The Lancet

Steatotic liver disease

--Manuscript Draft--

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Abstract:	Steatotic Liver Disease (SLD) is the overarching term for conditions characterised by abnormal lipid accumulation in the liver (liver/hepatic steatosis). SLD encompasses what was previously termed non-alcoholic fatty liver disease (NAFLD), which is now called metabolic dysfunction associated steatotic liver disease (MASLD). Additionally, SLD includes alcohol-related liver disease (ALD) and MetALD, the new classification for the overlap between MASLD and ALD, as well as rare causes of liver steatosis. Cirrhosis is globally the 11th leading cause of death, and SLD has become the leading cause of cirrhosis in the EU and USA. SLD affects around 30% of the global population being mainly driven by obesity, type 2 diabetes, and alcohol use, but only a minor proportion with SLD progress to cirrhosis. The presence and progression of liver fibrosis, led by hepatic inflammation, is the main predictor of liver-related death across the entire spectrum of SLD. A combination of recent advancements in widely available biomarkers for early detection of liver fibrosis together with significant advancements in therapeutic interventions offer the possibility to reduce morbidity and mortality in patients with SLD. This seminar covers the recent reclassification of SLD and how it reflects clinical practice and prognosis. For early detection of liver fibrosis, we propose a collaborative diagnostic framework between primary care and liver specialists. Finally, we discuss current best practices for managing SLD, explore therapeutic targets across the spectrum of SLD and review the pipeline of drugs in development for MASLD.

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Title: Seminar: Steatotic liver disease

Dear Senior Executive Editor Sabine Kleinert and the Lancet Editorial Team,

We thank the editors of The Lancet for the opportunity to submit a revised version of the Seminar “Steatotic liver disease”, THELANCET-D-24-01868. We would like to thank the editors and the external reviewers for all their thoughtful comments, which have helped improving our manuscript.

We hereby resubmit our revised version.

We hope you will be pleased with our revised manuscript.

Sincerely,

Mads Israelsen and Aleksander Krag, On Behalf of All Authors

Point-to-point replies

Senior Executive Editor Sabine Kleinert's comments:

1) Authors need to clarify the evidence For their flow charts (Figs 2,3,5) - why should readers heed these above others? Also could be clearer about management in primary care (not just at initial diagnosis), esp given that specialist units eg Fig 5 will only see the tip of the iceberg.

Reply:
We agree with this observation and have added the evidence on which the figures are based in the legend for each figure. Additionally, we have specified how the management of SLD without advanced fibrosis should be handled in the primary care sector.

Figure 2:
We have added the following to the legend:

"*Based on the diagnostic criteria for steatotic liver disease nomenclature as established by the multisociety Delphi consensus statement in 2023.*[1]"

Reference added:

1) Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023.

Figure 3:
We have highlighted (*) the orange box, which outlines how to manage patients without advanced fibrosis in primary care and added the following underlined text to legend:

"*Patients who are classified as not having advanced fibrosis should return to primary care and/or their already ongoing non-hepatology specialised care. Risk factors for SLD should be managed at these levels according to standard guidelines (see Panel 4). If risk factors for SLD persist, patients should be re-tested after 3 years. Due to the relatively slow fibrosis progression in MASLD, re-testing may be omitted in patients with MASLD who are older than 65 years, as the ten-year risk of developing decompensated liver disease or hepatocellular carcinoma is less than 0.5% in patients with MASLD without advanced fibrosis.[2]"

We have also added references for the evidence underlying the algorithm.

1) Three-tier testing:
Canivet CM, Costentin C, Irvine KM, et al. Validation of the new 2021 EASL algorithm for the noninvasive diagnosis of advanced fibrosis in NAFLD. *Hepatology* 2023; **77**(3): 920-30.[3]

European Association for the Study of the Liver. Electronic address eee, Clinical Practice Guideline P, Chair, representative EGB, Panel m. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021; 75(3): 659-89. [4]

2) Rationalize testing and reduce the burden for healthcare systems, by using the frailty and the Charlson:

   Abeysekera KWM, Valenti L, Younossi Z, et al. Implementation of a liver health check in people with type 2 diabetes. Lancet Gastroenterol Hepatol 2024; 9(1): 83-91. [5]

3) Re-testing may be omitted in patients with MASLD who are older than 65 years, due to the relatively slow fibrosis progression in MASLD:

   Sanyal AJ, Van Natta ML, Clark J, et al. Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease. The New England journal of medicine 2021; 385(17): 1559-69. [2]

4) The statement “Although significant fibrosis would be a reasonable target, the diagnostic accuracy of existing non-invasive tests is suboptimal and we therefore focus on advanced liver fibrosis.”

   Zoncape M, Liguori A, Tsochatzis EA. Non-invasive testing and risk-stratification in patients with MASLD. Eur J Intern Med 2024; 122: 11-9.[6]

   European Association for the Study of the Liver. Electronic address eee, Clinical Practice Guideline P, Chair, representative EGB, Panel m. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021; 75(3): 659-89.[4]

Figure 5:
We agree that references for the risk estimates should be added to present the underlying evidence for this. The lower part of the figure is conceptual and covers the guidelines for follow-up care in patients with SLD, which is why we have included references to the EASL and AASLD recommendations in this area:

“… This estimation should be considered when planning follow-up care for each individual patient with SLD in alignment with current guidelines.[7-10]…

… Risk estimates for hepatic decompensation are based on the following references.[2,11-13]
Risk estimates for cardiovascular risk are based on the following references.[14-18]…”

2) you cite a reference as 'in press', we would need to see this one unless it has now been published

Reply:
This relates to two reference:

PMID: 39020089, which is now published and added to the reference list in the manuscript.

The second one is: Sripongpun et al; ”Characteristics and long-term mortality of individuals with MASLD, MetALD, and ALD, and the utility of SAFE Score”; JHEP Reports 2024.

This has been published online in JHep Reports and is Open Access on their website. The link can be found below. To avoid errors in the reference list, we have not inserted it into the manuscript via our reference software (EndNote), as it is not yet indexed on PubMed. However, we expect it to be indexed soon, as the article was published online as of June 3, 2024.

Please find this article at: https://doi.org/10.1016/j.jhepr.2024.101127

3) Your figure 3 and 4 are not fully editable, so please provide in editable format

Reply:
In the updated version, these figures have been uploaded and should now be fully editable.

4) we are going to include steatotic liver disease as a Lancet Clinic page, we there fore need a 1-page Fast Fact sheet, summarising the main pints in bulleted format, please look at an example on The Lancet Clinic site.

Reply:
We are very pleased with this, as many clinicians across various specialties encounter steatotic liver disease during their daily work. Please see below for a '1-page Fast Fact sheet.’

While reviewing examples on The Lancet Clinic site, we noticed that the Seminar: Cirrhosis includes a two-page infographic, which we believe effectively highlights the most important information. We were wondering if it might be possible to create something similar for this seminar?

Steatotic Liver Disease

Fast facts

Definition: Steatotic Liver Disease (SLD) is the overarching term for conditions characterised by abnormal lipid accumulation in the liver (hepatic steatosis). This is the new name for what was previously called fatty liver disease.

Subclasses: SLD includes several subtypes

- Metabolic dysfunction associated steatotic liver disease (MASLD): This is the new name for what was previously known as non-alcoholic fatty liver disease (NAFLD) in people with an alcohol intake <20/30 (female/male) grams of alcohol intake/day
- Alcohol-related liver disease (ALD): A subtype of SLD related to increased alcohol consumption defined as >50/60 (female/male) grams of alcohol intake/day.
- MetALD: A newly defined category that represents the overlap between MASLD and ALD defined as 20-50 / 30-60 (female/male) grams of alcohol intake/day.
- Other rare causes: Includes less common conditions that lead to hepatic steatosis.

Prevalence: SLD affects approximately 33% of the global adult population. The major risk factors include obesity, type 2 diabetes, and alcohol use. SLD has become the leading cause of cirrhosis in both the EU and USA. However, only a minor proportion of individuals with SLD progress to cirrhosis.

Early Detection: The presence and progression of liver fibrosis, driven by hepatic inflammation, is the primary predictor of liver-related death across the SLD spectrum. Recent advancements in widely available biomarkers facilitate the early detection of liver fibrosis. A diagnostic framework between primary care providers/non-liver specialists on the one hand and liver specialists on the other hand is recommended to enhance early detection efforts.

Management and Treatment: Current management focuses on preventing progression to cirrhosis through early detection of liver fibrosis. Treatment strategies for SLD combine lifestyle interventions with therapeutic approaches to reduce risk factors for progression. Recently, significant advancements in drug development for MASLD have led to a broad pipeline of therapies currently undergoing evaluation in clinical trials.

5) and finally you have declared that you have used generative AI, but I could not see this specified further in the paper, we need an exact clarification what you have used it for, which version/type...etc and a statement that you have verified and are accountable for output.

Reply
We apologize that this was not directly reported in the paper but was only mentioned as a comment to the manuscript. Based on your feedback, we have added the following to the manuscript.

“During the preparation of this work the authors used AI (ChatGTP version 4 and 4o) in order to improve language and readability. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.”

Editorial comments

All these comments are copied from the first revision's response, except for comment 7 on unpublished references, which is addressed in comment #2 from Senior Executive Editor Sabine Kleinert (see above).

1. Please provide: one preferred degree qualification per author and indicate any full professors; affiliation details (department, institute, city, state, country) for each author; full institutional correspondence address for corresponding author.

Reply: Check.

2. Please check that all author details and affiliations are correct in both the main text and appendix investigator lists (if applicable). We do not guarantee that we will fix errors or omissions after publication (if your article is accepted)

Reply: Check.

3. Please add a conflict of interest statement that matches the ICMJE forms. Authors should be referred to by their initials in this section. If there are none, then please state "The authors declared no conflicts of interest" or "The other authors declared no conflicts of interest".

Reply: Check.

4. Please add a contributors section, detailing specifically what each author did in the preparation of this manuscript. These statements should match those in your author statement forms.

Reply: This section is included in both the original and revised versions of this paper. Please see page 35, line 1.

5. We require written consent from any individuals who are cited in acknowledgments or personal communications. The following format can be used:
"I permit <corresponding author> et al to list my name in the acknowledgments section of their manuscript and I have seen a copy of the paper <full article title>"
"I permit <corresponding author> et al to cite a personal communication from me in their manuscript <full article title>"

Reply: This is not relevant for this paper.

6. We require confirmation that the paper has not been submitted to another journal, and has not been published in whole or in part elsewhere previously.

Reply: we hereby confirm, that the has not been submitted to another journal, and has not been published in whole or in part elsewhere previously

7. For papers listed in references that are "in press" we need to see a galley proof and letter from the publisher stating that it is 'in press' as well as the full expected citation (ie, publication date/volume/issue etc).

Reply: This only applies to two references:

Please see comment #2 from Senior Executive Editor Sabine Kleinert.

8. Images that have been published previously should be accompanied by a statement indicating permission to reproduce the image. If you have borrowed published images from colleagues, you must obtain permission from the publisher of the paper, not just from the authors. If all the figures are your own and have not been published before then this requirement does not apply.

Reply: After revising the figures, there are no figures that are not original, and therefore, no rights are required for reproduction.

9. Please ensure that you provide your figures in editable formats. For trial profiles (clinical trials) and study selection diagrams (systematic reviews and meta-analyses), figures must be provided as Word files (.doc or .docx) or powerpoint files (.ppt or .pptx) and made of boxes with editable text.
For any statistical images such as histograms, survival or time-to-event curves, line graphs, scatter graphs, and forest plots you should provide editable vector files (ie, the original artwork generated by the statistical package used to make the image, typically by using "Export" or "Print to file" commands); our preferred formats for these files are .eps, .pdf, or .ai. Photographic images must be provided at a minimum of 300 dpi at 107 mm wide. We cannot guarantee accurate reproduction of images without these files. For more information, please see our artwork guidelines here.

Reply: Check.

10. References should be in the Vancouver style and numbered in the order in which they first appear in the manuscript. If the references "move" from the body text into tables or figures, please maintain the sequence of citation. Please ensure tables and figures are cited correctly in the body text to prevent the need for renumbering of references should the table and figure citations subsequently move. Please ensure that reference numbering throughout the manuscript is not inserted with electronic referencing software, such as Endnote.

Reply: Check. Reference are in the Vancouver/Lancet style. Endnote is used.

11. Please supply a 150-200 word summary of your manuscript. References should not be cited in the Summary.

Reply: The original version of the paper includes a 240-word summary. Since the paper introduces new definitions of fatty liver diseases, it is essential to present these new terms in the summary to give readers the best understanding for reading the full text. As a result, the summary exceeds the recommended 200 words. We hope the editors will recognise the importance of this introduction despite the increased length.

12. Please supply a section entitled "Search strategy and selection criteria". This should state clearly the sources (databases, journals, or book reference lists, etc) of the material covered and the criteria used to include or exclude studies. Please state which search terms, languages and date ranges were used.

Reply: This section is included in both the original and revised versions of this paper. Please see page 6.

13. If your paper is a systematic review, please check our Systematic reviews and meta-analyses formatting guidelines here to ensure that your paper is formatted correctly. Please note that you will need to provide a PRISMA flowchart if so.

Reply: The paper is a Seminar.

