on overall survival
- **Supplementary Table 11.** Subgroup analysis of the impact of psychiatric intervention on overall survival by gender

Supplementary Table 1. Detailed information of psychiatric medication in alcohol-associated liver disease

Psychiatric intervention (N = 497)	
Psychiatric medication (N = 345, 69.4%)	
Category	N (%)
Anticraving	50 (10.1%)
Disulfiram	5 (1.0%)
Acamprosate	14 (2.8%)
Topiramate	4 (0.8%)
Gabapentin	27 (5.4%)
Antidepressant	271 (54.5%)
Fluoxetine	64 (12.9%)
Escitalopram	13 (2.6%)
Paroxetine	14 (2.8%)
Sertraline	25 (5.0%)
Duloxetine	8 (1.6%)
Venlafaxine	28 (5.6%)
Mirtazapine	35 (7.0%)
Amitriptyline	94 (18.9%)
Nortriptyline	4 (0.8%)
Anxiolytic	52 (10.5%)
Lorazepam	2 (0.4%)
Alprazolam	1 (0.2%)
Diazepam	34 (6.8%)
Carbamazepine	8 (1.6%)
Chlordiazepoxide	7 (1.4%)

Data are described as n (%).

Supplementary Table 2. Used data codes for psychiatric consultation in UK Biobank

Code	Description
1050	Addiction Services
1060	Adult mental illness
1200	Child and adolescent psychiatry
1300	Clinical Psychology
1470	Forensic psychiatry
1720	Liaison Psychiatry
1765	Mental Health Recovery And Rehabilitation Service
1767	Mental Health Dual Diagnosis Service
1940	Old age psychiatry
2370	Perinatal Psychiatry
2420	Psychiatric Intensive Care
2430	Psychotherapy
2513	Sleep Medicine Service

These codes are used in “Treatment specialty of consultant” record (Field ID 41246).

Supplementary Table 3. Univariate and multivariate analysis for overall survival before propensity score matching

Characteristic	Univariate			Multivariate		
	HR ⁱ	95% CI ⁱ	P value	HR ⁱ	95% CI ⁱ	P value
Age at recruitment	1.027	1.019, 1.035	< 0.001	1.024	1.015, 1.033	< 0.001
Sex (Male)	1.240	1.075, 1.429	0.003	1.091	0.930, 1.281	0.285
Presence of F10	1.400	1.232, 1.591	< 0.001	1.428	1.233, 1.654	< 0.001
Body mass index (kg/m ²)	1.000	0.989, 1.010	0.939			
Protein (g/L)	1.014	1.002, 1.027	0.027	1.011	0.997, 1.025	0.120
Albumin (g/L)	0.948	0.934, 0.962	< 0.001	0.955	0.938, 0.971	< 0.001
AST (U/L)	1.005	1.004, 1.006	< 0.001	1.003	1.000, 1.005	0.001
GGT (U/L)	1.001	1.001, 1.001	< 0.001	1.000	1.000, 1.001	0.082
Cr (μmol/L)	1.000	0.998, 1.003	0.693			
HbA1c (mmol/mol)	1.004	0.998, 1.009	0.207			
LDL (mmol/L)	0.929	0.873, 0.988	0.019	0.985	0.921, 1.054	0.664
Coffee intake (< 3 cups/day)	1.021	0.894, 1.146	0.849			
Alcohol intake frequency (Less than 3 times a week)	0.652	0.582, 0.731	< 0.001	0.762	0.667, 0.872	< 0.001
Physical activity frequency (< 4 times a week)	1.140	1.017, 1.278	0.024	1.097	0.966, 1.246	0.119
Psychiatric medication	0.664	0.560, 0.787	< 0.001			
Psychiatric consultation	0.786	0.648, 0.952	0.014			
Psychiatric intervention (Medication or consultation)	0.700	0.607, 0.808	< 0.001	0.727	0.618, 0.856	< 0.001

HR = Hazard Ratio, CI = Confidence Interval

AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein.

