Validation of the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake: a prospective cohort study

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Abstract (344/300):

Background: Steatotic liver disease (SLD) is a new overarching term including metabolic-dysfunction associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol related SLD~~combined with alcohol use exceeding limits of MASLD~~ (MetALD), and alcohol-related liver disease (ALD). We aimed to validate the prognostic importance of SLD ~~and the~~ subclasses MASLD, MetALD and ALD.

Methods: A prospective cohort of patients with current or previous excessive alcohol intake for at least one year and no prior hepatic decompensation was characterised by SLD subclasses. We classified cases into MASLD, MetALD and ALD in accordance with the nomenclature definitions, based on metabolic comorbidity and self-reported average alcohol intake in the three months leading up to inclusion. We compared prognosis between classes using Cox regression analyses on hepatic decompensation and overall mortality as the two outcome measures. Patients not meeting SLD criteria were classified as No-SLD and served as a reference group.

Findings: We enrolled 450 patients with a history of excessive alcohol intake (75% male). The median age was 57 years. Cirrhosis was present in 14%, and 98% had at least one cardiometabolic risk factor. Among them, 324 (72%) met SLD criteria and 126 did not have SLD meaning no evident liver steatosis and no significant fibrosis (≥F2). Based on SLD criteria, 49% had MASLD, 24% had MetALD, and 27% had ALD. During follow-up (70 months, IQR 53-94), 64 of the 450 patients decompensated (62 with SLD), and 97 died (87 with SLD). Patients with SLD had a significantly higher risk of hepatic decompensation and overall mortality compared to those without SLD independent of age, sex, liver stiffness, and cardiometabolic risk factors. The risk of decompensation increased in a stepwise manner: MASLD (HR=5.21, 95%CI 1.13-24.0), MetALD (HR=8.74, 95%CI 1.87-40.8), ~~to~~ and ALD (HR=12.0, 95%CI 2.62-55.3). Similarly, overall mortality increased from MASLD (HR=2.45, 95%CI 1.14-5.25), MetALD (HR=3.11, 95%CI 1.38-7.03), to ALD (HR=3.84, 95%CI 1.74-8.45), independent of age, sex, liver stiffness, and cardiometabolic risk factors.

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Interpretation: SLD and its subclasses portend distinct prognoses. There is a need to specify how historical alcohol intake should be integrated into the SLD nomenclature.

Funding: The EU Horizon 2020 Research

Keywords: Steatotic liver disease, MASLD, MetALD, ALD, Alcohol, prognosis

Research in context:

Evidence before this study

We searched Medline for full papers in any language published in peer-reviewed journals up to September 25th, 2023, using the term "steatotic liver disease," (SLD) and we identified 91 files. We manually reviewed these files and identified 12 ~~validating~~ assessing the overlap between non-alcoholic fatty liver disease (NAFLD) and metabolic-dysfunction associated liver disease (MASLD) ~~the new nomenclature of steatotic liver disease~~ in historical NAFLD cohorts and population studies. Among the population studies, we found two papers assessing the prognosis of SLD and its most common subclasses (MASLD, MetALD, and ALD), both using the National Health and Nutrition Examination Survey (NHANES) III dataset. These studies reported that patients with MetALD and ALD had elevated all-cause mortality compared to individuals without SLD. However, there was a discrepancy in the two studies regarding whether patients with MASLD had increased all-cause mortality. We did not find any studies validating the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake. Furthermore, none of the studies assessed whether SLD and its most common subclasses carry distinct risks of liver-related outcomes.

Added value of this study

In a cohort of 450 patients with a history of excessive alcohol intake, we validated that the new nomenclature is applicable to this patient group. Furthermore, we found that SLD and its most common subclasses indicate distinct prognoses. The risk of hepatic decompensation and all-cause mortality worsens progressively from MASLD to MetALD, and finally to ALD. We also identified ~~limitations~~ opportunities for further

clarification in the new nomenclature regarding how historical alcohol intake should be addressed and ~~what~~ if different criteria for alcohol intake should apply to individuals moving between subclasses.

Implications of all the available evidence

The new nomenclature should be applied in the assessment to individuals with a history of excessive alcohol intake as the subclasses portend distinct prognoses. It is necessary to establish clear criteria for incorporating historical alcohol intake into the SLD nomenclature.

Introduction

Steatotic liver disease (SLD) is the new overarching term for diseases that lead to hepatic steatosis, ~~such as~~including metabolic dysfunction-associated SLD (MASLD) and alcohol-related liver disease (ALD).[1] Additionally, a new category, metabolic dysfunction and alcohol-related liver disease (MetALD) was defined to address the common scenario of MASLD in the context of alcohol intake in excess of the limits (<20/30 (female/male) grams per day) imposed by the NAFLD definition ~~and~~ (~~now~~as well as~~,~~ the MASLD definition)~~,~~ but <50/60 (female/male) grams per day. The new definition acknowledges the co-existence and synergistic impact of alcohol use and metabolic risk factors as reported in previous studies.[2-5] Furthermore, it reflects the reality of the disease as a spectrum rather than mutually exclusive conditions. However, beyond simply semantic changes, the new nomenclature provides a framework for the classification and subclassification of SLD.

This framework is rooted in consensus-driven criteria. As they are not data-driven, these criteria demand validation for their clinical applicability and significance in terms of prognosis, since the framework will be decisive for clinical trials and upcoming treatment.[6] Importantly, the framework of the new nomenclature does not include specifications for how to account for and measure current and historic alcohol use. For example, it is not specified over what duration the average alcohol intake should be based on. ~~Further, the~~The nomenclature does not consider severity of liver disease~~, . Thus, there is a need to assess the new nomenclature in this context.~~ , since the staging of MASLD does not differ from that of NAFLD. However, staging and prognosis of the newly formed category, MetALD, requires further clarification.[1]

In this study, we aimed to explore the usefulness and impact ~~validate~~ the new SLD nomenclature in patients with current or previous excessive alcohol use, by determining whether the risk of decompensation and death differ between the three classes, MASLD, MetALD and ALD.

Methods

Study design and participants

~~Patients with a history of excessive alcohol intake were subclassified according to the new nomenclature of SLD and prognosis of the subgroups assessed. The study was based on a prospective, observational, biopsy based study with patient recruitment from 2013 to 2018 and followed until 2022 September (Danish Data Protection Agency ID 13/8204) (Ethical ID S-20120071, S-20160021, S-20170087). The study methods are described in detail in previously published studies.[4,7-9] All patients gave written, informed consent prior to inclusion.~~

This study was based on a prospective, observational, cohort-study of individuals with current or previous excessive alcohol intake with the primary aim to identify and study early/compensated liver disease (Danish Data Protection Agency ID 13/8204) (Ethical ID S-20120071, S-20160021, S-20170087). The study methods have previously been reported in detail.[4,7-9] All patients gave written, informed consent prior to inclusion. Patient recruitment took place from 2013 to 2018 and followed until September 2022. During this period, we included 458 patients, of whom 450 reported their current alcohol consumption. In this study we used the data available from these 450 patients to classify patients according to the new nomenclature of SLD and assess the prognosis according to subgroups.

Patients

We recruited patients with current or previous excessive alcohol intake for at least one year, defined as >24 grams/day for women and >36 grams/day for men. These limits of alcohol intake ~~was~~ were based on the Danish Health Care Authority's limits for harmful alcohol intake in 2013.

Additional inclusion criteria were age 18-75 years and informed consent to undergo a liver biopsy.

As previously described,[9] exclusion criteria included the presence or a history of decompensated cirrhosis (indicated by clinically evident ascites, overt hepatic encephalopathy, previous endoscopy showing significant esophageal varices with or without variceal bleeding); competing etiologies of chronic liver disease (such as chronic viral hepatitis, autoimmune disorders affecting the liver and bile ducts, or hereditary disorders associated with the accumulation of iron, copper, or α-1-antitrypsin); diagnoses of cancer or other incapacitating illnesses with an expected survival of fewer than 12 months; severe alcoholic hepatitis as determined by the Glasgow Alcoholic Hepatitis Score; indications of hepatic congestion or bile duct dilation as observed through ultrasound; and contraindications to percutaneous liver biopsy.

All investigations were performed on the same day, after a 10-minute rest, preceded by an overnight fast. Investigations included standardized questionnaires to obtain the patient's medical history and current medication.

From 2013 to 2016 all patients underwent liver biopsy. Following a modification in the study protocol in 2016, patients with a transient elastography (TE) measurement less than 6 kPa were exempt from undergoing liver biopsy. This exemption was based on the absence of advanced fibrosis in any of the previously 199 enrolled patients with TE measurements below 6 kPa.[7]

Evaluation of steatotic liver disease

According to the new nomenclature patients were classified as having SLD based on following criteria:[1] 1) A liver biopsy showing hepatic steatosis; 2) ultrasound or

controlled attenuation parameter (≥290 dB/m)[10] suggesting hepatic steatosis in patients where a biopsy was not performed); 3) A liver biopsy showing significant fibrosis (≥F2) (Regardless of whether the biopsy showed steatosis).

We classified patients as not having SLD (No-SLD) if not fulfilling any of these criteria.