14. *The Lancet* endorses the SAGER guidelines for reporting of sex and gender information in study design, data analyses, results and interpretation of findings: https://www.equator-network.org/reporting-guidelines/sager-guidelines/. For all study types, we encourage correct use of the terms sex (when reporting biological factors) and gender (when reporting identity, psychosocial, or cultural factors). Where possible, please report the sex and/or gender of study participants, and describe the methods used to determine sex and gender. Separate reporting of data by demographic variables, such as age and sex, facilitates pooling of data for subgroups across studies and should be routine, unless inappropriate. Please also discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data.

Reply: Sex is only briefly addressed in this paper. We adhere to the SAGER guidelines regarding this matter.

15. When discussing findings in relation to race or ethnicity, please mention how the original data defined these categories. Race and ethnicity are sociocultural constructs, not biologic traits. Thus we ask that, instead of making race-based statements about disease (“disease X is more common in Y race”), you could instead mention the original observations (eg “disease X has been observed to be more common in Y race”) and the limitations of the original data eg possible role of unmeasured socioeconomic confounders, wider structural drivers for which race or ethnicity may be surrogate measures. Consider a strengths-based approach to writing rather than a deficit discourse eg how findings might promote health and wellbeing, instead of focusing on problems (https://www.lowitja.org.au/wp-content/uploads/2023/05/deficit-discourse-strengths-based.pdf).

Reply: This paper does not discuss race or ethnicity.

16. Please supply tables as separate Word files (not excel or fdf/pdf). Each row of data should be in a separate line. Please ensure that rows and columns are not tabbed; data should be entered in cell form.

Reply: Check. To maintain an overview of the reference, we have kept also the tables and figures at the end of the manuscript, ensuring that references from these are also included in the reference list.

17. Please supply the web appendix as a single PDF file, with the pages paginated - when you refer to an item in the appendix, please refer to the page number on which it appears, not the table or section. Please note that we will be unable to correct any errors in the web appendix, including errors or omissions in author names or affiliations, following publication; as such, please check carefully when submitting.

Reply: There is no appendix for this paper.

18. Please ensure ICMJE and author statement forms have been submitted for all authors.

Reply: Check

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3. Canivet CM, Costentin C, Irvine KM, et al. Validation of the new 2021 EASL algorithm for the noninvasive diagnosis of advanced fibrosis in NAFLD. *Hepatology* 2023; **77**(3): 920-30.
4. European Association for the Study of the Liver. Electronic address eee, Clinical Practice Guideline P, Chair, representative EGB, Panel m. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *J Hepatol* 2021; **75**(3): 659-89.
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Manuscript Click here to view linked References

Seminar: Steatotic liver disease

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Main text: 5883
References: 139
Tables and Figures: 2 tables, 4 panels, 6 Figures

Abbreviations

AUDIT, Alcohol Use Disorders Identification Test-Consumption
ALD, Alcohol-related liver disease
AUD, Alcohol use disorder
AI, Artificial intelligence
AST, Aspartate aminotransferase
CDT, Carbohydrate deficient transferrin
CMRF, Cardiometabolic risk factors
CPAP, Continuous positive airway pressure
CAP, Controlled attenuation parameter
F0, No fibrosis
F1, Mild fibrosis
F2, Moderate fibrosis
F3, Severe fibrosis
F4, Cirrhosis
≥F2, Significant fibrosis ≥F2
≥F2, Advanced fibrosis
FIB-4, Fibrosis-4
GLP1, Glucagon-like protein 1
HCC, Hepatocellular carcinoma
HSD17B13, Hydroxysteroid 17-Beta Dehydrogenase 13 gen
MRI-PDFF, Magnetic Resonance Imaging Proton Density Fat Fraction
MetALD, Metabolic dysfunction and alcohol-related liver disease
MAFLD, Metabolic Dysfunction Associated Fatty Liver Disease
MASLD, Metabolic Dysfunction Associated Steatotic Liver Disease
MASH, Metabolic Dysfunction Associated Steatohepatitis
MBOAT7, Membrane Bound O-Acyltransferase Domain Containing 7
NAFLD, Non-alcoholic fatty liver disease
NASH, Non-alcoholic steatohepatitis
PNPLA3, Patatin-like phospholipase domain-containing protein 3 gen
PPAR, Peroxisome proliferator-activated receptor
PEth, Phosphatidylethanol
SGLT2i, Sodium Glucose Co-Transporter 2-inhibitors
SLD, Steatotic Liver Disease
AASLD, The American Association for the Study of Liver Disease
EASL, The European Association for the Study of the Liver
WHO, The World Health Organization
TRH, Thyroid hormone receptor
TM6SF2, Transmembrane 6 Superfamily Member 2 gen
FDA, U.S. Food and Drug Administration

Abstract

Steatotic Liver Disease (SLD) is the overarching term for conditions characterised by abnormal lipid accumulation in the liver (liver/hepatic steatosis). SLD encompasses what was previously termed non-alcoholic fatty liver disease (NAFLD), which is now called metabolic dysfunction associated steatotic liver disease (MASLD). Additionally, SLD includes alcohol-related liver disease (ALD) and 'MetALD', the new classification for the overlap between MASLD and ALD, as well as rare causes of liver steatosis. Cirrhosis is globally the 11th leading cause of death, and SLD has become the leading cause of cirrhosis in the EU and USA. SLD affects around 30% of the global population being mainly driven by obesity, type 2 diabetes, and alcohol use, but only a minor proportion with SLD progress to cirrhosis. The presence and progression of liver fibrosis, led by hepatic inflammation, is the main predictor of liver-related death across the entire spectrum of SLD. A combination of recent advancements in widely available biomarkers for early detection of liver fibrosis together with significant advancements in therapeutic interventions offer the possibility to reduce morbidity and mortality in patients with SLD.

This seminar covers the recent reclassification of SLD and how it reflects clinical practice and prognosis. For early detection of liver fibrosis, we propose a collaborative diagnostic framework between primary care and liver specialists. Finally, we discuss current best practices for managing SLD, explore therapeutic targets across the spectrum of SLD and review the pipeline of drugs in development for MASLD.

Introduction

In this seminar we address the recent reclassification and new nomenclature of fatty liver disease as Steatotic Liver Disease (SLD), encompassing what was formerly known as non-alcoholic fatty liver disease (NAFLD) (and its subtype non-alcoholic steatohepatitis (NASH)) and alcohol-related liver disease (ALD), along rare causes of liver steatosis.[1] This reclassification and new nomenclature, initiated by several regional liver societies, has resulted from a large multi-stakeholder, consensus-driven process following a strict methodology and now claims global endorsement from more than 75 societies.[2] Importantly, this shift integrates SLD within a spectrum encompassing ALD and recognises the potential co-existence of factors that synergistically drive disease progression. Given that more than 30% of the global population has liver steatosis,[3,4] and that in most countries the majority of the populations concurrently consume alcohol (with 5-15% engaging in harmful alcohol consumption),[5,6] these figures underline the far-reaching implications of this reclassification for clinical practice. The new framework, acknowledging both cardiometabolic risk factors (CMRF) and alcohol consumption, is of critical importance for various medical fields, including primary care, internal medicine, hepatology, gastroenterology, endocrinology, and obesity medicine. It also holds significant importance for public health and healthcare systems.[7] Furthermore, the SLD framework facilitates the conceptualization of SLD subclasses as a dynamic and overlapping spectrum allowing for the integration of diagnostic and management recommendations across these subclasses. This review builds on this new approach and integrates the evidence across SLD subclasses.

While liver steatosis is a common feature in many liver diseases, the vast majority of cases are associated with alcohol consumption and CMRF, particularly type 2 diabetes and overweight, or a

combination of these.[1] The group of less common causes of liver steatosis are distinct and are not the focus of this Seminar. The naming of this condition as SLD underscores liver steatosis as a central feature. However, it is well recognized that liver inflammation and fibrosis are the key clinical targets due to their association with disease severity and prognosis.[8-10]

***Panel 1*: Liver steatosis and chronic liver disease**

Liver steatosis is defined as the accumulation of lipids in the liver parenchymal cells. Alcohol use has long been recognised as a cause of liver steatosis, yet there are reports on cases of liver steatosis in people not consuming alcohol date from the 19th century, and some of these reports even already linked it to obesity and diabetes.[11] In 1980, Ludwig *et al.* described a series of patients with liver steatosis not consuming alcohol and proposed the term 'Non-Alcoholic Fatty Liver Disease' (NAFLD) as to oppose it to the well-known cause of alcohol use.[12] Since, NAFLD has been linked to metabolic dysfunction characterised mainly by obesity and diabetes.[13] NAFLD was in 2023 redefined and integrated in the spectrum of steatotic liver disease (SLD) based on a global consensus process and now endorsed by more than 75 societies across the world.

The clinical significance of liver steatosis remains debated; however, the factors that contribute to steatosis (obesity, diabetes, and alcohol) can also trigger hepatic inflammation and fibrosis. Over time, progression of liver fibrosis can lead to cirrhosis and its complications associated with significant mortality. Therefore, the detection of liver fibrosis, rather than steatosis, is the cornerstone of most initiatives aimed at identifying, intervening, and preventing symptomatic SLD.

Search strategy and selection criteria

We searched the Cochrane Library (inception – 01-24), MEDLINE (inception – 01-24), and EMBASE (inception – 01-24). We used the search terms “Steatotic Liver Disease” or “fatty liver disease” or “Non-alcoholic liver disease” or “Non-alcoholic steatohepatitis” or “Alcohol related/associated liver disease” “alcoholic liver disease” alone and in combination with the terms “fibrosis” or “biomarker”. We largely selected publications in the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are cited to provide readers with more details and more references than this Seminar has room for.

Epidemiology of Steatotic Liver Disease

The predominant risk factors for SLD include obesity, insulin resistance, and alcohol consumption. The World Health Organization (WHO) estimates that in 2022, 43% of all individuals ≥18 years were overweight (BMI>25 kg/m^2) and 16% were living with obesity (BMI>30 kg/m^2). In 2021, there were 529 million (95% uncertainty interval [UI], 500–564) people living with diabetes, and the global age-standardised total diabetes prevalence was 6.1% (5.8 to 6.5).[14] More than half of the entire global population reports regular alcohol use[15] with 1.03 billion (95% UI, 0.85 to 1.19) males (35.1% [29.1–40.7] of the male population aged ≥15 years) and 312 million (95% UI, 199–432) females (10.5% [6.72–14.6] of the female population aged ≥15 years) engaging in harmful alcohol consumption.[16] The last decades, there has been a noticeable increase in the prevalence of these risk factors, a trend projected to persist.[15] This increase is mirrored in the rising prevalence of liver steatosis, liver fibrosis, and cirrhosis.[3,6,17-19]

Presently, 33% (ranging from 25% in Western Europe to 44% in Latin America) of the global population has SLD with significant regional differences attributed to disparities in lifestyle, dietary habits, and alcohol use.[3,19] It is anticipated that the majority of individuals with liver steatosis are related to CMRF, but studies have reported that 58% underreport alcohol use when being assessed for liver disease,[20] and 12-30% with heavy alcohol use are not classified as ALD due to significantly underreporting.[21,22]

Cirrhosis is globally the 11th leading cause of death, the 2nd in Europe for years of working life lost, with 2-4% of all deaths attributed to it.[6,23,24] There are several genetic single nucleotide polymorphisms that increase the risk of developing cirrhosis in individuals with SLD. Among these, the best described are genetic risk alleles in PNPLA3, particularly the rs738409 variant. [25]These alleles are carried by approximately 20-25% of the world's population, with prevalences ranging

from 10% to 75% in different populations.[26] This genetic variation is significantly associated with increased susceptibility to liver steatosis, fibrosis, and cirrhosis.[25] The combined increase of alcohol consumption and CMRF, particularly type 2 diabetes and overweight has become the leading cause of cirrhosis in the EU and USA,[24,27] and is projected to be the same in Asia following the expected reduction of viral hepatitis B and C.[28]

1

***Panel 2*: Global prevalence of risk factors for SLD**

Risk factors for SLD:

43% have overweight.

16% live with obesity.

6% live with type 2 diabetes.

50% consume alcohol regularly.

20% drink heavy at least once a month.

16% engaging in harmful alcohol consumption.

25% carries genetic risk alleles in *PNPLA3.*

2

The new concept of steatotic liver disease

Since the first description of NAFLD,[12] it became clear that the disease was linked to what is currently known as the components of the metabolic syndrome, in particular overweight/obesity, insulin resistance, (pre)diabetes and dyslipidaemia.[13] It was rapidly acknowledged that the term 'non-alcohol fatty liver disease' did not reflect this cause of the disease, as well as the fact that the exclusionary definition of NAFLD did not allow to accurately describe chronic liver disease in the context of combined metabolic and alcohol related factors, but the nomenclature remained unchanged.