Supplementary Table 4. Univariate and multivariate analysis for overall survival in patients with F10

Characteristic	Univariate			Multivariate		
	HR ^I	95% CI ^I	P value	HR ^I	95% CI ^I	P value
Age at recruitment	1.030	1.020, 1.039	< 0.001	1.021	1.011, 1.032	< 0.001
Sex (Male)	1.187	1.003, 1.404	0.046	1.018	0.846, 1.224	0.852
Body mass index (kg/m ²)	1.002	0.990, 1.015	0.756			
Protein (g/L)	1.016	1.001, 1.030	0.031	1.011	0.995, 1.027	0.173
Albumin (g/L)	0.961	0.944, 0.977	< 0.001	0.962	0.944, 0.981	< 0.001
AST (U/L)	1.005	1.003, 1.006	< 0.001	1.003	1.000, 1.005	0.003
GGT (U/L)	1.001	1.001, 1.001	< 0.001	1.000	1.000, 1.001	0.352
Cr (μmol/L)	1.000	0.996, 1.003	0.848			
HbA1c (mmol/mol)	1.004	0.997, 1.010	0.225			
LDL (mmol/L)	0.952	0.888, 1.022	0.173			
Coffee intake (< 3 cups/day)	1.062	0.920, 1.228	0.413			
Alcohol intake frequency (Less than 3 times a week)	0.639	0.559, 0.731	< 0.001	0.745	0.637, 0.872	< 0.001
Physical activity frequency (< 4 times a week)	1.094	0.958, 1.250	0.183			
Psychiatric medication	0.638	0.528, 0.772	< 0.001			
Psychiatric consultation	0.692	0.568, 0.843	< 0.001			
Psychiatric intervention (Medication or consultation)	0.638	0.546, 0.747	< 0.001	0.709	0.593, 0.847	< 0.001
HR = Hazard Ratio, CI = Confidence Interval						

AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein.

Supplementary Table 5. Univariate and multivariate analysis for overall survival in patients with F10 after diagnosis of ALD

Characteristic	Univariate			Multivariate		
	HR [†]	95% CI [†]	P value	HR [†]	95% CI [†]	P value
Age at recruitment	1.020	1.005, 1.036	0.011	1.013	0.996, 1.031	0.138
Sex (Male)	1.291	0.975, 1.708	0.074			
Body mass index (kg/m ²)	1.002	0.982, 1.022	0.834			
Protein (g/L)	1.013	0.989, 1.037	0.301			
Albumin (g/L)	0.961	0.935, 0.989	0.006	0.967	0.938, 0.997	0.031
AST (U/L)	1.006	1.004, 1.009	< 0.001	1.004	1.000, 1.007	0.041
GGT (U/L)	1.001	1.000, 1.001	< 0.001	1.000	1.000, 1.001	0.291
Cr (μmol/L)	1.001	1.000, 1.001	0.565			
HbA1c (mmol/mol)	1.009	0.999, 1.018	0.070			
LDL (mmol/L)	0.972	0.861, 1.098	0.650			
Coffee intake (< 3 cups/day)	1.089	0.856, 1.386	0.487			
Alcohol intake frequency (Less than 3 times a week)	0.596	0.477, 0.745	< 0.001	0.716	0.550, 0.931	0.013
Physical activity frequency (< 4 times a week)	1.035	0.823, 1.288	0.756			
Psychiatric medication	0.591	0.415, 0.841	0.003			
Psychiatric consultation	0.669	0.429, 1.044	0.077			
Psychiatric intervention (Medication or consultation)	0.616	0.456, 0.831	0.001	0.613	0.428, 0.878	0.008

HR = Hazard Ratio, CI = Confidence Interval

AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein.