During the study period the histological scoring was conducted in batches of around 50. The scoring was performed by the same pathologist with expertise in steatotic liver disease, who was~~Liver histology was assessed by a single pathologist,~~ blinded to the clinical ~~data, evaluated all liver~~data. Liver biopsies of adequate quality (>10mm length and >5 portal tracts or presence of cirrhotic nodules) was scored in accordance with the NAFLD activity score (NAS) of the Clinical Research Network (NAS-CRN) for steatosis and fibrosis stages according to the NAS-CRN system.[11]

Cardiometabolic risk factors

At inclusion, we measured blood pressure, body mass index (BMI), fasting blood glucose, glycosylated hemoglobin (HbA1c), plasma triglycerides and high-density lipoproteins (HDL). Use of antihypertensive drugs, treatment for type 2 diabetes and lipid lowering treatment was recorded at time of inclusion. We used the well described criteria of cardiometabolic risk factors[12] used for in definition of steatotic liver disease (SLD):[1] 1) BMI ≥ 25 kg/m² OR waist circumference > 80/94 cm (female/male), 2) Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol/L [140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes, 3) Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug treatment, 4) Plasma triglycerides ≥ 1.70 mmol/L

[150 mg/dL] OR lipid lowering treatment and, 5) Plasma HDL-cholesterol ≤ 1.3/1.0 mmol/L [40/50 mg/dL] (female/male) OR lipid lowering treatment.[12]

Alcohol intake

We surveyed the alcohol history of patients with a standardised interview including questions on 1) the average alcohol intake over the past three months leading up to inclusion, 2) alcohol abstinence in the week leading up to inclusion, 3) Duration of alcohol abstinence (<1 year, 1-5 years, >5 years) 4) the former maximal intake and 5) the duration of excessive intake. For the subclassification of SLD according to alcohol intake, we used the average alcohol intake over the past three months leading up to inclusion. Duration of alcohol abstinence was used for sensitivity analyses in patients reporting low alcohol intake (not exceeding limits of MASLD).

Subclassification according to the new nomenclature

Patients were subclassified ~~into subclasses~~ according to the new nomenclature:[1] 1) **MASLD** defined patients with SLD, presence of ≥1 cardiometabolic risk factor and self-reported intake of alcohol <20/30 (female/male) gram per day; 2) **MetALD** was defined as patients with SLD, presence of ≥1 cardiometabolic risk factor and self-reported intake of alcohol 20-50 / 30-60 (female/male) gram per day; 3) **ALD+** defined patients with SLD, presence of cardiometabolic risk factors and self-reported intake of alcohol >50/60 (female/male) gram per day; 4) **ALD-only** defined patients with SLD, without cardiometabolic risk factors and self-reported intake of alcohol >20/30 (female/male) gram per day. 5) **No-SLD** defined patients without hepatic steatosis and without significant fibrosis (~~fibrosis stage~~ <F2) according to their biopsy. If a liver biopsy was not performed, the assessment was based on ultrasound

and controlled attenuation parameter (<290 dB/m)[10] suggesting no presence of steatosis and a transient elastography score below 6 kPa.

It should be noteiced that according to the new nomenclature, advanced fibrosis (≥F3) in absence of steatosis is sufficient to diagnose SLD if the underlying aetiology is presumed to be MASLD. [1] However, clinically significant fibrosis (≥F2) in absence of steatosis, is sufficient to diagnose SLD if the underlying aetiology is presumed to be alcohol-related.[1] Such a classification based on the cause of steatotic liver disease makes sense from a clinical perspective. Firstly, F2 fibrosis in ALD/MetALD carries a prognosis as unfavorable as F3 fibrosis in MASLD.[13] Secondly, presence of steatosis significantly depends on alcohol consumption. Many patients with alcohol-related liver damage reduce alcohol intake before examination leading to absence of steatosis (~30%).[10] Here, we decided to use significant fibrosis (≥F2) because the underlying liver damage was at least partially due to alcohol.[4]

For the prognostic analyses, the groups with ALD+ and **ALD-only** were combined in one group named **ALD**.

~~*Follow-up*~~

~~We tracked the patients by systematic, manual reviewing of their electronic medical records which encompassed all contacts with Danish hospitals. Patients were followed from inclusion and until death, lost to follow-up, or data censoring in 2022 September. Patients who were lost to follow-up were censored after last hospital contact.~~

~~*Outcomes*~~

~~Hepatic decompensation during follow-up was defined according to the Baveno VII criteria[14] defined as the development of either major ascites, variceal bleeding, or overt hepatic encephalopathy during the follow-up period. Survival status of each patient was recorded at the end of the data collection. Reports of excessive alcohol intake in electronic medical records was recorded along with the clinical outcomes.~~

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Statistical analysis

We report categorical data as counts and frequencies, and continuous data as mean with standard deviations (SD) or medians with interquartile ranges (IQR) according to the distribution. Chi-square and Wilcoxon ~~signed~~ rank-sum test were used to compare SLD and no-SLD. Chi-square and Kruskal-Wallis tests were used to compare the subclasses of SLD.

Complete data on cardiometabolic risk factors were available in 416 (92%) of the 450 patients. We had missing data on BMI for three patients, fasting plasma glucose and HbA1c for nine patients without known type 2 diabetes, triglycerides for 21 patients without known dyslipidemia, HDL-cholesterol for 25 patients without known dyslipidemia, and blood pressure for five patients without known hypertension. The data were assumed to be missing completely at random. We present the distribution of the number of cardiometabolic risk factors for complete cases, as well as the distribution in the best and worst-case scenarios. In the best-case scenario, all individuals with missing data are assumed to be absent of the cardiometabolic risk factors, while in the worst-case scenario, they are assumed to have the presence of these risk factors. We examined the potential consequences of the missing cardiometabolic data on the subclassification of the patients according to the new

nomenclature (Supplementary Table 1). Based on this, we could classify 449 out of 450 patients according to the criteria of the new nomenclature without any assumption on missing data. The last single patient had no data for blood pressure but was otherwise free of any cardiometabolic risk factors. In the context of the SLD subclassification, we assumed that the patient had normal blood pressure since all other parameters indicated that he was healthy from a cardiometabolic perspective.

Cox regression analyses were performed to compare the prognosis for hepatic decompensation and all-cause mortality. We tracked the patients by systematic, manual reviewing of their electronic medical records which encompassed all contacts with Danish hospitals. Patients were followed from inclusion and until event (hepatic decompensation and all-cause mortality), lost to follow-up, or data censoring in September 2022. Patients who were lost to follow-up were censored after last hospital contact. Hepatic decompensation during follow-up was defined according to the Baveno VII criteria[14] defined as the development of either major ascites, variceal bleeding, or overt hepatic encephalopathy during the follow-up period. Survival status of each patient was recorded at the end of the data collection. Reports of excessive alcohol intake in electronic medical records was recorded along with the clinical outcomes. First, we compared the prognosis between patients with and without SLD. Next, we looked at the subclasses of SLD (MASLD, MetALD and ALD) and compared the prognosis with patients without SLD (No-SLD). We performed univariable and multivariable Cox regression analysis. In multiple Cox regression analysis, we adjusted for age, sex, liver stiffness by transient elastography and presence of cardiometabolic risk factors at inclusion. Kaplan-Meier curves are all based on the models derived from the multivariable Cox regression analyses. Sensitivity analyses were performed based on duration of alcohol abstinence. We

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only included patients with adequate measurements for the presence and severity of liver disease. ~~In cases of missing data related to the features used for the criteria of cardiometabolic risk factors (1-6% missing per risk factor), we assumed data were missing at random and that these patients did not fulfil that criterium for that specific risk factor.~~ We considered P <0.05 as statistically significant, and used STATA 18 (College Station, TX, US) for all calculations.

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Results

Patients

We included 450 patients with current or previous alcohol intake exceeding limits of MASLD for at least one year. Baseline, demographics, and clinical characteristics are presented in Table 1. ~~Median~~Mean age was ~~57~~ 56 (±10) years ~~(IQR 50–64)~~among 337 (75%) were men and 113 (25%) were women. Significant fibrosis (≥F2) was seen in 191 (43%) of the patients and cirrhosis in 61 (14%).

A liver biopsy was not performed on 94 patients with a liver stiffness below 6 kPa.

Prevalence of steatotic liver disease

At inclusion, 324 (72%) of 450 patients met the criteria of SLD (Figure 1). Of these, 267 (82%) had hepatic steatosis on biopsy or imaging, whereas the remainder 57 (18%) patients without steatosis, were found to have >F2 and hereby met the criteria of SLD. The last 126 patients did not fulfil the criteria of SLD (No SLD) meaning no evident liver steatosis and no significant fibrosis (≥F2).

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Cardiometabolic risk

In the overall cohort of 450 patients, 439 (98%) met at least one of the cardiometabolic criteria and only 11 (2%) presented with none. Among the 324 patients with SLD, 318 (98%) met at least one of the cardiometabolic criteria and only 6 (2%) had no cardiometabolic risk factors (Figure 1 and Figure 2A) leading to a categorisation of these as ALD-only.

The majority (67%) of patients with SLD had at least three cardiometabolic risk factors. Elevated BMI, hypertension and prediabetes/diabetes were the most common, each were recorded in more than two third of the patients (Table 1).

Alcohol use

Patients with SLD and cardiometabolic risk factors were divided into the three subclasses based on their self-reported average alcohol intake within the last three months; 155 (49%) of 318 had a low alcohol intake and met the MASLD criteria, 76 (24%) had an excessive alcohol intake matching the MetALD criteria, and 87 (27%) had an excessive alcohol intake matching the ALD criteria (Figure 1).