In 2020, Elslam *et al* proposed a new name and definition, with a positive criteria of Metabolic Dysfunction Associated Fatty Liver Disease (MAFLD) when steatosis was detected in the presence of metabolic alterations.[29] The proposal was an attempt to solve the problems, but had inherent limitations, most notably the fact that it allowed for co-existing disease drivers to be present without appropriately acknowledging their contributively and separate roles. Also, there is increasing evidence on the role of stigma associated with the term "fatty" in some cultures.[30] Finally, the MAFLD proposal did not result from a rigorous consensus process.[31]

Recently, a large consensus process involving a wide and comprehensive range of stakeholders and following a stringent methodology, issued a new framework of terminology and definitions to settle the issues.[1] First, the term "fatty" was replaced by "steatotic" to avoid stigma. The "old" NAFLD referring to liver steatosis in the context of CMRF is now named Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD). Second, the new nomenclature introduced the overarching concept of SLD, hence with the starting point of diagnosis being the feature of steatosis, regardless of the aetiology. This concept deliberately favours a broad differential diagnosis, stressing the

potential co-existence of multiple risk factors of liver steatosis and hence supporting a holistic care. Under the SLD umbrella there are subcategories of all potential causes of liver steatosis, with alcohol and metabolic dysfunction being the two leading aetiologies. MASLD and ALD share several central pathophysiological features starting with liver steatosis that can be accompanied by hepatic inflammation (steatohepatitis), which is considered the driver of liver fibrosis and ultimately leads to cirrhosis with complications (**Figure 1**).[32,33] Furthermore, both conditions share common genetic risk factors including single nucleotide polymorphisms in *PNPLA3*, *TM6SF2* and *HSD17B13*.[34-36] Historically, MASLD and ALD have been regarded as distinct entities, but in clinical practice many individuals have risk factors for both conditions, and this overlap adversely affects prognosis.[37,38]

The SLD subcategories are based on presence of at least one CMRF and level of alcohol use (**Figure 2**). Individuals with at least one CMRF and alcohol use below 20/30 g/day are labelled MASLD. Individuals with SLD and both at least one CMRF and alcohol use above 20/30 g/day but below 50/60 g/d are labelled MetALD and bridges the gap between MASLD and ALD (**Figure 1**).[39] If alcohol use exceeds 50/60 g/d, the main diagnosis is still Alcohol-related Liver Disease (ALD), although a contribution of CMRF to disease progression is also important in these individuals.[38,40,41] Individuals without CMRF but alcohol above 20/30 g/day are also labelled ALD.

The subclassification not only mirrors the clinical phenotype of SLD more accurately but also provide positive criteria for each subclass enabling targeted clinical trials. In this framework, people combining different risk factors for SLD and chronic liver disease can be appropriately diagnosed and managed for all contributing factors. The new framework did not change the concepts of steatohepatitis (only changing NASH to Metabolic Dysfunction Associated Steatohepatitis (MASH))

nor the liver fibrosis staging. This, and the large overlap between NAFLD and MASLD also implies that the scientific data gathered so far with the "old" nomenclature are still valid.[42,43]

A particular diagnostic challenge is posed in patients who exhibit liver fibrosis but without any diagnostic modality showing steatosis and in whom presence or history of CMRF and/or alcohol use are the only aetiological clues. Alcohol-induced steatosis typically resolves with abstinence, why many patients with a history of excessive alcohol use do not present with steatosis when undergoing assessment for liver disease.[44] Furthermore, features of steatosis and steatohepatitis tend to disappear in SLD when cirrhosis progresses.[45] Therefore, steatosis is not mandatory for the diagnosis of MASLD/MASH with advanced fibrosis or cirrhosis.[1] This also applies to patients with MetALD and ALD with significant fibrosis.[1] In these cases, excluding other relevant aetiologies is key.

Panel 3: Changes in terminology to reduce stigma

Old terms	Abbreviation	**New terms**	Abbreviation
Fatty liver disease	-	Steatotic liver disease	SLD
Non-alcoholic fatty liver disease	NAFLD	Metabolic dysfunction associated steatotic liver disease	MASLD
Non-alcoholic steatohepatitis	NASH	Metabolic dysfunction associated steatohepatitis	MASH
-	-	Metabolic and alcohol-related liver disease	MetALD
Alcoholic liver disease	ALD	Alcohol-related liver disease	ALD
Alcoholic cirrhosis		Alcohol-related cirrhosis	

Alcoholic		Person with alcohol use disorder	
Alcoholic hepatitis	AH	Alcohol-related hepatitis/ Alcohol-associated hepatitis	AH
Alcoholism	-	Alcohol use disorder	AUD

1

Clinical presentation of SLD

SLD is mostly asymptomatic in the pre-cirrhotic stages, as is the case with most causes of chronic liver disease.[46] Typically, patients present either with incidentally discovered abnormal liver blood tests or with steatotic liver on an ultrasound, most commonly performed for another indication. Of incident cases of cirrhosis, 70% are first diagnosed on an acute admission with hepatic decompensation.[17] Symptoms such as dull right upper quadrant pain or fatigue are non-specific but may impact quality of life.[47] Patients with MASLD are usually overweight or obese and might have additional features of the metabolic syndrome, such as type 2 diabetes, dyslipidaemia and/or arterial hypertension. The diagnosis of an alcohol problem is best made by the history but may be hindered by underreporting. Therefore, alcohol consumption biomarkers can be useful to help reveal and quantify recent alcohol intake.[48] There is a higher prevalence of patients with SLD among individuals with lower socioeconomic status, and these individuals are at an increased risk of developing advanced liver disease.[49,50] Once cirrhosis develops, patients can exhibit spider naevi, palmar erythema, splenomegaly or experience muscle cramps. Decompensated cirrhosis presents with ascites, hepatic encephalopathy or variceal bleeding.[46] Hepatocellular cancer is a complication of cirrhosis in SLD, but can also present in patients without cirrhosis in MASLD[51]. Laboratory findings may include increased transaminases, however patients can have persistently normal liver enzymes, even with advanced fibrosis or cirrhosis.[52] An aspartate aminotransferase (AST) higher than alanine aminotransferase (ALT) can indicate either the presence of cirrhosis or alcohol as the main driver of SLD. Hyperferritinaemia with normal transferrin saturation is a common finding and does not indicate the need for venesections, but can be associated with an increased risk of liver related events.[53] Patients with ALD might exhibit macrocytosis due to the long-term toxic effect of alcohol on the bone marrow.[54]

1

Diagnostic approach

Steatosis

SLD is usually diagnosed by ultrasound, which is often performed for an unrelated indication. Ultrasound is not very sensitive, as it can be negative when steatosis is less than 20% and is operator-dependent.[55] Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) is considered the non-invasive gold standard, but is only available in specialist centres and is currently used predominantly in the context of clinical trials.[56] Laboratory-based scores such as the Fatty Liver Index can be used in population studies.[56] The controlled attenuation parameter (CAP™) value, as part of liver assessment by Fibroscan®, has emerged as an alternative way for assessing steatosis, but needs further validation, requires specific equipment and is not widely available in non-hepatology settings.[57]

Aetiology

SLD is an umbrella term, therefore the diagnosis liver steatosis should trigger a comprehensive investigation of all potential causes.[1] The presence of abnormal liver blood tests should lead to a screen for all potential causes of liver disease, even in the presence of obvious causes such as increased alcohol use or cardiometabolic comorbidities.[46] Specifically for liver steatosis, the three most common causes (*i.e.*, alcohol, metabolic dysfunction, and drug induced liver injury) should be looked for, whereas the search for more rare causes should be triggered if the findings cannot be explained or are disproportionate to the degree of alcohol use or CMRF.

The distinction between MASLD, MetALD and ALD is not always straightforward as it is mainly based in clinical history and self-reported alcohol use.[21] Accurate assessment of alcohol history is paramount for the proper classification of individuals with SLD.[31] However, self-reported alcohol use is frequently underreported, leading to diagnostic misclassification: A retrospective study of 279

patient diagnosed with chronic liver disease, showed that 161 (58%) underreported alcohol use compared to phosphatidylethanol (PEth) levels.[20] In a study of 184 consecutive patients with presumed MASLD, 28.6% had moderate to excessive ethanol consumption based on hair ethylglucuronide testing[22]. Similarly, a register-based study from Sweden among more than 15.000 patients diagnosed with MASLD found 17% of patients to have a prior or later diagnosis of an alcohol-related illness.[21] Those patients had a considerably poorer prognosis than patients with only MASLD, underlying the clinical significance of a correct diagnosis.[21,44] For the assessment of alcohol use, the Alcohol Use Disorders Identification Test-Consumption (AUDIT) tool, developed by the WHO, or its shorter version AUDIT-C, which includes the first three questions of the full questionnaire, has been validated and translated into multiple languages.[58] Biomarkers for alcohol consumption such as the carbohydrate deficient transferrin (CDT)[59] and PEth[60] can be of value. PEth is excellent for confirming low alcohol intake and abstinence with high accuracy.[61] However, both PEth and CDT are less accurate in quantifying high alcohol intake,[61] making them less useful for differentiating between MetALD and ALD.

Steatohepatitis

Steatohepatitis is considered the primary driver of liver fibrosis, making presence of steatohepatitis an inclusion criterion in the EMA and FDA guidance of designing drug trials in patients with MASLD.[62] Both agencies also recommend the histological resolution of steatohepatitis as a surrogate marker for clinical benefit in these trials on a par with the improvement of liver fibrosis. The diagnosis of steatohepatitis is based on three histological features: steatosis (lipid droplets within hepatocytes), inflammation (infiltration of inflammatory cells in the liver lobules), and hepatocyte ballooning (cellular swelling). However, there is significant intra and inter-observer variation in the histological diagnosis of steatohepatitis,[63] and

no non-invasive methods can accurately assess hepatocyte ballooning or lobular inflammation.[64] Therefore, the assessment of steatohepatitis is not part of the diagnostic framework for early detection of fibrosis in SLD (**Figure 3**), but it currently remains mandatory for inclusion in drug trials for patients with MASLD.

Fibrosis

The presence and progression of liver fibrosis is the main predictor of liver-related events across the whole spectrum of SLD,[9,10,44] therefore biomarker development and testing approaches have been focusing on staging of liver fibrosis. Fibrosis severity has traditionally been staged on liver biopsy on a 5-point semiquantitative scale from 0 to 4: F0 (no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis), and F4 (cirrhosis).[65] Scores of ≥F2 denote significant fibrosis, while ≥F3 indicates advanced fibrosis. The presence of significant and most importantly advanced fibrosis is associated with liver-related morbidity and mortality.[9,10,66] Although SLD is prevalent in up to 30% of the adult population, only a minority has advanced liver fibrosis.[3] This implies that most patients with SLD can be managed for their metabolic comorbidities and/or excessive alcohol use in primary care, community centres and/or obesity and endocrinology clinics and will not require dedicated follow up by a hepatologist. It also has important implications for identification of liver fibrosis, as it calls for a stepwise approach using non-invasive tests for case finding of liver fibrosis with the first-tier testing performed in primary care settings (**Figure 3**).

A range of biomarkers with varying strengths are commonly used for case-finding of liver fibrosis (**Table 1**). For first-tier testing, Fibrosis-4 (FIB-4) is the most used biomarker and recommended in leading guidelines.[67,68] It is inexpensive, easy to calculate and works as a traffic light in terms of risk stratification. A value of below 1.3 has a high sensitivity and negative predictive value for advanced

fibrosis and is associated with a very low risk of liver-related events. It can therefore serve to rule-out significant liver fibrosis and need for referral and further fibrosis testing. Patients with a FIB-4 of above 1.3 should undergo further fibrosis testing with either a serum biomarker or an elastography method, usually transient elastography.[67] The Enhanced Liver Fibrosis test (ELF®) is a proprietary serum biomarker which has been validated both in MASLD and in ALD[69,70]. A cut-off of 9.8 can be used to guide secondary care referrals, while a cut-off of 11.3 is indicative of cirrhosis[71]. Values of vibration controlled transient elastography of 8 and 12 kPa have 90% sensitivity and specificity respectively for advanced fibrosis[72]. Due to the low pre-test probability of advanced fibrosis in unselected populations, a two-tier testing system will still produce over 40% of false positive results. The use of concordant independent fibrosis tests is therefore recommended in order to reduce the need for confirmatory liver biopsies.[73] This is particularly important for the selection of patients with MASLD and fibrosis who would benefit from pharmacotherapy. Liver biopsy might be required in patients with discordant results of non-invasive fibrosis assessment or in diagnostic uncertainty.