Supplementary Table 6. Univariate analysis and multivariate for overall survival in patients with F10 after diagnosis of ALD (PSM)

Characteristic	Univariate			Multivariate		
	HR ^I	95% CI ^I	P value	HR ^I	95% CI ^I	P value
Age at recruitment	1.041	1.018, 1.064	< 0.001	1.041	1.017, 1.065	0.001
Sex (Male)	1.101	0.758, 1.597	0.614			
Body mass index (kg/m ²)	1.001	0.975, 1.029	0.916			
Protein (g/L)	1.006	0.973, 1.041	0.718			
Albumin (g/L)	0.932	0.894, 0.971	0.001	0.947	0.908, 0.989	0.014
AST (U/L)	1.004	1.004, 1.015	0.001	1.006	0.998, 1.013	0.139
GGT (U/L)	1.001	1.000, 1.001	0.017	1.000	0.999, 1.001	0.945
Cr (μmol/L)	1.003	0.993, 1.012	0.582			
HbA1c (mmol/mol)	1.005	0.993, 1.017	0.414			
LDL (mmol/L)	1.000	0.832, 1.201	0.998			
Coffee intake (< 3 cups/day)	0.978	0.669, 1.369	0.898			
Alcohol intake frequency (Less than 3 times a week)	0.505	0.365, 0.699	< 0.001	0.642	0.441, 0.936	0.021
Physical activity frequency (< 4 times a week)	0.941	0.686, 1.290	0.705			
Psychiatric medication	0.690	0.473, 1.008	0.055			
Psychiatric consultation	0.806	0.508, 1.279	0.359			
Psychiatric intervention (Medication or consultation)	0.712	0.509, 0.997	0.048	0.690	0.491, 0.969	0.032
HR = Hazard Ratio, CI = Confidence Interval						

AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein.

Supplementary Table 7. Univariate and multivariate analysis for overall survival after 2-year landmark analysis

Characteristic	Univariate			Multivariate		
	HR ¹	95% CI ¹	P value	HR ¹	95% CI ¹	P value
Age at recruitment	1.028	1.017, 1.039	< 0.001	1.029	1.017, 1.041	< 0.001
Sex (Male)	1.264	1.048, 1.525	0.014	1.108	0.897, 1.369	0.341
Presence of F10	1.787	1.498, 2.133	< 0.001	1.853	1.516, 2.265	< 0.001
Body mass index (kg/m ²)	0.990	0.976, 1.005	0.188			
Protein (g/L)	1.020	1.004, 1.037	0.015	1.027	1.010, 1.046	0.002
Albumin (g/L)	0.921	0.903, 0.938	< 0.001	0.926	0.906, 0.946	< 0.001
AST (U/L)	1.005	1.004, 1.007	< 0.001	1.002	0.999, 1.004	0.160
GGT (U/L)	1.001	1.001, 1.001	< 0.001	1.000	1.000, 1.001	0.120
Cr (μmol/L)	1.001	0.998, 1.003	0.535			
HbA1c (mmol/mol)	1.004	0.997, 1.012	0.233			
LDL (mmol/L)	0.863	0.796, 0.936	< 0.001	0.927	0.848, 1.012	0.090
Coffee intake (< 3 cups/day)	1.095	0.928, 1.292	0.282			
Alcohol intake frequency (Less than 3 times a week)	0.675	0.581, 0.786	< 0.001	0.798	0.669, 0.951	0.012
Physical activity frequency (< 4 times a week)	1.126	0.970, 1.306	0.119			
Psychiatric medication	0.680	0.552, 0.838	< 0.001			
Psychiatric consultation	0.880	0.701, 1.106	0.274			
Psychiatric intervention (Medication or consultation)	0.726	0.609, 0.866	< 0.001	0.709	0.579, 0.869	0.001

HR = Hazard Ratio, CI = Confidence Interval

AST, aspartate transaminase; GGT, gamma-glutamyl transferase; Cr, creatinine; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein.

Supplementary Table 8. Prognostic effect of psychiatric intervention on the liver-related mortality

Cohorts	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Total cohort before propensity score matching	0.638	0.499, 0.816	< 0.001	0.570	0.430, 0.756	< 0.001
Total cohort after propensity score matching	0.638	0.490, 0.830	0.001	0.621	0.476, 0.810	< 0.001
ALD patients with F10	0.547	0.420, 0.714	< 0.001	0.543	0.402, 0.735	< 0.001
F10 patients after diagnosis of ALD before propensity score matching	0.616	0.456, 0.831	0.014	0.403	0.199, 0.818	0.012
F10 patients after diagnosis of ALD after propensity score matching	0.520	0.288, 0.939	0.027	0.496	0.273, 0.902	0.022
2-year landmark analyses	0.712	0.518, 0.979	0.035	0.573	0.396, 0.830	0.003

HR, hazard ratio; CI, confidence interval; ALD, alcohol-associated liver disease.