Characterisation of steatotic liver disease and its subclasses

Characteristics of the patients with SLD and without SLD are presented in Table 1. When comparing the two groups, patients with SLD were older (58 (SD±1) years versus 52 years (SD±9)~~59 (IQR 52-65) years versus 53 (IQR 46-60) years, P-value < 0.001~~) and fewer reported to be alcohol abstinent for at least one week prior to inclusion (37% versus 56%~~, P-value < 0.001~~). Both groups had high prevalence of cardiometabolic risk factors (Figure 2A) but the median load of cardiometabolic risk factors was three ~~significantly higher~~ in patients with SLD compared to two the group without SLD ~~(P value < 0.001)~~. All cardiometabolic risk factors, except prediabetes/diabetes, were more frequent in patients with SLD ~~(P value < 0.001)~~. Only one (<0.5 %) patient with SLD and current excessive alcohol intake (>20/30 g (female/male) per day) had no cardiometabolic risk factors.

The characteristics according to the subclasses of SLD are presented in Table 2. When comparing the SLD subclasses (MASLD, MetALD and ALD+), the group with MetALD was slightly older. The ALD+ group had the highest representation of males. The load of cardiometabolic risk factors (Figure 2B) was similar between the groups. Hypertension and elevated plasma triglycerides were seen more frequently in patients with MetALD and ALD+ compared to patients with MASLD, while decreased HDL-cholesterol was seen more frequently in patients with MASLD compared to MetALD and ALD+. A ~~significantly~~ higher proportion of patients had significant fibrosis (≥F2) in the MASLD group compared to the MetALD and ALD+ groups (69% versus 53% versus 48%~~, P-value = 0.001~~). Also, a ~~significant~~ higher proportion of patients had cirrhosis in the MASLD group compared to the MetALD and ALD+ groups (28% versus 8% versus 13%~~, P-value < 0.001~~).

Follow-up

~~We followed the patients for a median follow-up period of 70 (IQR 53-94) months. During follow-up, 64 patients developed hepatic decompensation of which 62 patients had SLD at inclusion. Death occurred in 97 patients of which 87 patients had SLD at inclusion.~~

We followed patients until first episode of hepatic decompensation, lost to follow up, death or central data censoring in September 2022. Four patients did not consent for electronic follow up and were not included in the analysis. Within the follow up period seven patients left the region and were lost to follow up. At time of censoring, none of the seven patients had developed hepatic decompensation. During follow up, hepatic decompensation occurred in 67 patients and 53 patients died without

having developed hepatic decompensation within a median follow-up period of 67 (IQR 52-92) months. Patients who died without having developed hepatic decompensation were censored at time of death. In total, 97 patients died within a median follow-up period of 70 (IQR 53-94) months. Of these, 48 of 97 (45%) died after developing hepatic decompensation, and one died of cholangiocarcinoma. Among the last 48 deaths, the cause of 35 deaths was not directly linked to liver disease, and the cause was unknown in 13 deaths.

Prognosis

Patients with SLD had a significantly worse prognosis compared to patients without SLD independent of cardiometabolic risk factors (Figure 3). This included a higher risk of hepatic decompensation and all-cause mortality in univariable, and multivariable Cox regression analyses adjusted for age, sex and~~,~~ liver stiffness ~~and presence of cardiometabolic risk factors~~ (Supplementary Table 2~~1~~, Supplementary Table 3~~2~~ and Figure 3).

In the following analysis of the subclasses of SLD the groups with ALD+ and ALD- only were combined in one group named ALD given small numbers in the ALD-only group. All three subclasses of SLD (MASLD, MetALD and ALD) had significantly higher risk of hepatic decompensation and all-cause mortality compared to the patients without SLD in univariable Cox regression analysis (Supplementary Table 3 and Supplementary Table 4). In multivariable Cox regression analyses, the risk of hepatic decompensation increased gradually with the level of alcohol intake from MASLD (HR=4.73, 95%CI 1.03-21.6) ~~(HR=5.21, 95%CI 1.13-24.0)~~, MetALD (HR =

7.69, 95%CI 1.66-35.6) ~~(HR = 8.74, 95%CI 1.87-40.8)~~ to ALD (HR=10.2, 95%CI 2.24-46.4) ~~(HR=12.0, 95%CI 2.62-55.3)~~ compared to patients without SLD adjusted for age, sex, liver stiffness and presence of cardiometabolic risk factors (Figure 4A). Overall mortality increased gradually with the level of alcohol intake level from MASLD (HR=2.30, 95%CI 1.08-4.90) ~~(HR=2.45, 95%CI 1.13-5.25)~~, MetALD (HR = 2.94, 95%CI 1.31-6.58) ~~(HR = 3.1, 95%CI 1.38-7.03)~~ to ALD (HR=3.57, 95%CI 1.64-7.80) ~~(HR=3.84, 95%CI 1.74-8.45)~~ compared to patients without SLD adjusted for age, sex, liver stiffness and presence of cardiometabolic risk factors (Figure 4B).

Sensitivity analysis for abstinence duration in MASLD

Among the 155 patients classified as MASLD, 40 (26%) patients had a low current alcohol intake (median 12 (IQR 3-24) grams), while 84 (54%) reported to be abstinent for less than one year, 14 (9%) patients between 1-5 years, and 16 (10%) patients for more than 5 years. We performed sensitivity analyses of the prognosis using the patients who had a low current alcohol intake as reference. The risk of hepatic decompensation decreased gradually with duration of abstinence: <1 year of alcohol abstinence (HR=0.73, 95% CI 0.32-1.69) ~~(HR=0.89, 95% CI 0.36-2.22)~~, 1-5 years (HR=0.65, 95%CI 0.17-2.54) ~~(HR=0.62, 95%CI 0.14-2.68)~~, and >5 years (0.22, 95%CI 0.03-1.87) ~~(0.27, 95%CI 0.03-2.35)~~. The risk of all-cause mortality was also lower in groups reporting abstinence at inclusion: <1 year of alcohol abstinence (HR=0.64, 95% CI 0.30-1.36) ~~(HR=0.62, 95% CI 0.29-1.32)~~, 1-5 years (HR=0.97, 95%CI 0.33-2.82) ~~(HR=0.91, 95%CI 0.30-2.72)~~, and >5 years (0.37, 95%CI 0.08-1.74) ~~(0.38, 95%CI 0.08-1.77)~~.

During follow-up, ~~in electronic medical records,~~ we identified~~recorded~~ reports of excessive alcohol intake in 82 (54%) out of 155 patients classified as MASLD. The proportion of patients with excessive drinking during follow-up was 50-65% in all subgroups except for the group with more than 5 years of alcohol abstinence~~t~~ having only one of the 16 patients had a report of during follow up~~6% cases of excessive alcohol intake~~ (Supplementary Table 5).

Sensitivity analysis for cardiometabolic risk factors in ALD

When comparing patients with ALD according to the presence of cardiometabolic risk factors (ALD+ versus ALD-only), the ALD-only group was ~~significantly~~ younger, ~~(~~51 (IQR 47-53) years versus 59 (IQR 52-65) years~~, P value = 0.001~~) and ~~they~~ had a lower average alcohol intake over the ~~past~~ preceding three months ~~leading up to~~before inclusion. Importantly, none of the patients without cardiometabolic risk factors had an average daily alcohol intake exceeding the threshold of >50/60 g (female/male) and only one patient had an average daily alcohol intake of 20-50/50-60 g (female/male). Thirteen of 87 (15%) patients with cardiometabolic risk factors and high alcohol intake at inclusion (ALD+) developed hepatic decompensation, and 14 (16%) of 87 died during follow-up. In patients without cardiometabolic risk factors at inclusion (ALD-only), one ~~(17%)~~ of six patients developed hepatic decompensation and two ~~(33%)~~ of six patients died during follow-up.
A formal statistical comparison between the groups could not be performed due to the low number of patients without cardiometabolic risk factors (ALD-only).

Discussion

In this prospective cohort study of patients with a history of excessive alcohol intake, we characterised and analysed the prognosis of patients with SLD according to the new nomenclature.[1] Our findings revealed that 72% of the patients met criteria for SLD, and a notable 98% exhibiting at least one cardiometabolic risk factor. We observed that the prognosis was driven by current level of alcohol intake with the risk of hepatic decompensation and mortality incrementally increasing from MASLD through MetALD to ALD.