Guidelines are moving from testing for fibrosis in patients with an established diagnosis of SLD to testing in patients with risk factors for SLD, such as those with type 2 diabetes, obesity or excessive alcohol use.[67,68,74] Such strategies have important resource implications for widespread implementation and would require a substantial increase in the biomarker testing capacity outside hepatology settings. This would also require the rationalisation of the tested population, with the exclusion from testing of individuals with significant comorbidities in which the diagnosis of advanced fibrosis would not change prognosis. Ongoing studies will provide more data on the validity of such approaches.[75]

Prognostication, monitoring and clinical follow-Up

Patients with SLD have excess non-liver related mortality, which argues for the need of multidisciplinary models of care. In unselected patients with MASLD, cardiovascular disease is the main cause of death, followed by non-liver related cancers.[76] The risk of cardiovascular disease increases with worsening fibrosis severity.[77] Among people who consume alcohol, there is an almost 20% excess risk of death from cardiovascular disease, cancers, non-medical causes and all-cause mortality for every 100 g/week higher alcohol intake.[78]

Disregarding the uncommon instances of ALD without CMRF, SLD is effectively a spectrum influenced by alcohol consumption, transitioning from MASLD over MetALD to ALD with increasing worsening of prognosis.[79] Looking at the risk of hepatic decompensation, the subclasses show a stepwise increase going from MASLD, through MetALD, to ALD, with hazard ratios escalating from 5, to 8, and then to 10, compared to patients without SLD (**Figure 4**).[44] In a prospective study of 1,773 adults with MASLD, the incidence of liver-related events was 0.99 and 2.69 per 100 persons/years in patients with F3 and F4 respectively.[10] Conversely, in a prospective cohort of 462 patients with ALD, 18% developed a liver-related event after a median of 18 months.[9] Although studies suggest that the prognosis for MetALD falls between MASLD and ALD, [1+80-82] data are still limited, and the prognosis will likely to vary across populations depending on how individuals with MetALD present in terms of socioeconomic status and the severity of cardiovascular co-morbidity.[83]

[1] Sripongpun et al " Characteristics and long-term mortality of individuals with MASLD, MetALD, and ALD, and the utility of SAFE Score" JHEP Reports 2024, In Press
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Historically, MASLD and ALD have been regarded as distinct conditions, but in clinical practice many individuals have risk factors for both conditions, and this overlap adversely affects the prognosis.[37,38] Indeed, observational studies suggest a supra-additive interaction of metabolic comorbidities and alcohol intake in terms of liver-related events.[84] In a cohort of over 50,000 patients with diabetes, the attributable fraction of alcohol to the liver burden was 55%.[85] Variations in alcohol intake[44] and the level of control of metabolic comorbidities[86] have a significant impact on liver disease progression in SLD. The profound interaction between alcohol, type 2 diabetes and obesity suggests that patients harbouring multiple risk factors require more aggressive assessment, monitoring, and treatment.[84,87,88] The presence of genetic factors, such as single nucleotide polymorphisms in *PNPLA3*, *TM6SF2*, *MBOAT7* and *HSD17B13*, can influence the progression of fibrosis and the development of hepatocellular carcinoma (HCC).[89] The combination of these polymorphisms with clinical characteristics in polygenic risk scores has the potential to offer personalised monitoring strategies in the near future.[90] **Figure 5** summarizes the multiple factors that need to be taken into account when assessing patients with SLD in specialised liver units.

The level of alcohol use strongly correlates with the risk of disease progression and prognosis at any stage of SLD.[9,44,91,92] A study involving 461 individuals with a history of alcohol use and early-stage ALD demonstrated a 15% lower risk of liver-related events after 5 years among those who ceased drinking.[9] Similar findings were observed in advanced stages of ALD with decompensated disease.[91] Changes in alcohol intake can also strongly affect hypertension and dyslipidaemia, necessitating reassessment when patients alter their alcohol use.

The intensity and setting (primary *vs.* secondary care) of monitoring depends on the burden of cardiometabolic comorbidities and the presence and severity of liver fibrosis. Patients with minimal or no fibrosis can be managed in alcohol services in the presence of alcohol use disorder and/or

primary care/endocrinology settings with a focus on cardiometabolic risk in MASLD. If there is significant liver fibrosis, patients should be also managed by a hepatologist with the aim of monitoring liver disease progression, treating liver fibrosis and screening for complications of cirrhosis. Non-invasive fibrosis tests can also be used for risk stratification and longitudinal monitoring.[67] These tests including FIB-4, transient elastography and ELF also have prognostic information in SLD.[9,93] A FIB-4 < 1.3 is associated with very low risk of liver-related events. Scores specifically developed to predict the risk of liver-related events are emerging to reduce the false positive rates associated with use of current diagnostic fibrosis biomarkers.[94-96] The LiverRisk score was recently developed in a general population cohort and independently validated against clinical outcomes and can stratify people across four risk categories for predicting the liver-related prognosis.[97] Similarly, the MAF-5 score, comprising of waist circumference, BMI, diabetes, AST and platelets, was developed in the general population and validated in multiple cohorts, and also predicts the liver-related prognosis.[98] The Baveno rule-of-5 (elastography values of >5, >10, >15 and >20 KPa) can be used to stratify patients at different risks of hepatic decompenstaion.[99] Changes (improvement or worsening) in the results of non-invasive tests may be used for monitoring of the disease as they indicate improved or worsening prognosis.[100,101]

Current management of SLD

The SLD concept subsequently implies that if multiple risk factors for steatosis are present, management of all these causes is required. However, for patients with newly diagnosed SLD, initiating the treatment of all risk factors at once can be extensive and overwhelming. Therefore, it is essential to conduct a risk assessment to prioritise care, bearing in mind that the goal of any treatment is to achieve a clinically meaningful benefit (**Figure 5**). In case of a combination of both alcohol and metabolic dysfunction as causes, it can be argued that, if a combined approach is not feasible, priority is given to manage the excessive alcohol use and to tackle the cardiometabolic disease drivers as a second step. Patients with SLD who are identified with significant fibrosis should be offered a more intensive liver-directed management by a hepatologist. To date, for MASLD, these benefits have been defined by histological response, both for practice guideline recommendations and for drug development: resolution of MASH and/or improvement of fibrosis.[62] Although plausible, whether these surrogates truly result in better outcomes, still needs to be validated as only one study so far could demonstrate, in a cohort of cirrhotic patients, that fibrosis regression indeed reduces the risk of liver-related events.[102]

Body composition and weight loss

The cornerstone of treating the metabolic dysfunction associated component of SLD, whether isolated or combined with other risk factors for chronic liver disease, is the control of the CMRF as drivers of disease (**Figure 5**).[86,103] As adipose tissue dysfunction is a crucial aetiological factor, weight loss, resulting in improved adipose tissue function, improves the liver condition. Studies with paired biopsy have shown that patients need achieve 7-10% of body weight loss in order to achieve fibrosis improvement.[103] It is currently unclear whether the strategy to obtain weight (*e.g.*, caloric

restriction and increased physical activity, bariatric/metabolic surgery or weight lowering treatments) adds to the amount of weight loss. Weight lowering drugs such as glucagon-like protein 1 (GLP1) receptor agonists have been best documented, with semaglutide showing an effect size (for a subcutaneous dose of 0.4 mg) of 42% over placebo in terms of MASH resolution in non-cirrhotic patients in phase II.[104] However, eighteen months of treatment with semaglutide did not result in fibrosis regression, illustrating that a pure metabolic approach tackling the extrahepatic disease drivers is not enough to achieve fibrosis regression in such time period. Furthermore, in patients with MASH cirrhosis, despite weight loss and cardiometabolic improvement, there was no benefit in terms of fibrosis improvement.[105] However, reports from post bariatric surgery series of up to 5 years do show the possibility of fibrosis improvement by weight loss,[106] but long term maintenance of the weight loss seems necessary and does not occur in all patients.[107]

Dual and triple GLP1 receptor agonists, glucagon receptor and glucose-dependent insulinotropic polypeptide, are all being tested as specific MASH treatments and some of them are approved already for diabetes and/or obesity. Data on non-invasive markers, in particular liver steatosis content by MRI-PDFF, show promising results but data on histology have not been published yet and[108] whether they have a benefit beyond the induced weight loss remains to be established. The same holds true for Sodium Glucose Co-Transporter 2-inhibitors (SGLT2i).[109] Some guidelines recommend that these drugs can be used in for MASH in individuals meeting the criteria of the approved indications, and an associated benefit on MASH is likely,[74] but the impact on long term outcomes still needs to be established.

Pioglitazone, a peroxisome proliferator-activated receptor (PPAR) gamma agonist has Phase 2 and 4 data showing histological benefit on NASH resolution (but not fibrosis regression) and can also be used within its approved indication.[110,111] It improves overall atherosclerotic cardiovascular events

and outcomes, but caution is warranted in patients with reduced cardiac function (New York Heart Association (NYHA) class I and II heart failure) and contraindicated in NYHA class III or IV heart failure.[112]

Other CMRF treatments

Other drugs used to treat the CMRF also might have some benefit for the treatment of MASLD. Statins might slow down disease evolution towards decompensation and HCC, probably due to the vascular effect which is considered an important pathophysiological mechanism for MASH disease progression.[113,114] Aspirin and other anti-platelet treatment may have the same beneficial effect.[115] Physicians should therefore be informed and encouraged to prescribe statins and aspirin in SLD when indicated for primary or secondary prophylaxis of cardiovascular events, as these could have additional benefits of preventing liver disease progression and development of HCC.[116,117]. Besides a potential beneficial role of angiotensin-converting enzyme inhibitors[118,119] there are little or no data on the potential liver benefit of antihypertensive treatment.

Licensed anti-MASH treatments

Finally, the thyroid hormone receptor (TRH) beta agonist resmetirom has shown beneficial effect on both NASH resolution (effect size 20% for the 100 mg arm) and fibrosis regression (12% effect size for the highest dose) in phase III[120] and is the first drug to have obtained U.S. food and drug administration (FDA) accelerated approval (March 2024) for the treatment of patients with MASH and fibrosis consistent with F2-F3 and therefore likely to bring it to the market. It is hence the first drug for MASH as a formal indication. No other drugs currently are licensed for indication of MASH.

Alcohol

Any reduction in alcohol use leads to improved outcomes and should be actively pursued. Behavioural interventions and relapse prevention medications, either alone or in combination, represent the first line treatment. Screening for alcohol use, providing information, and referring patients to local addiction services are imperative. Brief motivational interventions, feasible for most clinicians, have been demonstrated to reduce alcohol consumption in a meta-analysis (mean difference −20 g/week, CI, −29 to −12).[121,122] Pharmacotherapy should be considered in all people with harmful alcohol use who cannot reduce intake with behavioural approaches. Drugs include acamprosate that reduces craving and has shown efficacy in supporting abstinence compared to placebo in a meta-analysis (risk reduction = 0.83, 95% CI 0.77 to 0.88), and naltrexone for preventing relapse (risk reduction = 0.83, 95% CI 0.75 to 0.91).[123,124] Disulfiram is not recommended due to the risk of liver toxicity and limited efficacy.

A subset of patients suffering from SLD may present with addiction to either food or alcohol, necessitating specialized treatments tailored to address conditions such as alcohol use disorder, alcohol dependence, or eating disorders. However, the majority of patients can significantly mitigate their behaviour-related risk factors through interventions readily implemented in most clinical settings.[125] Recent research involving nearly 5000 individuals revealed that providing specific information regarding liver damage, coupled with appropriate advice, led to notable improvements in behaviours related to alcohol use (excessive drinking reduced from 46% to 32%), 35% improved diet, 13% lost body weight, and 22% increased exercise.[126]

Holistic & multidisciplinary management

Management of SLD needs a holistic and multidisciplinary approach to adequately address all risk factors and associated conditions.[127] The practical implementation hereof is still maturing, and several models of care can be envisioned, tailored to local resources and organisation of health care systems.[128] Depending on the health care system, the management of cardiometabolic risk factors typically takes place with primary care physicians, but it can also occur in clinics specialising in the management of cardiometabolic risk factors and alcohol services. Such a multidisciplinary approach has, in an observational study, shown that patients with MASLD benefit from lifestyle advice, signposting to weight loss services, and pharmacological treatment of diabetes and cardiovascular risk factors, which improved both cardiovascular and liver-related parameters.[129] Another example from UK community alcohol services showed that the introduction of liver stiffness assessment for patients with alcohol problems improved their engagement and retention and also suggested that it could support the reduction in alcohol intake.[125]

Multidisciplinary care models should become the standard of care in order to tackle the multiple comorbidities of SLD and should be combined with preventive measures at a societal and individual level.[130,131]

1

Panel 4: **Standard treatments for cardiometabolic risk factors and alcohol use**

Overweight / obesity: Target is at least 7-10% weight loss through a staged approach. Start with counselling for lifestyle modification diet and exercise. Consider GLP1 receptor agonists or dual agonists or bariatric surgery if lifestyle modifications are unsuccessful in patients who fulfil the criteria for these treatments (e.g., weight lowering drugs usually BMI>30 kg/m^2 or >35 kg/m^2 with comorbidities, and surgery BMI>40 kg/m^2 or >35 kg/m^2 and comorbidities).

Type 2 diabetes: Preference for drugs that might impact on liver inflammation and/or liver fibrosis, such as GLP1 receptor agonists, SGLT2i and pioglitazone. Choice depends on BMI and comorbidities.

Hyperlipidaemia: Offer statins for primary or secondary prevention of cardiovascular events according to guidelines and treatment thresholds.

Hypertension: Start on treatment if blood pressure above 140/90 mm Hg or 130/80 mm Hg in patients with type 2 diabetes at higher cardiovascular risk. No preference for a particular drug class.

Smoking: Encourage smoking cessation and offer pharmacotherapy if required.

Sleep apnoea: Evaluate for sleep apnoea and offer continuous positive airway pressure (CPAP) if required.

Alcohol use: Any reduction at any stage of disease improves outcomes**.** Advise complete abstinence in patients with advanced fibrosis or cirrhosis. Advise avoiding binge drinking. Combination of behavioural motivational modalities and relapse prevention medication such as acamprosate or naltrexone is recommended. Individuals with AUD should be referred to specialised community programs.