Supplementary Table 9. Prognostic effect of psychiatric intervention on the incidence of liver cirrhosis

Cohorts	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Total cohort before propensity score matching	0.655	0.516, 0.832	0.001	0.643	0.491, 0.842	0.001
Total cohort after propensity score matching	0.641	0.496, 0.830	0.001	0.654	0.505, 0.847	0.001
ALD patients with F10	0.616	0.476, 0.797	< 0.001	0.670	0.504, 0.889	0.006
F10 patients after diagnosis of ALD before propensity score matching	0.564	0.350, 0.910	0.017	0.517	0.286, 0.934	0.029
F10 patients after diagnosis of ALD after propensity score matching	0.575	0.340, 0.973	0.037	0.591	0.348, 1.004	0.052
2-year landmark analyses	0.647	0.497, 0.842	0.001	0.599	0.443, 0.809	0.001

HR, hazard ratio; CI, confidence interval; ALD, alcohol-associated liver disease.

Supplementary Table 10. Subgroup analysis on the impact of different AUD-related medications on overall survival

Total cohort before propensity score matching			
Medication	HR	95% CI	<i>P</i> value
Anticraving	0.940	0.642, 1.377	0.750
Antidepressant	0.651	0.537, 0.788	< 0.001
Anxiolytic	0.700	0.467, 1.049	0.044
Total cohort after propensity score matching			
Medication	HR	95% CI	<i>P</i> value
Anticraving	1.063	0.723, 1.562	0.755
Antidepressant	0.701	0.582, 0.867	0.001
Anxiolytic	0.772	0.514, 1.161	0.114
ALD patients with F10			
Medication	HR	95% CI	<i>P</i> value
Anticraving	0.807	0.528, 1.233	0.321
Antidepressant	0.642	0.518, 0.796	< 0.001
Anxiolytic	0.673	0.432, 1.048	0.050
F10 patients after diagnosis of ALD before propensity score matching			
Medication	HR	95% CI	<i>P</i> value
Anticraving	0.532	0.198, 1.427	0.210
Antidepressant	0.641	0.441, 0.932	0.020
Anxiolytic	0.575	0.184, 1.794	0.341
F10 patients after diagnosis of ALD after propensity score matching			
Medication	HR	95% CI	<i>P</i> value
Anticraving	0.634	0.235, 1.715	0.370
Antidepressant	0.761	0.511, 1.011	0.037
Anxiolytic	0.688	0.219, 1.459	0.322
2-year landmark analyses			
Medication	HR	95% CI	<i>P</i> value
Anticraving	0.988	0.618, 1.578	0.959
Antidepressant	0.667	0.527, 0.843	0.001
Anxiolytic	0.755	0.467, 1.023	0.052

HR, hazard ratio; CI, confidence interval; ALD, alcohol-associated liver disease.

Supplementary Table 11. Subgroup analysis of the impact of psychiatric intervention on overall survival by gender

Cohorts	Male subgroup			Female subgroup		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Total cohort before propensity score matching	0.683	0.581, 0.803	< 0.001	0.701	0.527, 0.955	0.027
Total cohort after propensity score matching	0.736	0.616, 0.881	0.001	0.763	0.622, 0.994	0.059
ALD patients with F10	0.616	0.516, 0.736	< 0.001	0.737	0.525, 1.035	0.038
F10 patients after diagnosis of ALD before propensity score matching	0.544	0.384, 0.771	0.001	0.866	0.728, 1.169	0.313
F10 patients after diagnosis of ALD after propensity score matching	0.627	0.424, 0.929	0.020	0.889	0.774, 1.175	0.351
2-year landmark analyses	0.693	0.567, 0.846	< 0.001	0.785	0.683, 1.094	0.132

HR, hazard ratio; CI, confidence interval; ALD, alcohol-associated liver disease.