The new SLD nomenclature, based on a consensus process involving 224 experts and patient advocates, primarily aimed to rename non-alcoholic fatty liver disease.[1] However, the framework also covers other aetiologies of hepatic steatosis, thereby including patients with excessive alcohol intake. In our study of patients with excessive alcohol intake, we found the criteria to be easily applicable and the subclassification straightforward with simple parameters available in most healthcare settings. Importantly, we found that the subclasses had different prognoses, underlining the significance of considering SLD (MASLD, MetALD and ALD) as a spectrum rather than distinct conditions (NAFLD or ALD).[6]

However, our study also unearthed certain ~~limitations within~~areas where further clarification is warranted within the framework of the new nomenclature. The nomenclature of SLD defines specific levels of alcohol intake to allow subclassification and ideally better prognosticate and

511 determine the relative contribution of alcohol or cardiometabolic risk factors to
512 liver disease progression. This subclassification bears significant implications
513 for clinical trials and future treatments for metabolic dysfunction associated
514 steatohepatitis (MASH). Therefore, several aspects require further
515 specification and careful consideration. First of all, it is important to define the
516 timeframe during which alcohol intake should be taken into account. At what
517 point does alcohol cease to be a relevant disease driver, allowing patients with
518 a former excessive alcohol intake to be categorised as MASLD/MASH? Or
519 vice versa moving from MASLD/MASH to MetALD or ALD after a period of
520 increased alcohol intake. We also need consensus on how to handle this in
521 the setting of clinical trials. Second, how can we reliably assess alcohol intake,
522 given that self-reported alcohol is usually inaccurate, and underreporting is
523 further influenced by culture and stigma.[15,16] Our sensitivity analyses revealed
524 that nearly 50% of those reporting low alcohol consumption at inclusion did
525 not have reports of excessive alcohol use during the follow-up period.
526 Additionally, we observed a trend indicating that patients reporting more than
527 5 years of abstinence prior to inclusion had the lowest risk of excessive
528 alcohol use during the follow-up period.
529
530 This study and previous studies,[17,18] have underscored the fluctuating nature
531 of alcohol intake, which suggests that quantification should encompass a
532 defined observation period. While single measurements of phosphatidyl
533 ethanol (PEth) show promise as an operational tool to assess alcohol intake

within the preceding 2-4 weeks,[19] we advocate for sequential measurements in clinical practice, as well as in the context of clinical trials ~~over a six-month period~~ as often used when evaluating patients with ALD for liver transplantation, especially when correct classification has significant clinical implications.

Another limitation within the framework of the new nomenclature is the substantial heterogeneity it encompasses in the ALD subclass, as it categorises individuals with both cardiometabolic risk factors and a daily alcohol intake exceeding 50/60 grams, alongside individuals without cardiometabolic risk factors but a daily alcohol intake exceeding 20/30 grams. In this study, we identified only a small group of patients with ALD without cardiometabolic risk factors (ALD-only), which differed notably in age and exhibited a considerably lower daily alcohol intake. Given the known association between alcohol intake and metabolic dysfunction[20] leading to the development of cardiometabolic risk factors, our findings raise practical challenges. These are particularly pertinent when classifying almost all SLD patients consuming 20-50/30-60 g of alcohol per day (female/male) as MetALD, thereby practically shifting the threshold for ALD to >50-60 g (female/male). These data strongly advocate for a thoughtful refinement of the ALD definition within the SLD spectrum.

This study is not without limitations. First, our study was an observational design with the potential presence of unmeasured confounders. However, to address unmeasured confounders, we carefully selected variables based on a causal directed acyclic graph (Supplementary Figure 1). It is worth noting that hepatic genetic risk factors were not included in the Cox regression models. We decided against including hepatic genetic risk variants since genetic analyses is not recommended as part of the clinical assessment for steatotic liver disease.[21] Furthermore, hepatic genetic risk variants influence on liver disease have most impact on the fibrosis stage at time of diagnosis[4] and less on the prognosis.[22] Moreover, variations in alcohol intake over time and the management of cardiometabolic risk factors are likely to have an impact on the prognosis. In this regard, the prognosis estimates are presented as hazard ratios (HRs) which inherently carry a selection bias that could have influenced our findings.[23]

Second, the classification of many patients as MASLD, despite documented excessive alcohol intake during the follow-up period, likely does not accurately represent the prognosis of "~~traditional~~pure" MASLD without a history of excessive drinking. There are no studies that specifically assess this issue, however, harmful alcohol consumption in 28.9% of patients perceived as NAFLD has been reported.[24] However, to delve into this further, we did a comparison for the risk of hepatic decompensation between a 'pure' MASLD cohort[25] and the MASLD subclass in this study (Supplementary Figure 3). The estimates showed that our study may overestimate the risk of disease

progression in MASLD, especially in patients with transient elastography >12 kPa indicating advanced liver disease. This is in line with other MASLD studies of the natural history showing that liver disease driven by cardiometabolic risk factors without alcohol occurs at a much slower pace.[13,26] The question is whether the period of abstinence required to transition a patient from ALD/MetALD to MASLD should be determined based on the cause of the disease or the implications for disease management. With the expectation of upcoming medications for MASH patients, a critical question for individuals with a history of excessive alcohol use becomes: How long should a patient reduce alcohol consumption (or remain abstinent) before ongoing liver disease activity is considered due to MASH and thus eligible for MASH directed therapeutics.[25] ~~Still, we acknowledge that it is likely that our study overestimate the risk of disease progression in the MASLD group. Disease driven by cardiometabolic risk factors without alcohol occurs at a much slower pace.[13,26] This difference may explain why the burden of cardiometabolic risk factors had a minimal impact on the prognosis. In contrast, ALD follows a steeper curve before the impact of cardiometabolic risk factors reaches its maximum effect. This difference may explain why the burden of cardiometabolic risk factors had a minimal impact on the prognosis.~~ Also, when considering that alcohol is a strong driver of the disease, it may appear peculiar that more individuals in the MASLD group had advanced liver disease. However, a plausible explanation for this could be that there were more sick quitters in the MASLD group. The term sick quitters describes the

phenomenon in which individuals reduce their alcohol consumption as they develop serious illness.[27] Interestingly, we observed that individuals in the MASLD group with more than 5 years of abstinence were at the lowest risk of relapse into excessive alcohol use and developing decompensated liver disease.

Third, it is noteworthy that the high prevalence of cardiometabolic risk factors observed in our study may vary in a younger population with a history of excessive alcohol intake, potentially resulting in differing rates of MetALD. Conversely, younger individuals without metabolic risk factors may not develop SLD.

Fourth, ~~Additionally,~~ alcohol intake was based on self-reported information, and the accuracy may differ between cultures[28], which could complicate the correct subclassification. We considered conducting sensitivity analyses within the MASLD group, taking into account excessive alcohol intake during follow-up. Nevertheless, we opted against conducting these analyses to prevent the introduction of immortal time bias.

In conclusion, the criteria of SLD are easy to apply in clinical studies and the subclasses are of clinical relevance, as they divide patients into populations of significantly different prognoses. Further specification on how historical alcohol intake should be incorporated into the nomenclature is needed, because this subclassification is decisively for clinical studies and ~~upcoming~~

~~treatment~~management. Criteria for moving between subclasses also need to be defined.

Acknowledgement

We wish to thank the research nurses and medical student team at FLASH and the administrators of the GALAXY consortium: Louise Skovborg Just and Vibeke Nielsen.

Author contribution

Conceptualization: MI, MR, AK. Data curation: MI, NT, SJ, CDH, KT, JKH, KPL, PA, MT. Formal Analysis: MI, NT. Funding acquisition: AK Investigation: MI, NT, SJ, CDH, KT, JKH, KPL, PA, MT. Methodology: MI, NT, MT, MR, AK. Project administration: MT, AK. Supervision: MT, MR, AK. Validation: MT, AK. Visualization: MI Writing – original draft: MI, NT, MR, AK. Writing – review & editing: MI, NT, SJ, CDH, EDH, KT, JKH, IV, KB, CW, PA, KPL, ET, MT, MR, AK

Data availability

Data are available on request after approval from the Danish Data Protection Agency in a pseudonymised manner upon request to mads.israelsen@rsyd.dk. The study protocol and statistical analysis plan are available online.

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Tables and Figures

	Overall cohort	SLD	No SLD
	N=450	**N=324**	**N=126**
Age, years	56 (±10)~~57 (50-64)~~	59 (±12)~~59 (52-65)~~	52 (±9)~~52 (46-60)~~
Sex, male (%)	337 (75%)	259 (80%)	78 (62%)
BMI, kg/m^2	27 (±5)~~27 (24-31)~~	28 (±5)~~28 (24-31)~~	26 (±4)~~25 (23-28)~~
Alcohol use			
Average alcohol intake, g/day†	12 (0-51)	24 (0-60)	0 (0-27)
Alcohol abstinence last week, n (%)‡	258 (57%)	121 (37%)	71 (56%)
Years of excessive use (>20/30 g/day)[1], 1-10 years >10-20 years >20 years	 134 (32%) 110 (26%) 180 (42%)	 94 (31%) 73 (24%) 139 (45%)	 40 (34%) 37 (31%) 41 (35%)
Cardiometabolic risk factors			
BMI ≥ 25 kg/m^2 [2]	311 (~~69~~70%)	240 (~~74~~75%)	71 (~~56~~57%)
Fasting glucose ≥5.6 mmol/L OR HbA1c ≥ 39 mmol/mol OR T2DM OR anti-diabetic treatment [3]	~~339~~ 365 (~~75~~83%)	~~257~~ 265 (~~83~~83%)	100 (~~79~~82%)
Blood pressure ≥130/85 mmHg OR antihypertensive drug treatment [4]	321 (~~71~~72%)	249 (~~77~~78%)	72 (~~57~~58%)
Triglycerides ≥1.7 mmol/L OR treatment with lipid lowering drugs [5]	186 (~~41~~43%)	151 (~~47~~49%)	35 (~~28~~29%)
HDL ≤1.0/1.3 mmol/L (male/female) OR treatment with lipid lowering drugs [6]	152 (~~34~~36%)	123 (~~38~~40%)	29 (~~23~~24%)
Liver parameters			
Significant fibrosis (≥F2), yes (%) [6]	191 (43%)	191 (60%)	0 (0%)
Cirrhosis (F4), yes (%) [7]	61 (14%)	61 (19%)	0 (%)
Liver stiffness measurement by TE, kPa	6.5 (4.8-11.8)	8.8 (5.6-20.9)	4.5 (3.8-5.5)
Presence of steatosis (S1-S3) [7],	193 (66%)	193 (76%)	0 (0%)

Table 1: Characteristics of patients.
SLD: Histological or radiographic evidence of hepatic steatosis ~~, Biopsy with steatosis OR imaging suggesting steatosis~~ OR significant fibrosis (≥F2). **No SLD**: No histological or radiographic evidence of ~~biopsy OR imaging suggesting no~~ hepatic steatosis AND no significant fibrosis (<F2).
† The average alcohol intake over the past three months leading up to inclusion. ‡ Alcohol abstinence in the week leading up to inclusion.
Data from [1]424, [2]447, [3]441, [4]429, [5]425, [6]445 patients. [7]Data from 293 biopsies

BMI, Body mass index; T2DM, Type 2 diabetes mellitus; TE, transient elastography.