2

Drug Development Across the SLD Spectrum

New therapeutic modalities for SLD are developed along the lines of the underlying aetiologies, mainly referring to MASLD [132] or ALD. MetALD represents a novel target population for drug development, with a rapidly growing interest of drug developers in this specific population that target both causes cardiometabolic and alcohol-related drivers.[132]

Novel treatments for MASLD focus mainly on endoscopic procedures and on drugs. Therapeutical targets can conceptually be separated into primarily metabolic pathways, mechanisms of cell stress and apoptosis, inflammation, fibrogenesis and genetic targets[110,133] some of them being common with MetALD and ALD (**Figure 6**). Many approaches have combined effects directly on several targets.

Many drugs are under investigation targeting MASH (**Table 2**). As mentioned, resmetirom is now licensed by the FDA for patients with MASH and moderate (F2) or severe (F3) fibrosis, but not yet in cirrhosis for which the phase III trial is ongoing. The other drugs tested in phase III are the GLP1RA semaglutide, the panPPAR agonist lanifibranor, the fibroblast growth factor 21 analogues efruxifermin and pegozafermin and the fatty acid synthase inhibitor denifanstat. The phase 2b trial of lanifibranor showed an effect size of 19% for fibrosis regression and 27% for MASH resolution after six months of treatment.[134] There were no major safety issues, and the drug was generally well tolerated, some weight gain was noted attributable most probably to the peroxisome proliferator-activated receptor gamma activity. Two studies with Fibroblast growth factor 21 (FGF21) analogues have shown positive results in phase II. The highest doses pegozafermin showed an effect size of 20% for fibrosis regression and 24% for MASH resolution after 6 months of treatment.[135] Efruxifermin showed an effect size of 21% for fibrosis regression and 61% for MASH resolution after 24 weeks of treatment.[136] However, the effect size of the trials cannot be compared due to

substantial differences in trial design and primary analysis presented. Side effects were mainly gastrointestinal in nature, sometimes leading to treatment discontinuation. Denifanstat showed an effect size of 23% for fibrosis regression and 24% for MASH resolution after 52 weeks of treatment (company announcement). Side effects were mainly gastrointestinal and dermatological.

A plethora of drugs with many different modes of action are currently under investigations, including genetic target, e.g., an siRNA lowering the mRNA expression of *PNPLA3* and a siRNA directly reducing hepatic Hydroxysteroid 17β dehydrogenase 13 *(HSD17B13)* expression.[110] The gut-liver axis can be target at several steps preventing translocation of microbial products from gut to the liver and hereby reduce liver inflammation and fibrosis progression, e.g., a gut-specific antibiotic, rifaximin-α, that is considered to improve the gut barrier might reduce progression of liver fibrosis in patients with ALD.[137]

Many drug trials primarily involve non-cirrhotic patients, a trend arisen by repeated failures in trials involving cirrhotic subjects. Such failures may stem from the disparity between drug targets and the varied disease drivers spanning the disease severity (see **Figure 6**). The prevailing model for drug approval necessitates trials in cirrhosis patients with clinical endpoints, as conducting outcome studies in earlier stages is challenging due to the slow and unpredictable progression of disease. Acknowledging this challenge, several phase III compounds are concurrently undergoing separate trials targeting cirrhotic patients. Non-invasive disease markers have been insufficiently validated as substitutes for histology or clinical outcomes to be accepted by the regulatory authorities for both accelerated/conditional and final approvals. Resmetirom nevertheless secured FDA approval without explicitly necessitating a liver biopsy, suggesting potential shifts in regulatory positions.

The group of MetALD patients represents a new important target group for clinical trials, as these patients have previously been excluded from MASH trials and as the cardiometabolic disease drivers have largely been neglected in ALD. Furthermore, there is the substantial overlap in pathophysiological, behavioural, metabolic, and genetic risk factors among MASH, MetALD and ALD (**Figure 5 and 6**) opening a promising opportunity to evaluate numerous drugs currently in development for MASH in patients with MetALD and ALD.[132,138] Preclinical evidence indicates that GLP-1 analogues and the hormone FGF21 can mitigate alcohol consumption through central neurotransmission pathways.[139,140] Clinical observations further suggest that FGF21 attenuated alcohol use individuals with SLD.[141] Semaglutide and tirzepatide have been shown to reduce the intake of alcohol additionally to inducing weight loss in people with obesity,[142] and are therefore potentially attractive in MetALD patients.

Challenges and controversies

The evolving landscape of liver disease and implementation of the SLD nomenclature as a spectrum from MASLD and MASH to ALD, presents a complex array of challenges and potential controversies that must be addressed going forward. This shift in terminology is not just semantic; it reflects a deeper understanding of the multifactorial nature of liver disease. However, it also introduces several uncertainties and research questions.

The criterium for alcohol use critically needs specificity in defining the timeframe for current and historical alcohol use to ensure correct subclassification of SLD.[44] Determining when alcohol ceases to be a primary disease driver is essential, as it influences the transition between subclasses. This is particularly significant in clinical trials, where accurate classification impacts both treatment strategies and outcome assessment. Moreover, the reliability of self-reported alcohol use is problematic due to the inaccuracies imposing a high risk of misclassification.[21,22] While biomarkers like PEth and CDT can rule out alcohol use, they are less effective in quantifying alcohol use needed for SLD subclassifcation.[59,60] Furthermore, the fluctuating nature of alcohol use over time adds another diagnostic challenge in case of absence of steatosis at the time of liver assessment. Approximately 40% of individuals show no signs of liver steatosis yet they may be at high risk of hepatic decompensation.[143] This raises the question of which fibrosis thresholds should be used.

Since the introduction of the SLD nomenclature, studies have demonstrated that almost all individuals with a current excessive alcohol use also present with CMRF. In the NHANES cohort 0.08% (95% CI 0.04–0.22) presented with ALD without CMRF.[42] In a Danish cohort of individuals with a history of excessive alcohol use, only one in 446 (0.2%) individuals presented with ALD without CMRF.[44] This shows that excessive alcohol use is closely associated with CMRF indicating that ALD without CMRF is a subgroup that will rarely be seen.

The importance of the individual CMRF is also contentious. While conditions like type 2 diabetes and obesity are strongly associated with risk of liver-related mortality, other factors like hypertension and dyslipidaemia are less. Yet, according to the SLD criteria each CMRF weight equally, which may not accurately reflect their relative importance.

Monitoring treatment responses in clinical practice, particularly using non-invasive tests, is crucial to minimize the need for liver biopsies. This approach could enhance patient comfort and reduce healthcare costs. Resmetirom, a drug for treatment of MASLD, recently secured FDA approval without explicitly necessitating a liver biopsy, suggesting potential shifts in regulatory positions.

Additionally, screening asymptomatic individuals with risk factors for liver fibrosis presents dilemmas about whom to test, the frequency of testing, and the methods employed.[144] Finally, the patient journey through the healthcare system, from home to primary care, to secondary care, and back to managing a chronic disease, is a critical aspect. The role of self-monitoring and artificial intelligence (AI) tools in managing liver disease is an emerging field that promises to revolutionise patient care. While the SLD nomenclature and diagnostic framework reflect a more nuanced understanding of liver disease, it also presents several new questions and challenges that necessitate careful consideration, consensus-building, and ongoing research.

Increasing awareness on steatotic liver disease to improve global liver health

There is a growing focus on advancing liver health through awareness and policy measures led by the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Disease (AASLD), the Lancet and the WHO.[145,146] The overall aim is to combat SLD through prevention and early detection and to inform policy measures to mitigate the structural determinants of poor liver health. Therefore, SLD should be included as part of the WHO programme on fighting non-communicable diseases.[24,145,147]

A key aspect for improving global liver health will be to change the dialogue around liver diseases to reduce stigma by shifting the narrative and adopting terminology that more accurately represents their multifactorial nature, recognising that factors beyond CMRF and alcohol contribute to SLD and promoting more open discussions about this.[30] In line with this is the aim to foster a deeper understanding of SLD among healthcare professionals, patients, and the broader public.[130] On a structural level, there is a need for a unified global effort to integrate liver health into broader health policy frameworks. This includes prevention and enhancing early diagnosis and treatment access.[24] Such structural improvements should aim to address not only liver health but also related metabolic and alcohol use disorders as part of a comprehensive approach to reduce non-communicable diseases on a broader scale.

Contributors

All authors contributed equally to both the writing and critical review of various sections of the Seminar, and all have given their approval for the final version to be submitted.

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Declaration of interests

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ET has served as a speaker for Abbvie, Dr Falk, Echosens, Novo Nordisk and Orphalan and participated in advisory boards for Alexion, Boehringer, Siemens, Merck Sharp & Dome, Novo Nordisk, Pfizer, Orphalan and Univar.

AK has served as speaker for Novo Nordisk, Norgine, Siemens and Nordic Bioscience and participated in advisory boards for Siemens, Boehringer Ingelheim and Novo Nordisk, all outside the submitted work. Research support; Norgine, Siemens, Nordic Bioscience, Astra, Echosense. Board member and co-founder Evido.

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Figures, Tables and Boxes

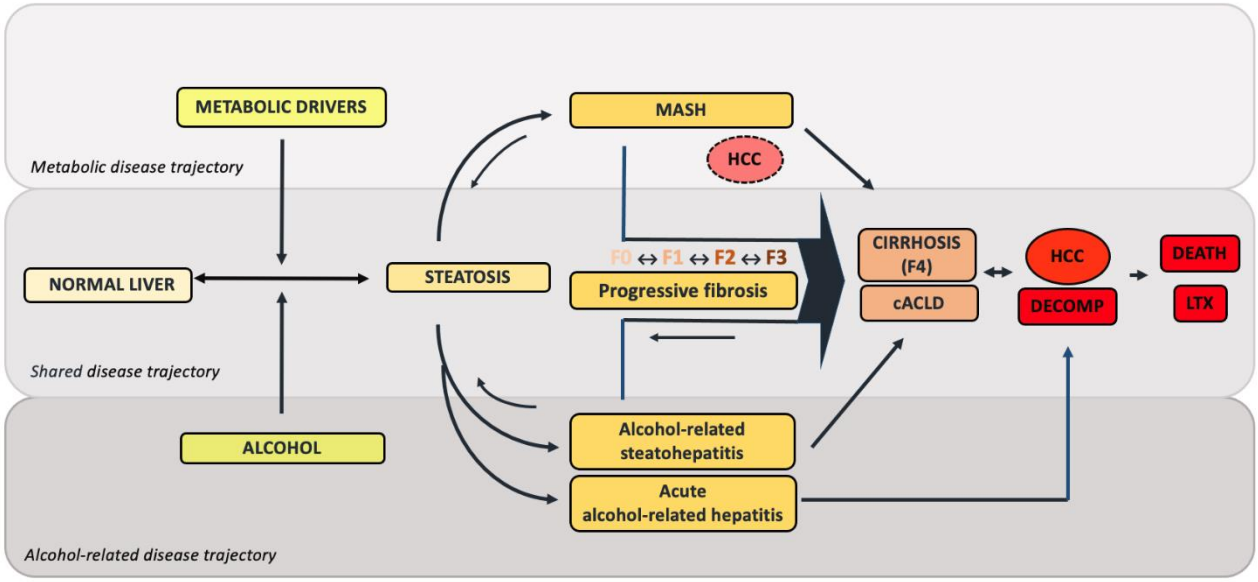

Figure 1: The natural history of SLD: In MASLD only, starting from a normal liver and depending on the balance between metabolo-inflammatory drivers and defence mechanisms, steatosis will be accompanied by steatohepatitis, which can result in progressive fibrosis ultimately leading to cirrhosis and the complications hereof.[32,33] Given the disease continuum and some intrahepatic heterogeneity, the concept of cACLD probably reflects better the transition from advanced fibrosis/F3 to cirrhosis/F4, as this is a gradual shift in severity. HCC can develop at any stage, although the risk is probably the highest in the cirrhotic stage and ill-defined in earlier stages.[148] At any stage, disease regression is possible pending improvements in the cardiometabolic milieu. Alcohol exposure induces steatosis and various degrees of hepatocyte damage depending on several risk factors.[149] Continuous exposure in susceptible people will lead to progressive fibrosis, the pattern of which might be somewhat different from MASLD but uses the same staging system. Episodes of acute severe alcohol-related hepatitis can accelerate disease progression or even lead by itself to liver decompensation. The occurrence of HCC is usually restricted to the cirrhotic stage. The natural history of people combining risk factors for MASLD and alcohol consumption is ill-defined, but they likely reinforce each other with an accelerated disease course and an increased risk of complications.
MASLD, Metabolic Dysfunction Associated Steatotic Liver Disease; MASH, Metabolic Dysfunction Associated Steatohepatitis; cACLD, compensated Advanced Chronic Liver Disease; HCC, hepatocellular carcinoma; LTX, liver transplantation.

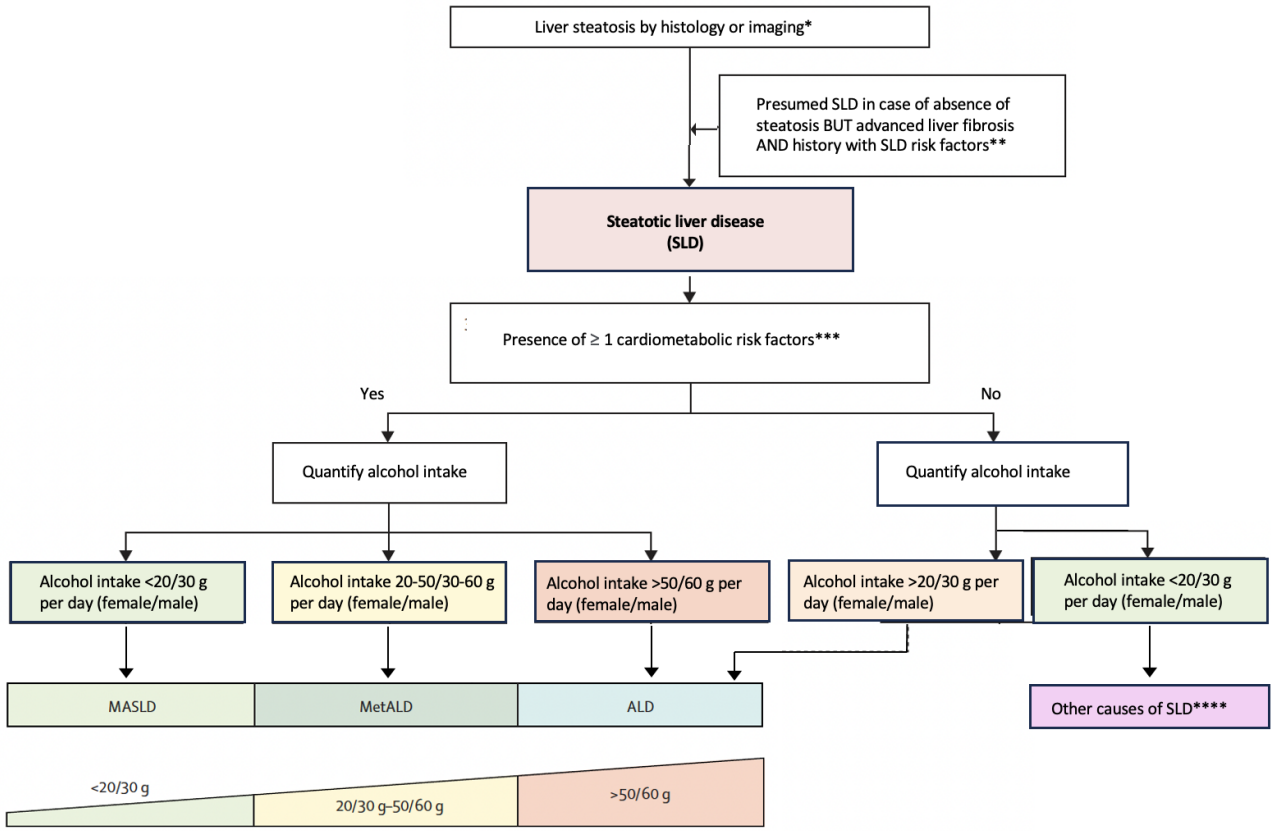

Figure 2: Flowchart showing classification and subclassification of steatotic liver disease. Based on the diagnostic criteria for steatotic liver disease nomenclature as established by the multisociety Delphi consensus statement in 2023. [1]
Specification of criteria:
* Liver steatosis is defined histologically as the presence of fat laden vacuoles in ≥ 5% of the hepatocytes.[65] Imaging including standard ultrasound and magnetic resonance imaging-proton density fat fraction can be used as non-invasive assessments for steatosis.
** Absence of steatosis may be observed if SLD risk factors are eliminated or reduced, or when extensive liver fibrosis is predominant in some cases of severe cirrhosis. However, other lesions, particularly fibrosis, are less dynamic and can persist. In cases of fibrosis without steatosis, a history of prior SLD risk factors could justify a diagnosis of presumed SLD. This includes cases with histologically confirmed advanced fibrosis (stages F3 and F4), or a corresponding liver stiffness measurement (transient elastography >12 kPa). In these cases, other causes of chronic liver disease should be carefully considered.
*** The criteria for cardiometabolic risk factors used in the definition of SLD: (1) BMI of ≥25 kg/m² (adjusted based on ethnicity), or a waist circumference ≥80 cm for women and ≥94 cm for men; (2) fasting serum glucose levels of ≥5.6 mmol/L (100 mg/dL), 2-hour post-load glucose concentrations of ≥7.8 mmol/L (140 mg/dL), glycated haemoglobin of ≥5.7% (39 mmol/mol), presence of type 2 diabetes, or treatment for type 2 diabetes; (3) blood pressure of ≥130/85 mm Hg, or the use of specific antihypertensive drugs; (4) plasma triglycerides of ≥1.70 mmol/L (150 mg/dL), or undergoing lipid-lowering treatment; and (5) plasma HDL-cholesterol levels of ≤1.3 mmol/L (40 mg/dL) for women and ≤1.0 mmol/L (50 mg/dL) for men, or receiving lipid-lowering treatment.
**** Drug-induced liver injury, monogenic diseases (Lysosomal Acid Lipase Deficiency (LALD), Wilson's disease, hypobetalipoproteinaemia, inborn errors of metabolism and miscellaneous liver disease (*e.g.*, genotype 3 Hepatitis C Virus (HCV) infection, malnutrition, celiac disease, and Human Immunodeficiency Virus (HIV) infection).

ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related liver disease; SLD, steatotic liver disease.

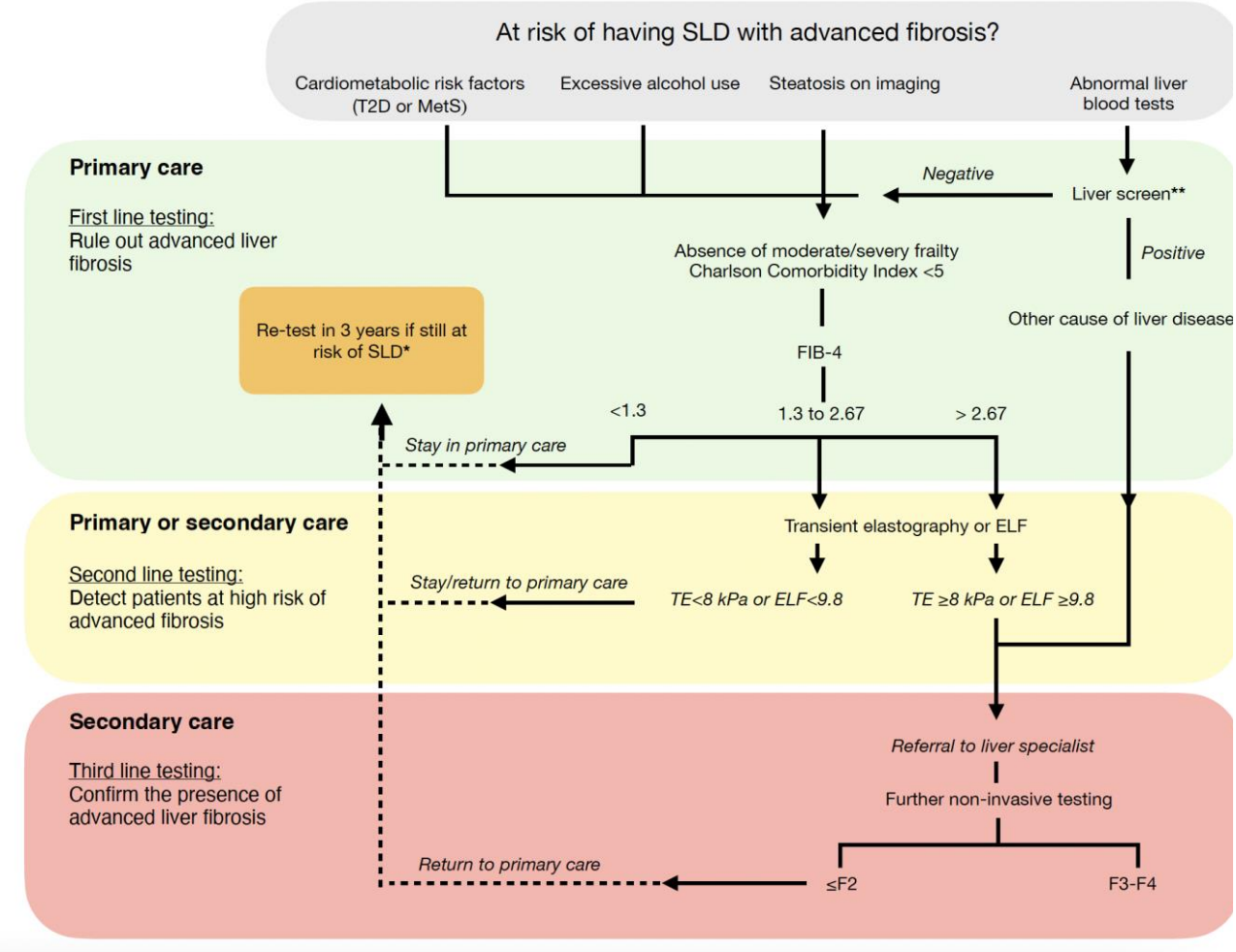

Figure 3: Diagnostic framework for early detection of advanced liver fibrosis in steatotic liver disease. The framework is validated[150] and structured around a three-tier testing process,[67] each with its specific purpose.

First-line Testing: Utilizes affordable, accessible index tests (*e.g.*, FIB-4) in primary care to rule out advanced liver fibrosis, emphasizing a high sensitivity and negative predictive value to limit further testing. Second-line Testing: Conducted in primary or secondary care depending on the healthcare system's structure. This more costly, specialized tests (*e.g.*, transient elastography or ELF) aim to detect patients at high risk of advanced fibrosis. Third-line Testing: Performed by liver specialists to confirm the presence of advanced liver fibrosis and plan a treatment strategy. This can involve further non-invasive testing or a liver biopsy, particularly in cases of discordant non-invasive test results.

In this diagnostic framework, we propose ways to rationalize testing and reduce the burden for healthcare systems, by using the frailty and the Charlson comorbidity index to select people who would benefit most.[151]

Although significant fibrosis would be a reasonable target, the diagnostic accuracy of existing non-invasive tests is suboptimal and we therefore focus on advanced liver fibrosis.[56,67]

*Patients who are classified as not having advanced fibrosis should return to primary care and/or their already ongoing non-hepatology specialised care. Risk factors for SLD should be managed at these levels according to standard guidelines (see Panel 4). If risk factors for SLD persist, patients should be re-tested after 3 years. Due to the relatively slow fibrosis progression in MASLD, re-testing may be omitted in patients with MASLD who are older than 65 years, as the ten-year risk of developing decompensated liver disease or hepatocellular carcinoma is less than 0.5% in patients with MASLD without advanced fibrosis.[10]

**Liver screen refers to the recommended investigation of an individual with prolonged abnormal liver blood tests.[152] In adults, a standard liver aetiology screen should include an abdominal ultrasound scan (USS), hepatitis B surface antigen, hepatitis C

antibody (with follow-on polymerase chain reaction (PCR) if positive), anti-mitochondrial antibody, anti-smooth muscle antibody, antinuclear antibody, serum immunoglobulins, ceruloplasmin levels in people <40 years, alpha 1-antitrypsin levels and simultaneous serum ferritin and transferrin saturation. In this context, a negative liver screen means that no other cause for the abnormal liver blood tests has been identified other than the risk factors for SLD. In the case of a negative liver screen, patients should be evaluated for liver fibrosis according to the recommended algorithm. A positive liver screen indicates that another cause for the abnormal liver blood tests has been found, and individuals should be referred directly to a liver specialist.

ELF, enhanced liver fibrosis (test); F2, significant (moderate) fibrosis; F3, Advanced (severe) fibrosis; F4, cirrhosis; FIB4, Fibrosis-4 score; MetS, metabolic syndrome; SLD, steatotic liver disease; T2D, type 2 diabetes; TE, transient elastography.