	MASLD	MetALD	ALD+	ALD-only	No SLD
	N=155	N=76	N=87	N=6	N=126
Age, years	57 (±10)~~58 (52-63)~~	60 (±9)~~61 (54-68)~~	58 (±9)~~59 (52-65)~~	49 (±7)~~51 (47-53)~~	52 (±9)~~52 (46-60)~~
Sex, male (%)	123 (79%)	57 (75%)	75 (86%)	4~~ (67%)~~	78 (62%)
BMI, kg/m^2	28 (±5)~~28 (25-31)~~	29 (±6)~~29 (26-32)~~	28 (±6)~~27 (25-32)~~	21 (±3)~~22 (20-23)~~	26 (±4)~~25 (23-28)~~
Alcohol use					
Average alcohol intake, g/day†	0 (0-0)	48 (36-51)	103 (72-288)	41 (0-72)	0 (0-27)
Alcohol abstinence last week, n (%)‡	117 (75%)	2 (3%)	0 (0%)	2~~ (23%)~~	71 (56%)
Years of excessive use (>20/30 g/day)[1], 1-10 years >10-20 years >20 years	 54 (38%) 31 (22%) 58 (41%)	 25 (35%) 18 (25%) 29 (40%)	 13 (15%) 22 (26%) 50 (59%)	 2~~ (33%)~~ 2~~ (33%)~~ 2~~ (33%)~~	 40 (34%) 37 (31%) 41 (35%)
Cardiometabolic risk factors					
BMI ≥ 25 kg/m² [2]	115 (74%)	58 (76%)	67 (77%)	0~~ (0%)~~	71 (56%)
Fasting glucose ≥5.6 mmol/L OR HbA1c ≥ 39 mmol/mol OR T2DM OR anti-diabetic treatment [3]	126 (81%)	63 (83%)	76 (87%)	0~~ (0%)~~	100 (79%)
Blood pressure ≥130/85 mmHg OR antihypertensive drug treatment [4]	111 (72%)	66 (87%)	72 (83%)	0~~ (0%)~~	72 (57%)
Triglycerides ≥1.7 mmol/L OR treatment with lipid lowering drugs [5]	65 (42%)	40 (53%)	46 (53%)	0~~ (0%)~~	35 (28%)
HDL ≤1.0/1.3 mmol/L (male/female) OR treatment with lipid lowering drugs [6]	72 (46%)	22 (29%)	29 (33%)	0~~ (0%)~~	29 (23%)
Liver parameters					
Significant fibrosis (≥F2), yes (%) [6]	107 (69%)	39 (53%)	41 (48%)	4~~ (80%)~~	0 (0%)
Cirrhosis (F4), yes (%) [7]	44 (28%)	6 (8%)	11 (13%)	0~~ (0%)~~	0 (%)
Liver stiffness measurement by TE, kPa	9.5 (6.1-28)	7.9 (5.5-13)	8.7 (5.4-17)	8.4 (6.2-11)	4.5 (3.8-5.5)
Presence of steatosis (S1-S3) [7],	76 (83%)	54 (74%)	60 (71%)	3~~ (60%)~~	0 (0%)

Table 2: Characteristics of patients according to the subclassification of steatotic liver disease.

MASLD, presence of cardiometabolic risk factors AND <20/30 (female/male) gram alcohol per day;
MetALD, presence of cardiometabolic risk factors AND 20-50 / 30-60 (female/male) gram alcohol per day;
ALD+, presence of cardiometabolic risk factors AND >50/60 (female/male) gram alcohol per day;
ALD-only, no cardiometabolic risk factors AND >20/30 (female/male) gram alcohol per day.
No SLD, biopsy OR imaging suggesting no hepatic steatosis AND no significant fibrosis (<F2).
† The average alcohol intake over the past three months leading up to inclusion. ‡ Alcohol abstinence in the week leading up to inclusion.
Data from [1]424, [2]447, [3]441, [4]429, [5]425, [6]445 patients. [7]Data from 293 biopsies

ALD, alcohol-related liver disease; BMI, Body mass index; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; T2DM, Type 2 diabetes mellitus; TE, transient elastography.

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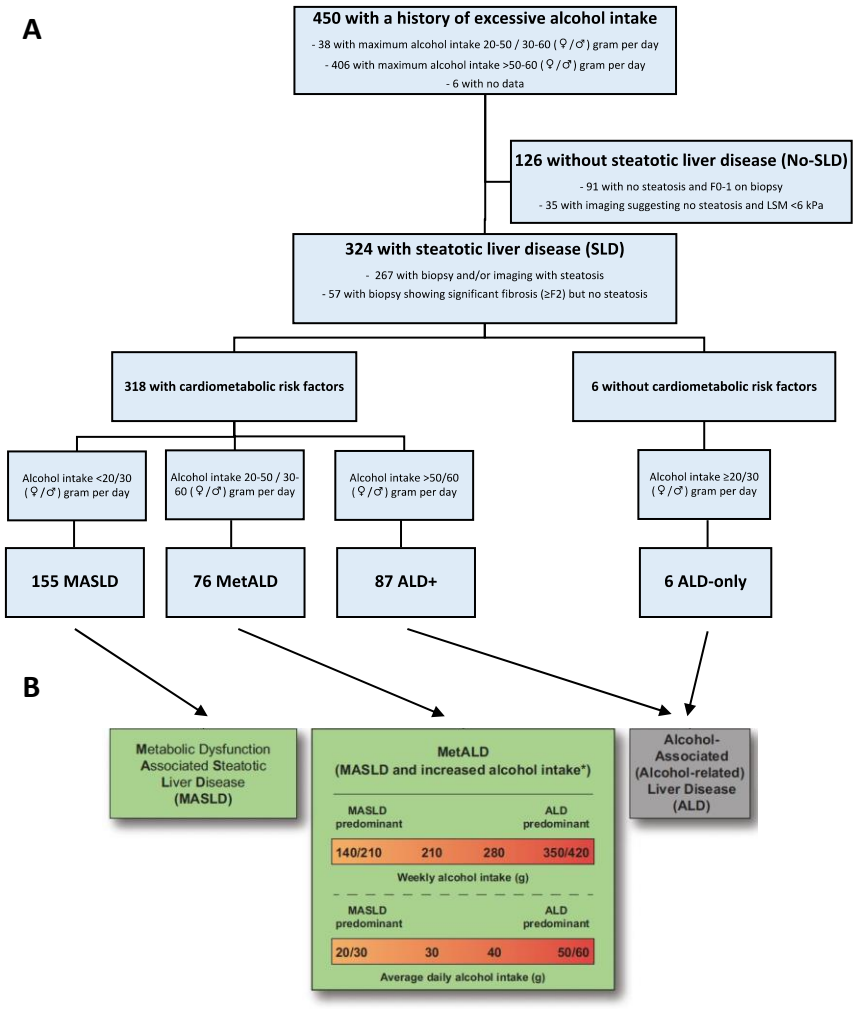

Figure 1: **Flow chart:** A) Subcategorising the patients with a history of excessive alcohol intake according to the new definition of steatotic liver disease. B) The original figure showing the (relevant) subcategorise of steatotic liver disease.