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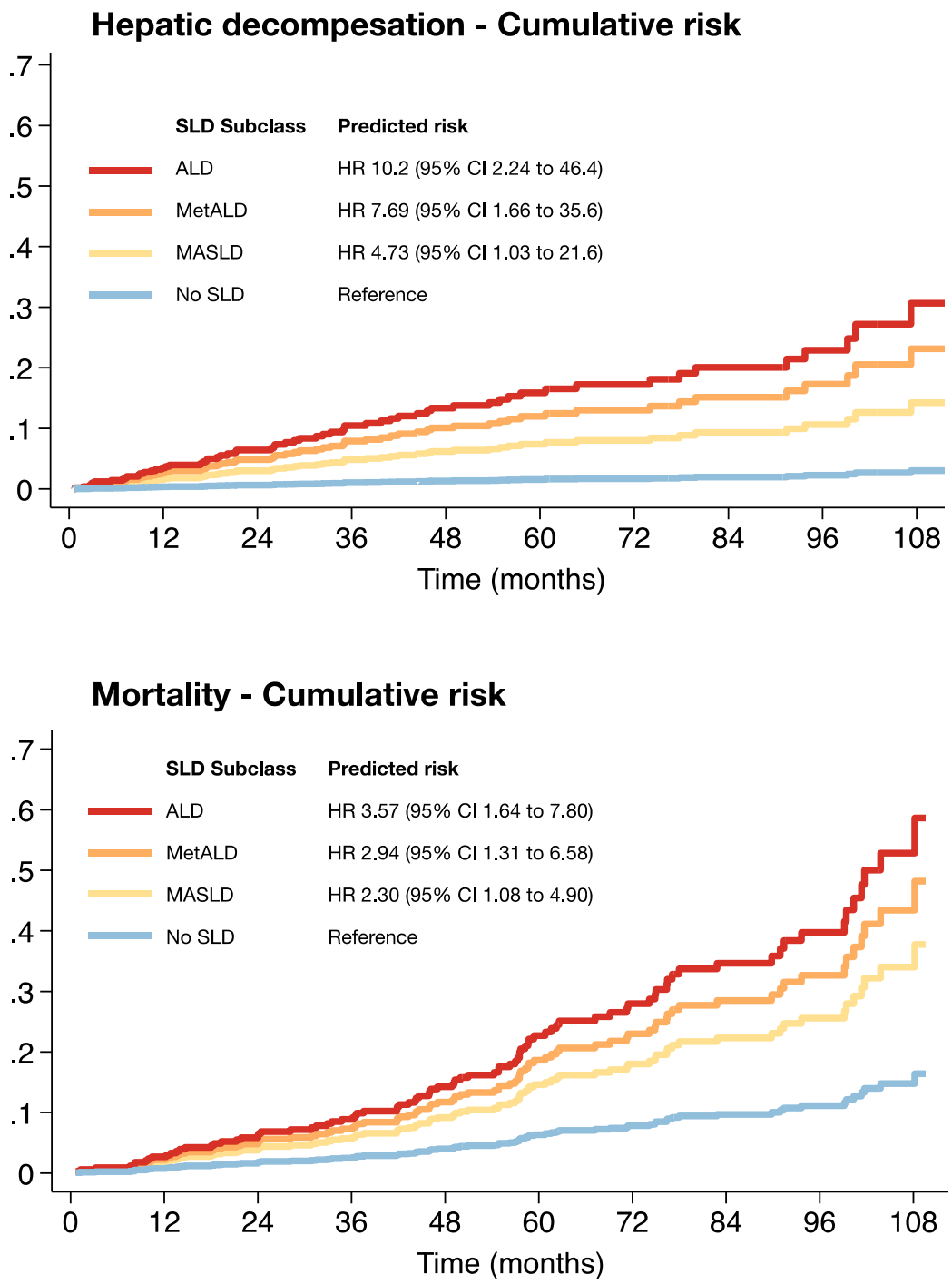

Figure 4: Predicted cumulative hazard risk curves showing distinct prognoses for the common subclasses of SLD. Models are adjusted for age, sex, and liver stiffness and based on data from[44].

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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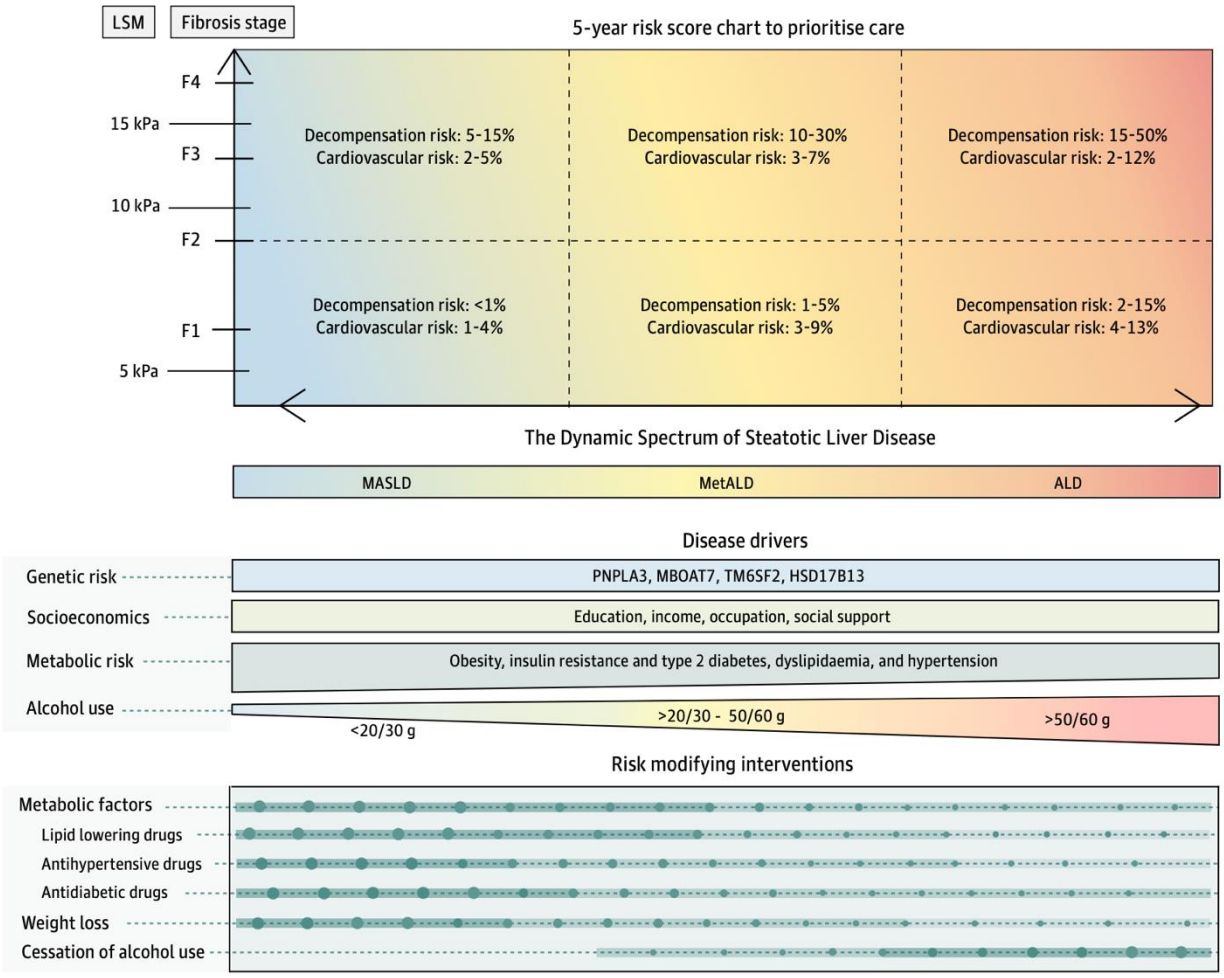

Figure 5: How to evaluate patients with steatotic liver disease in specialised liver units.
Based on the primary evaluation of a patient with SLD, the five-year risk of progression to clinically significant hepatic and cardiovascular disease can be estimated. This estimation should be considered when planning follow-up care for each individual patient with SLD in alignment with current guidelines.[64,68,153,154] The specified values for liver stiffness measurement (LSM) refer to measurements conducted with FibroScan®. *Inspired by*[138] *with an expansion on risk modifying interventions across the spectrum of SLD and data on cardiovascular risk for patients with SLD.*[31]

Risk estimates for hepatic decompensation are based on the following references.[9,10,44,155]
Risk estimates for cardiovascular risk are based on the following references.[156-160]

ALD, alcohol-related liver disease; LS, liver stiffness; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related liver disease; SLD, steatotic liver disease

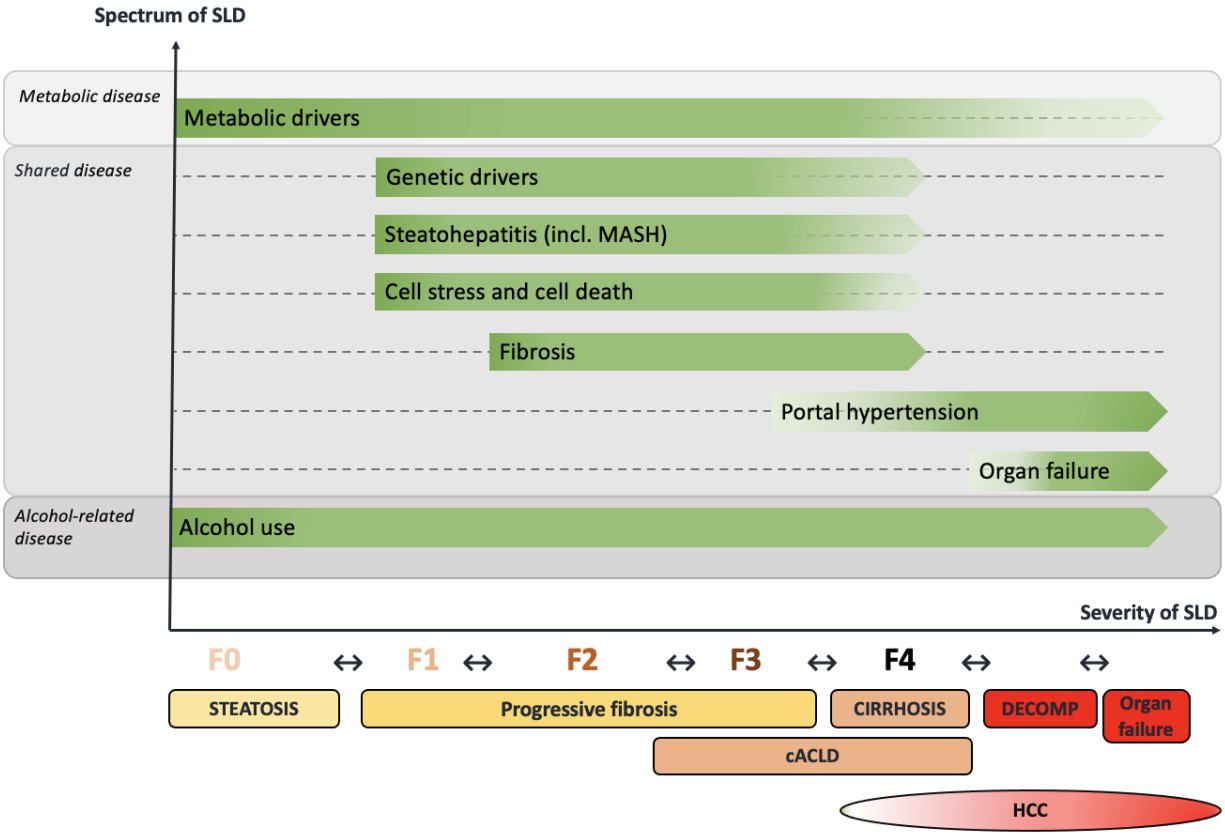

Figure 6: **Drug targets along the spectrum and severity of SLD:** Along the spectrum and severity of SLD, the role and target of different factors contributing to disease progression. The alcohol-related damage is a driver of at all severity stages of SLD. For metabolic disease (MASLD), the metabolic drivers play a dominant role. Across the spectrum of SLD, metabolic drivers and alcohol lead to steatosis and steatohepatitis. The steatohepatitis has its own intrahepatic mechanisms and drives fibrogenesis and progression towards advanced chronic liver disease and portal hypertension, and ultimately organ failure.[13] Although in more advanced disease stages and even in cirrhosis and portal hypertension, metabolic factors and intrahepatic mechanisms of cell damage and inflammation, cell stress and cell death may still play a role, even though they tend to diminish and disappear, and portal hypertension becomes a predominant driver of disease. **The green arrows** illustrate where drug targets are relevant along the spectrum and severity of SLD. Less colour intensity of the arrows symbolises less relevance of a given drug target. Drugs targeting metabolic drivers and/or intrahepatic mechanisms are more relevant at earlier time points in the disease severity and are less likely to be very efficacious in the advanced stages, where drugs tackling fibrogenesis and the (vascular) mechanisms underlying portal hypertension are more likely to be of clinical benefit.[161] Changing the lifestyle is crucial at all stages and might be supported by pharmacotherapy in the context of addiction management.

cACLD, compensated Advanced Chronic Liver Disease; DECOMP, (hepatic) decompensation; HCC, hepatocellular carcinoma; MASH, Metabolic Dysfunction Associated Steatohepatitis.

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Biomarker	Components	Setting	Cut-offs	Diagnostic accuracy for advanced fibrosis	Prognostic discrimination	Comments
LiverRisk score	Age, sex, glucose, cholesterol, AST, ALT, GGT, platelet count	First line testing	6, 10, 15	NA	HR 471 for the high-risk group	Derived in the general population.
FIB-4	Age, AST, ALT, platelet count	First line testing	<1.3, >2.67	AUROC 0.76	HR 18.76 for high cut-off	Not useful in <35 years. Age adjusted cut-off proposed for >65 years
NAFLD fibrosis score	Age, BMI, AST, ALT, type 2 diabetes, platelet count, albumin	First line testing	<-1.5, >0.67	AUROC 0.73	HR 18.51 for high cut-off	Only validated in MASLD. Performs worse than FIB-4.
ELF test	TIMP-1, PIIINP, hyaluronic acid	Second line testing	9.8	AUROC 0.83	HR 16.94 for >10.5 in ALD	Also increased in extra-hepatic fibrotic conditions. Influenced by age.
ADAPT	Pro-C3 (N-terminal type III collagen propeptide), age, diabetes and platelet count	Second line testing	6.32	AUROC 0.85	NA	Less well validated in SLD.
Transient elastography	Imaging	Second line testing	<8 KPa, >12 KPa	AUROC 0.85	HR 10.65 for >20 KPa	Needs to be performed in fasting state. Requires trained operator.
2D Shear wave elastography	Imaging	Second line testing	<8 KPa, >12 KPa	AUROC 0.85	HR 21.6 for >16.4 KPa in ALD	Needs to be performed in fasting state. Requires trained operator.
MR elastography	Imaging	Second/third line testing	3.5 KPa	AUROC 0.92	NA	Not widely available.