ALD, alcohol-related liver disease; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; MetALD, metabolic dysfunction and alcohol related liver disease; SLD, Steatotic liver disease

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Commented [MR3]: We might want to use the newer version of the figure that also has MASH - just published in final form Oct 30

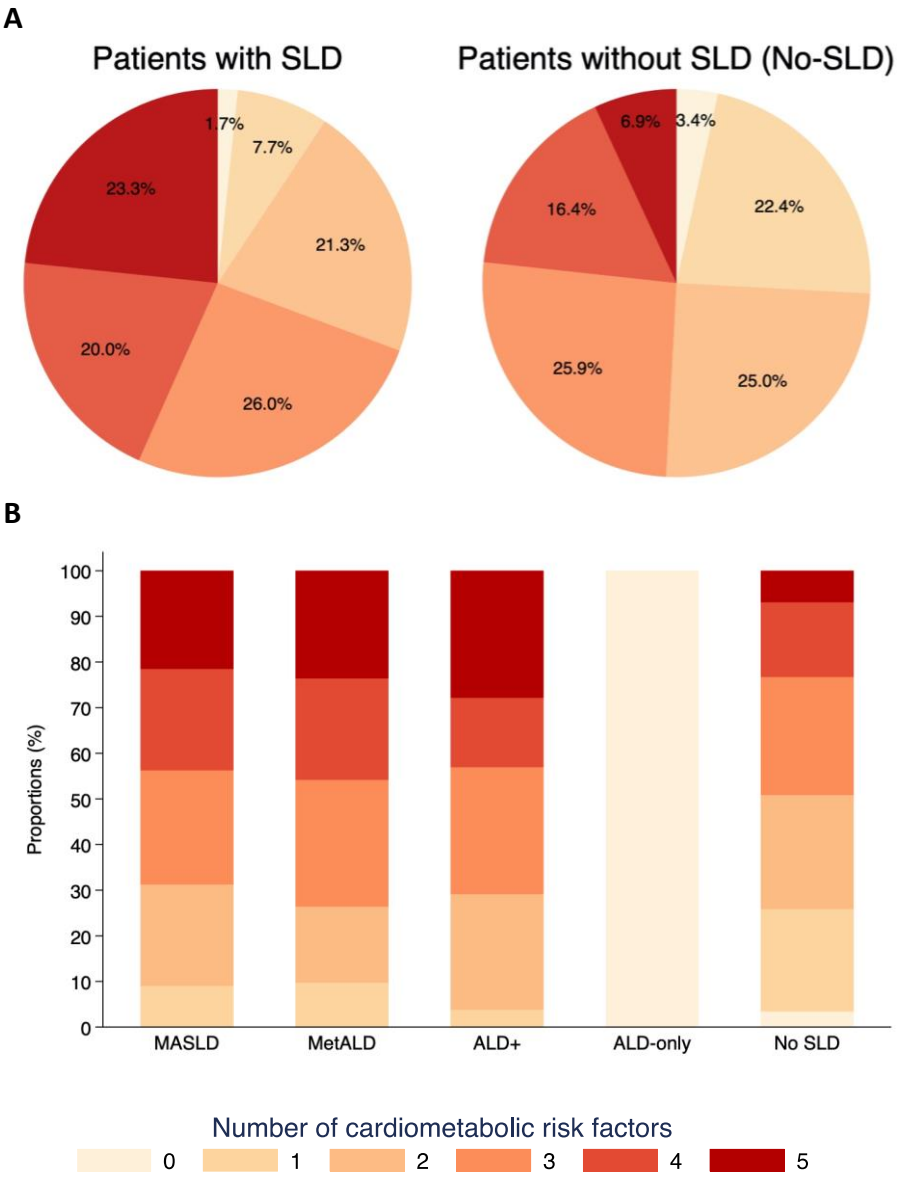

Figure 2: Proportion of cardiometabolic risk factors in the 416 (92%) patients with complete data on cardiometabolic risk factors A) Patients with SLD versus without SLD (No SLD), and B) according to the subclasses of SLD.
MASLD, presence of cardiometabolic risk factors AND <20/30 (female/male) gram alcohol per day;
MetALD, presence of cardiometabolic risk factors AND 20-50 / 30-60 (female/male) gram alcohol per day;
ALD+, presence of cardiometabolic risk factors AND >50/60 (female/male) gram alcohol per day;
ALD-only, no cardiometabolic risk factors AND >20/30 (female/male) gram alcohol per day.

No SLD, biopsy OR imaging suggesting no hepatic steatosis AND no significant fibrosis (<F2).
ALD, alcohol-related liver disease; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; MetALD, metabolic dysfunction and alcohol related liver disease; SLD, Steatotic liver disease
Similar figures for the entire cohort (including patients with missing data) can be found in Supplementary Figure 2, depicting both the best and worst-case scenarios.

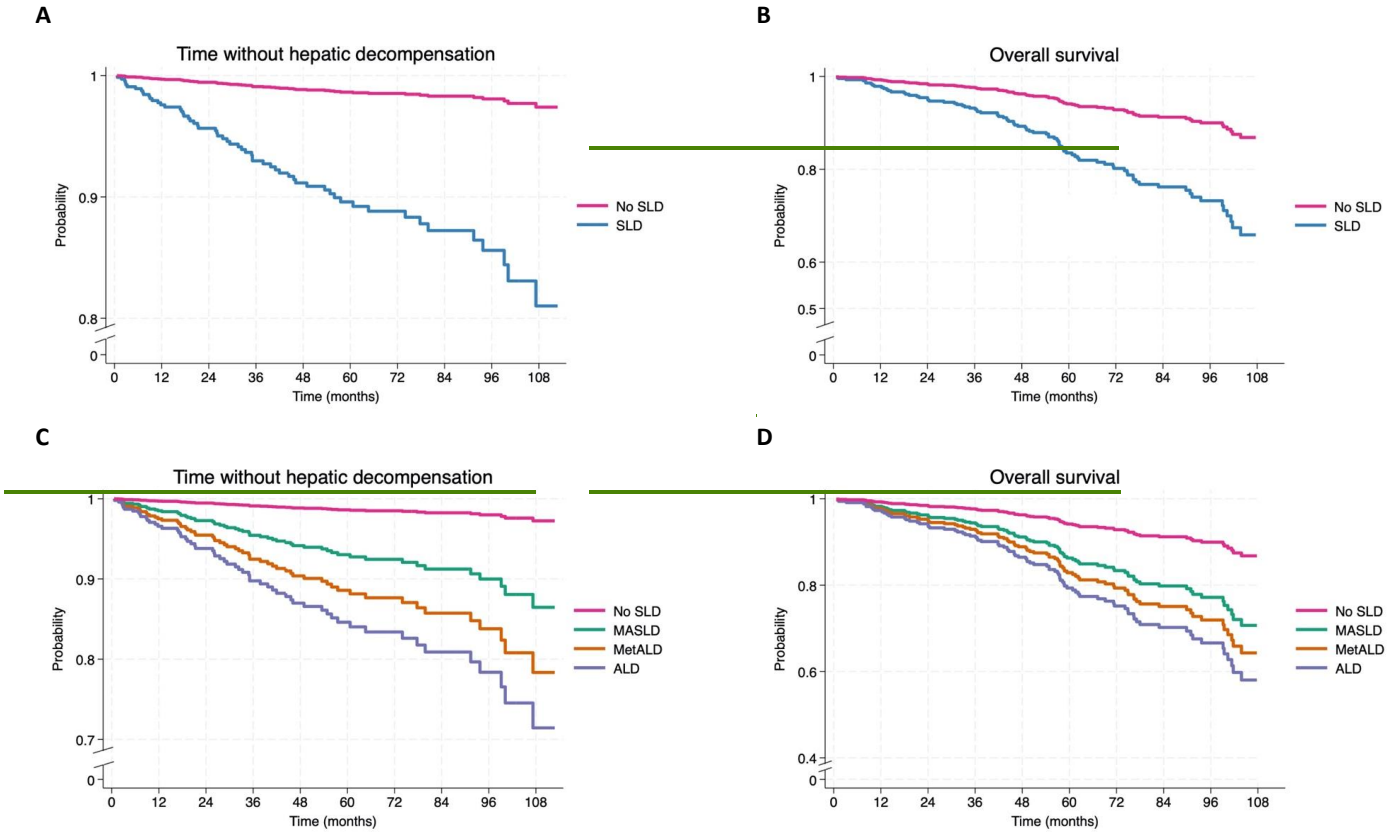

Figure 3: Kaplan-Meier curves derived from multivariable Cox regression showing A) the expected time without hepatic decompensation, B) overall survival comparing patients with and without. Subclasses of SLD are compared with C) the expected time without hepatic decompensation and D) overall survival. Models are adjusted for age, sex, liver stiffness and presence of cardiometabolic risk factors at inclusion (Table 3 and Table 4). *ALD, alcohol-related liver disease; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; MetALD, metabolic dysfunction and alcohol related liver disease; SLD, Steatotic liver disease*

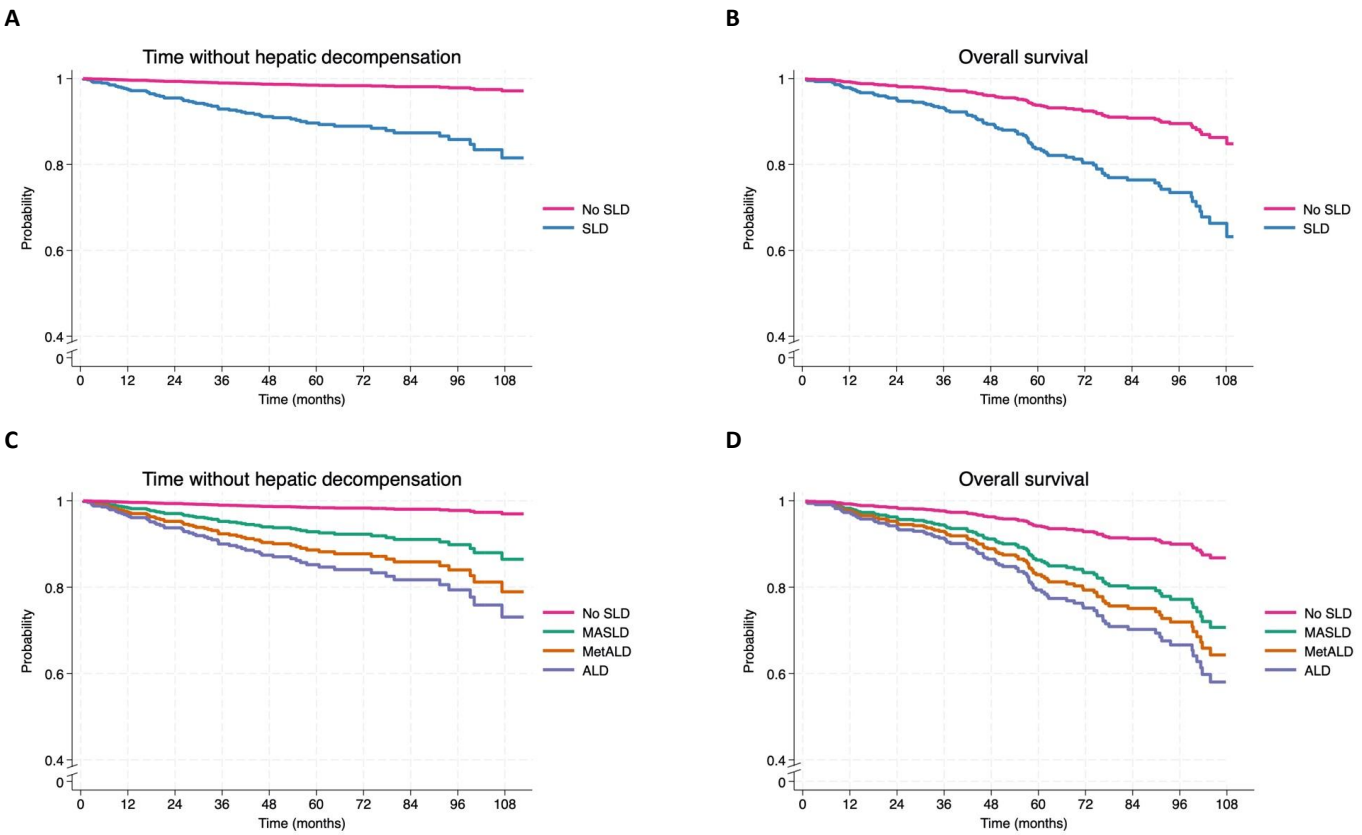

Figure 3: Kaplan-Meier curves derived from multivariable Cox regression showing A) the expected time without hepatic decompensation, B) overall survival comparing patients with and without. Subclasses of SLD are compared with C) the expected time without hepatic decompensation and D) overall survival. Models are adjusted for age, sex, liver stiffness and presence of cardiometabolic risk factors at inclusion (Table 3 and Table 4). *ALD, alcohol-related liver disease; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; MetALD, metabolic dysfunction and alcohol related liver disease; SLD, Steatotic liver disease*

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Supplementary

Validation of the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake: a prospective cohort study

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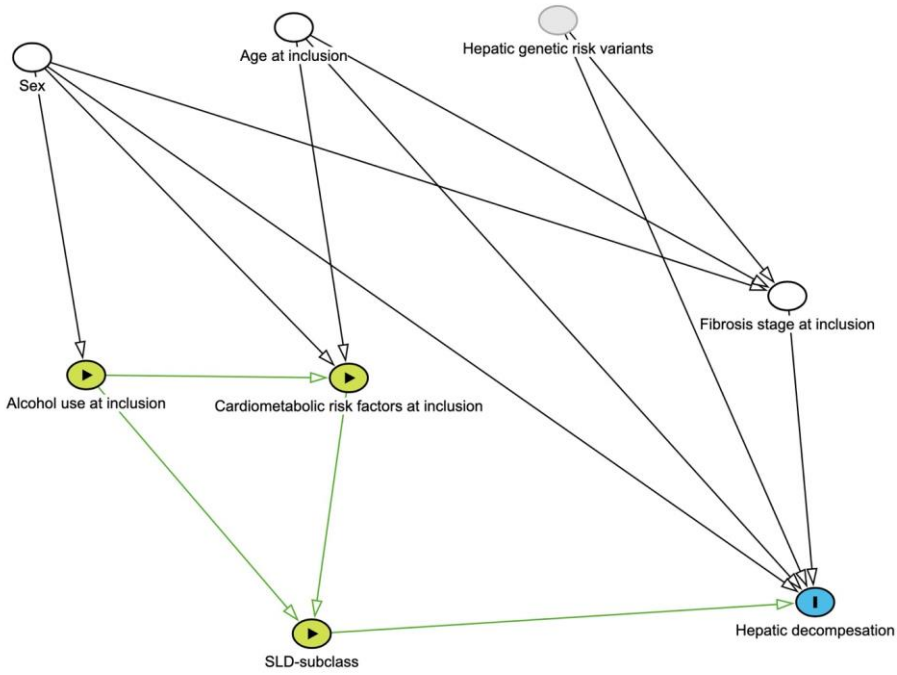

Supplementary Figure 1: Selection of potential confounders based on a causal directed acyclic graph. In our primary analyses, we investigated the impact of SLD and the subclasses on risk of hepatic decompensation. Potential confounders were identified through the literature. Hepatic genetic risk variants were not included in our models as potential confounders, as genetic testing is not recommended as part of the clinical assessment for steatotic liver disease.[21] Furthermore, hepatic genetic risk variants influence on liver disease have most impact on the fibrosis stage at time of diagnosis[4] and less on the prognosis.[22]

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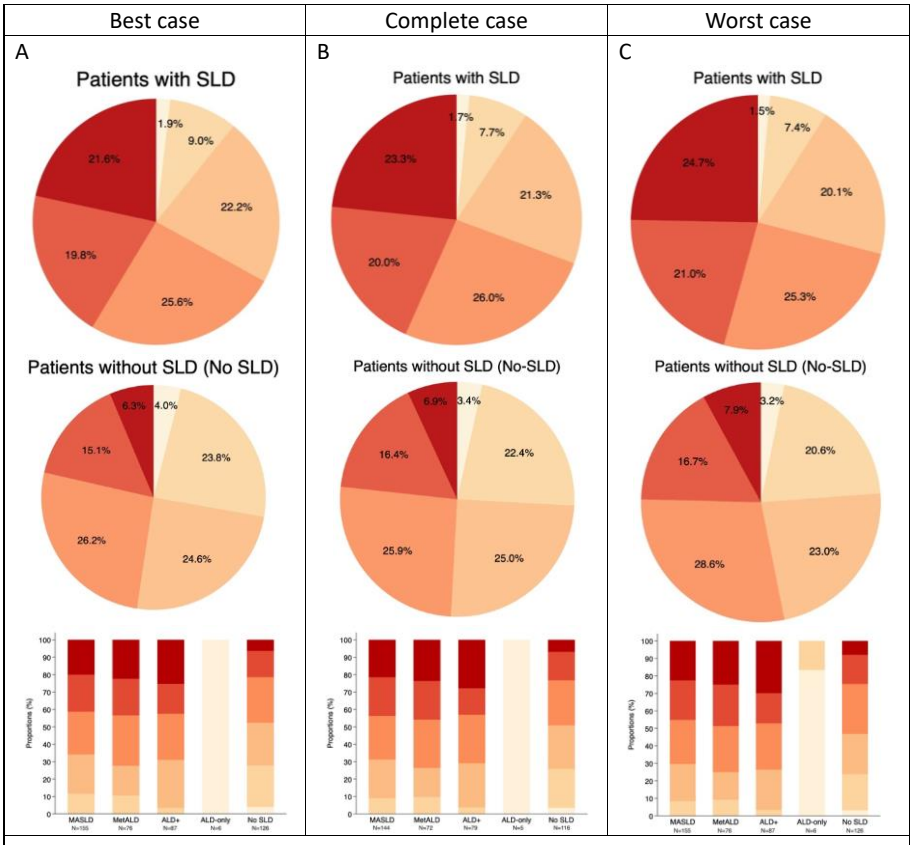

Supplementary figure 2: Proportion of cardiometabolic risk factors in A) In the best-case scenario, where all missing data are assumed to be absent in case of the cardiometabolic risk factors B) Complete cases, where 416 (92%) of the patients without missing cardiometabolic data are included C) In the worst-case scenario, where all missing data are assumed to have the presence of cardiometabolic risk factors.
MASLD, presence of cardiometabolic risk factors AND <20/30 (female/male) gram alcohol per day;
MetALD, presence of cardiometabolic risk factors AND 20-50 / 30-60 (female/male) gram alcohol per day;
ALD+, presence of cardiometabolic risk factors AND >50/60 (female/male) gram alcohol per day;
ALD-only, no cardiometabolic risk factors AND >20/30 (female/male) gram alcohol per day.
No SLD, biopsy OR imaging suggesting no hepatic steatosis AND no significant fibrosis (<F2).
ALD, alcohol-related liver disease; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; MetALD, metabolic dysfunction and alcohol related liver disease; SLD, Steatotic liver disease

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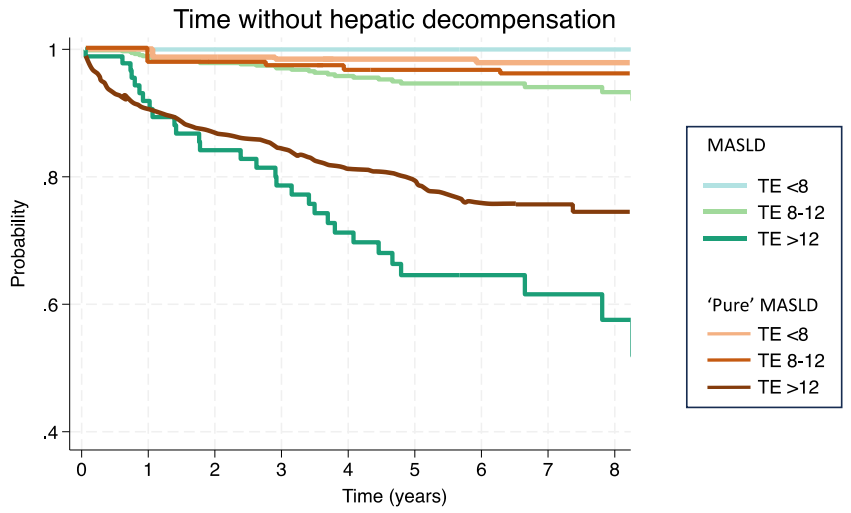

Supplementary Figure 3: Kaplan-Meier curves present risk comparisons for hepatic decompensation between the MASLD subclass in this cohort and a 'pure' MASLD cohort. The estimates for the 'pure' MASLD cohort are sourced from Boursier et al.[25] Each cohort is divided into three groups according to liver stiffness measured by transient elastography (kPa). TE, transient elastography

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Supplementary Tables

	Complete data (n=416)		Missing data (n=34)	
	≥1 CMRF	Zero CMRF	≥1 CMRF	Zero CMRF
- SLD (n=324)	295	5	23	1*
- No-SLD (n=126)	112	4	9	1
Total (n=450)	407	9	32	2

Supplementary Table 1: This table shows the distribution of the presence of at least one cardiometabolic risk factor for both patients with complete and missing cardiometabolic data. Furthermore, it illustrates how the distribution relates to whether the patients have steatotic liver disease, as it is only within this group of patients that cardiometabolic risk factors are relevant for the subclassification of patients. We identified 1 patient (marked *) who had no data for blood pressure but was otherwise free of any cardiometabolic risk factors (BMI<25 and normal levels blood glucose, HbA1c, HDL-cholesterol, Triglycerides and did not use antihypertensive drugs).

CMRF, cardiometabolic risk factors; SLD, steatotic liver disease.

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	Univariable		Multivariable	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Presence of SLD				
SLD, yes	15.39 (3.76-62.9))~~14.7 (3.58-60.0)~~	0.0001~~<0.001~~	7.01 (1.62-30.4)~~98 (1.83-34.8)~~	0.00926
Adjusting variables				
Age, years	1.01 (0.99-1.04)	0.22~~0.324~~	0.98 (0.95-1.01)	0.14~~232~~
Sex, female	1.35 (0.80-2.26)~~1.44 (0.86-2.43)~~	0.26~~0.170~~	1.68 (0.98-2.87)~~1.82 (1.06-3.12)~~	0.057~~0.030~~
~~Presence of >1 CMRF, yes~~	~~0.97 (0.49-1.91)~~	~~0.931~~	~~0.57 (0.26-3.13)~~	~~0.172~~
Liver stiffness by TE, kPa	1.05 (1.054-1.06)	<0.0001	1.05 (1.04-1.06)	<0.0001

Supplementary Table 21: Univariable and multivariable risk Cox regression analysis on hepatic decompensation.

SLD, Biopsy with steatosis OR imaging suggesting steatosis OR significant fibrosis (≥F2)
No SLD, biopsy OR imaging suggesting no hepatic steatosis AND no significant fibrosis (<F2).

~~CMRF, cardiometabolic risk factor;~~ SLD, Steatotic liver disease; TE, transient elastography

	Univariable		Multivariable	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Presence of SLD				
SLD, yes	4.34 (2.25-8.37)	<0.0001	2.78 (1.37-5.64)~~2.96 (1.45-6.05)~~	0.0045~~0.002~~
Adjusting variables				
Age, years	1.02 (1.00-1.04)	0.027	1.00 (0.98-1.02)	0.93~~27~~
Sex, female	1.12 (0.72-1.76)	0.61~~2~~	1.38 (0.87-2.20)~~1.39 (0.87-2.22)~~	0.17~~65~~
~~Presence of >1 CMRF, yes~~	~~0.99 (0.57-1.71)~~	~~0.960~~	~~0.69 (0.87-2.22)~~	~~0.245~~
Liver stiffness by TE, kPa	1.03 (1.02-1.04)	<0.0001	1.03 (1.02-1.034)	<0.0001

Supplementary Table 3~~2~~: Univariable and multivariable risk Cox regression analysis on overall survival.

SLD, Biopsy with steatosis OR imaging suggesting steatosis OR significant fibrosis (≥F2)
No SLD, biopsy OR imaging suggesting no hepatic steatosis AND no significant fibrosis (<F2).

CMRF, cardiometabolic risk factor; SLD, Steatotic liver disease; TE, transient elastography

	Univariable		Multivariable	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
SLD subclasses *(Reference No SLD)*				
MASLD	16.84 (4.05-70.0)~~15.5 (3.60-64.4)~~	0.0001~~<0.001~~	4.73 (1.03-21.6)~~5.21 (1.13-24.0)~~	0.045~~0.035~~
MetALD	14.0 (3.17-61.5)	0.0005~~<0.001~~	7.69 (1.66-35.6)~~8.74 (1.87-40.8)~~	0.0091~~0.006~~
ALD	13.8~~7~~ (3.13-60.3~~2~~)	0.0005~~0.001~~	10.2 (2.24-46.4)~~12.0 (2.62-55.3)~~	0.0027~~0.001~~
Adjusting variables				
Age, years	1.02~~1~~ (0.99-1.04)	0.22~~0.324~~	0.98 (0.95-1.01)	0.28~~2~~
Sex, female	1.35 (0.80-2.26)~~44 (0.86-2.43)~~	0.26~~0.170~~	1.96 (1.13-3.41)	0.035~~0.017~~
~~Presence of >1 CMRF, yes~~	~~0.97 (0.49-1.91)~~	~~0.931~~	~~0.58 (0.26-1.29)~~	~~0.183~~
Liver stiffness by TE, kPa	1.05 (1.05~~4~~-1.06)	<0.0001	1.06 (1.04-1.07)	<0.0001

Supplementary Table 4~~3~~: Univariable and multivariable risk Cox regression analysis on hepatic decompensation.

MASLD, presence of cardiometabolic risk factors AND <20/30 (female/male) gram alcohol per day;
MetALD, presence of cardiometabolic risk factors AND 20-50 / 30-60 (female/male) gram alcohol per day;
ALD, presence of cardiometabolic risk factors AND >50/60 (female/male) gram alcohol per day OR no cardiometabolic risk factors AND >20/30 (female/male) gram alcohol per day.
No SLD, biopsy OR imaging suggesting no hepatic steatosis AND no significant fibrosis (<F2).

ALD, alcohol-related liver disease~~; CMRF, cardiometabolic risk factor~~; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; MetALD, metabolic dysfunction and alcohol related liver disease; SLD, Steatotic liver disease; TE, transient elastography

	Univariable		Multivariable	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
SLD subclasses *(Reference No SLD)*				
MASLD	4.24 (2.13-8.43)	<0.0001	2.30 (1.08-4.90)~~2.45 (1.14-5.25)~~	0,031~~0.022~~
MetALD	4.04 (1.88-8.70)	0.0003~~<0.001~~	2.94 (1.31-6.58)~~3.11 (1.38-7.03)~~	0.0089~~0.006~~
ALD	4.88 (2.32-10.2)	<0.0001	3.57 (1.64-7.80)~~3.84 (1.74-8.45)~~	0.0013~~0.001~~
Adjusting variable				
Age, years	1.02 (1.00-1.04)	0.027	1.00 (0.98-1.02~~3~~)	0.95~~0.887~~
Sex, female	1.12 (0.72-1.76)	0.61~~2~~	1.44 (0.90-2.31)~~1.45 (0.91-2.33)~~	~~0.120~~0.13
~~Presence of >1 CMRF, yes~~	~~0.99 (0.57-1.71)~~	~~0.960~~	~~0.68 (0.37-1.27)~~	~~0.227~~
Liver stiffness by TE, kPa	1.03 (1.02-1.04)	<0.0001	1.03 (1.02-1.04)	<0.0001

Supplementary Table 54: Univariable and multivariable risk Cox regression analysis on all-cause mortality

MASLD, presence of cardiometabolic risk factors AND <20/30 (female/male) gram alcohol per day;
MetALD, presence of cardiometabolic risk factors AND 20-50 / 30-60 (female/male) gram alcohol per day;
ALD, presence of cardiometabolic risk factors AND >50/60 (female/male) gram alcohol per day OR no cardiometabolic risk factors AND >20/30 (female/male) gram alcohol per day.
No SLD, biopsy OR imaging suggesting no hepatic steatosis AND no significant fibrosis (<F2).

ALD, alcohol-related liver disease; ~~*CMRF, cardiometabolic risk factor;*~~ *MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease; MetALD, metabolic dysfunction and alcohol related liver disease; SLD, Steatotic liver disease; TE, transient elastography*

	Time of self-reported abstinence			
	None	**<1 year**	**1-5 years**	**>5 years**
Alcohol in follow-up	n=40	n=85	n=14	n=16
Excessive use, No	18 (47%)	30 (35%)	7 (50%)	15 (94%)
Excessive use, Yes	20 (53%)	55 (65%)	7 (50%)	1 (6%)

Supplementary Table ~~6~~5: The proportion of patients classified as MASLD with excessive alcohol intake during follow up according to the length abstinence at time of inclusion.

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