Table 1: The most commonly used biomarkers for fibrosis assessment and prognostication in SLD. The diagnostic accuracy and prognostic discrimination data presented derive from [9,69,93,97,162-165]. The diagnostic accuracy data refer to the diagnosis of advanced fibrosis. The prognostic discrimination refers to liver-related mortality. When dual cut-offs are presented, the low cut-off is used to rule out and the high cut-off to diagnose advanced fibrosis. Values for cut-offs, diagnostic accuracy, and prognostic discrimination are based on data from meta-analyses or studies with validation.

AUROC. Area under the receiver operating curve, GGT, gamma glutamyl transpeptidase; TIPM-1, Tissue inhibitor of metalloproteinases 1; PIIINP, aminoterminal propeptide of type III procollagen

Diagnostic accuracy refers to fibrosis stage ≥F3 (advanced fibrosis). Prognostic discrimination refers to the development of liver-related events.

Drug	Mode of action	Estimated patient enrolment	Fibrosis stage	Study duration	Endpoints	Sponsor	Clinical trial number
Semaglutide	GLP-1 receptor agonist	1200	F2-F3	Up to 5 years, interim analysis at 72 weeks	Clinical outcomes; histological for interim analysis	Novo Nordisk	NCT04822181
Resmetirom*	THRb agonist	1759 (actual)	F2-F3	Up to 5 years, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Madrigal Pharmaceuticals	NCT03900429
Resmetirom	THRb agonist	700	F4		Clinical outcomes	Madrigal Pharmaceuticals	NCT05500222
Lanifibranor	Pan-PPAR agonist	1000	F2-F3	72 weeks, with a further 48 week follow up for safety	Histological	Inventiva	NCT04849728
Pegozafermin	FGF21 analogue	1050	F2-F3	88 weeks, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	89Bio	NCT06318169
Efruxifermin	FGF21 analogue	1000	F2-F3	Unknown, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Akero Therapeutics	NCT06215716
Efruxifermin	FGF21 analogue	600	MASLD/MASH based on biopsy or non-invasive testing	52 weeks	Safety and tolerability	Akero Therapeutics	NCT06161571
Denifanstat	FASN inhibitor	TBC	TBC	TBC	TBC	Sagimet	TBC**

Table 2: Current phase III drug trials in MASLD.

*Results have been reported[120], **Phase III study has been announced, details to be confirmed

FASN; fatty acid synthase, FGF21, Fibroblast growth factor 21; GLP-1, glucagon-like peptide 1; MASLD: metabolic dysfunction associated steatotic liver disease; MASH, Metabolic Dysfunction Associated Steatohepatitis; PPAR, peroxisome proliferator-activated receptor, THRb: Thyroid hormone receptor b; TBC: to be confirmed

Manuscript with revisions highlighted Click here to view linked References

Seminar: Steatotic liver disease

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Abbreviations

AUDIT, Alcohol Use Disorders Identification Test-Consumption
ALD, Alcohol-related liver disease
AUD, Alcohol use disorder
AI, Artificial intelligence
AST, Aspartate aminotransferase
CDT, Carbohydrate deficient transferrin
CMRF, Cardiometabolic risk factors
CPAP, Continuous positive airway pressure
CAP, Controlled attenuation parameter
F0, No fibrosis
F1, Mild fibrosis
F2, Moderate fibrosis
F3, Severe fibrosis
F4, Cirrhosis
≥F2, Significant fibrosis ≥F2
≥F2, Advanced fibrosis
FIB-4, Fibrosis-4
GLP1, Glucagon-like protein 1
HCC, Hepatocellular carcinoma
HSD17B13, Hydroxysteroid 17-Beta Dehydrogenase 13 gen
MRI-PDFF, Magnetic Resonance Imaging Proton Density Fat Fraction
MetALD, Metabolic dysfunction and alcohol-related liver disease
MAFLD, Metabolic Dysfunction Associated Fatty Liver Disease
MASLD, Metabolic Dysfunction Associated Steatotic Liver Disease
MASH, Metabolic Dysfunction Associated Steatohepatitis
MBOAT7, Membrane Bound O-Acyltransferase Domain Containing 7
NAFLD, Non-alcoholic fatty liver disease
NASH, Non-alcoholic steatohepatitis
PNPLA3, Patatin-like phospholipase domain-containing protein 3 gen
PPAR, Peroxisome proliferator-activated receptor
PEth, Phosphatidylethanol
SGLT2i, Sodium Glucose Co-Transporter 2-inhibitors
SLD, Steatotic Liver Disease
AASLD, The American Association for the Study of Liver Disease
EASL, The European Association for the Study of the Liver
WHO, The World Health Organization
TRH, Thyroid hormone receptor
TM6SF2, Transmembrane 6 Superfamily Member 2 gen
FDA, U.S. Food and Drug Administration

Abstract

Steatotic Liver Disease (SLD) is the overarching term for conditions characterised by abnormal lipid accumulation in the liver (liver/hepatic steatosis). SLD encompasses what was previously termed non-alcoholic fatty liver disease (NAFLD), which is now called metabolic dysfunction associated steatotic liver disease (MASLD). Additionally, SLD includes alcohol-related liver disease (ALD) and 'MetALD', the new classification for the overlap between MASLD and ALD, as well as rare causes of liver steatosis. Cirrhosis is globally the 11th leading cause of death, and SLD has become the leading cause of cirrhosis in the EU and USA. SLD affects around 30% of the global population being mainly driven by obesity, type 2 diabetes, and alcohol use, but only a minor proportion with SLD progress to cirrhosis. The presence and progression of liver fibrosis, led by hepatic inflammation, is the main predictor of liver-related death across the entire spectrum of SLD. A combination of recent advancements in widely available biomarkers for early detection of liver fibrosis together with significant advancements in therapeutic interventions offer the possibility to reduce morbidity and mortality in patients with SLD.

This seminar covers the recent reclassification of SLD and how it reflects clinical practice and prognosis. For early detection of liver fibrosis, we propose a collaborative diagnostic framework between primary care and liver specialists. Finally, we discuss current best practices for managing SLD, explore therapeutic targets across the spectrum of SLD and review the pipeline of drugs in development for MASLD.

Introduction

In this seminar we address the recent reclassification and new nomenclature of fatty liver disease as Steatotic Liver Disease (SLD), encompassing what was formerly known as non-alcoholic fatty liver disease (NAFLD) (and its subtype non-alcoholic steatohepatitis (NASH)) and alcohol-related liver disease (ALD), along rare causes of liver steatosis.[1] This reclassification and new nomenclature, initiated by several regional liver societies, has resulted from a large multi-stakeholder, consensus-driven process following a strict methodology and now claims global endorsement from more than 75 societies.[2] Importantly, this shift integrates SLD within a spectrum encompassing ALD and recognises the potential co-existence of factors that synergistically drive disease progression. Given that more than 30% of the global population has liver steatosis,[3,4] and that in most countries the majority of the populations concurrently consume alcohol (with 5-15% engaging in harmful alcohol consumption),[5,6] these figures underline the far-reaching implications of this reclassification for clinical practice. The new framework, acknowledging both cardiometabolic risk factors (CMRF) and alcohol consumption, is of critical importance for various medical fields, including primary care, internal medicine, hepatology, gastroenterology, endocrinology, and obesity medicine. It also holds significant importance for public health and healthcare systems.[7] Furthermore, the SLD framework facilitates the conceptualization of SLD subclasses as a dynamic and overlapping spectrum allowing for the integration of diagnostic and management recommendations across these subclasses. This review builds on this new approach and integrates the evidence across SLD subclasses.

While liver steatosis is a common feature in many liver diseases, the vast majority of cases are associated with alcohol consumption and CMRF, particularly type 2 diabetes and overweight, or a

combination of these.[1] The group of less common causes of liver steatosis are distinct and are not the focus of this Seminar. The naming of this condition as SLD underscores liver steatosis as a central feature. However, it is well recognized that liver inflammation and fibrosis are the key clinical targets due to their association with disease severity and prognosis.[8-10]

***Panel 1*: Liver steatosis and chronic liver disease**

Liver steatosis is defined as the accumulation of lipids in the liver parenchymal cells. Alcohol use has long been recognised as a cause of liver steatosis, yet there are reports on cases of liver steatosis in people not consuming alcohol date from the 19th century, and some of these reports even already linked it to obesity and diabetes.[11] In 1980, Ludwig *et al.* described a series of patients with liver steatosis not consuming alcohol and proposed the term 'Non-Alcoholic Fatty Liver Disease' (NAFLD) as to oppose it to the well-known cause of alcohol use.[12] Since, NAFLD has been linked to metabolic dysfunction characterised mainly by obesity and diabetes.[13] NAFLD was in 2023 redefined and integrated in the spectrum of steatotic liver disease (SLD) based on a global consensus process and now endorsed by more than 75 societies across the world.

The clinical significance of liver steatosis remains debated; however, the factors that contribute to steatosis (obesity, diabetes, and alcohol) can also trigger hepatic inflammation and fibrosis. Over time, progression of liver fibrosis can lead to cirrhosis and its complications associated with significant mortality. Therefore, the detection of liver fibrosis, rather than steatosis, is the cornerstone of most initiatives aimed at identifying, intervening, and preventing symptomatic SLD.

Search strategy and selection criteria

We searched the Cochrane Library (inception – 01-24), MEDLINE (inception – 01-24), and EMBASE (inception – 01-24). We used the search terms “Steatotic Liver Disease” or “fatty liver disease” or “Non-alcoholic liver disease” or “Non-alcoholic steatohepatitis” or “Alcohol related/associated liver disease” “alcoholic liver disease” alone and in combination with the terms “fibrosis” or “biomarker”. We largely selected publications in the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are cited to provide readers with more details and more references than this Seminar has room for.

Epidemiology of Steatotic Liver Disease

The predominant risk factors for SLD include obesity, insulin resistance, and alcohol consumption. The World Health Organization (WHO) estimates that in 2022, 43% of all individuals ≥18 years were overweight (BMI>25 kg/m^2) and 16% were living with obesity (BMI>30 kg/m^2). In 2021, there were 529 million (95% uncertainty interval [UI], 500–564) people living with diabetes, and the global age-standardised total diabetes prevalence was 6.1% (5.8 to 6.5).[14] More than half of the entire global population reports regular alcohol use[15] with 1.03 billion (95% UI, 0.85 to 1.19) males (35.1% [29.1–40.7] of the male population aged ≥15 years) and 312 million (95% UI, 199–432) females (10.5% [6.72–14.6] of the female population aged ≥15 years) engaging in harmful alcohol consumption.[16] The last decades, there has been a noticeable increase in the prevalence of these risk factors, a trend projected to persist.[15] This increase is mirrored in the rising prevalence of liver steatosis, liver fibrosis, and cirrhosis.[3,6,17-19]

Presently, 33% (ranging from 25% in Western Europe to 44% in Latin America) of the global population has SLD with significant regional differences attributed to disparities in lifestyle, dietary habits, and alcohol use.[3,19] It is anticipated that the majority of individuals with liver steatosis are related to CMRF, but studies have reported that 58% underreport alcohol use when being assessed for liver disease,[20] and 12-30% with heavy alcohol use are not classified as ALD due to significantly underreporting.[21,22]

Cirrhosis is globally the 11th leading cause of death, the 2nd in Europe for years of working life lost, with 2-4% of all deaths attributed to it.[6,23,24] There are several genetic single nucleotide polymorphisms that increase the risk of developing cirrhosis in individuals with SLD. Among these, the best described are genetic risk alleles in PNPLA3, particularly the rs738409 variant. [25]These alleles are carried by approximately 20-25% of the world's population, with prevalences ranging

from 10% to 75% in different populations.[26] This genetic variation is significantly associated with increased susceptibility to liver steatosis, fibrosis, and cirrhosis.[25] The combined increase of alcohol consumption and CMRF, particularly type 2 diabetes and overweight has become the leading cause of cirrhosis in the EU and USA,[24,27] and is projected to be the same in Asia following the expected reduction of viral hepatitis B and C.[28]

1

***Panel 2*: Global prevalence of risk factors for SLD**

Risk factors for SLD:

43% have overweight.

16% live with obesity.

6% live with type 2 diabetes.

50% consume alcohol regularly.

20% drink heavy at least once a month.

16% engaging in harmful alcohol consumption.

25% carries genetic risk alleles in *PNPLA3.*

2

The new concept of steatotic liver disease

Since the first description of NAFLD,[12] it became clear that the disease was linked to what is currently known as the components of the metabolic syndrome, in particular overweight/obesity, insulin resistance, (pre)diabetes and dyslipidaemia.[13] It was rapidly acknowledged that the term 'non-alcohol fatty liver disease' did not reflect this cause of the disease, as well as the fact that the exclusionary definition of NAFLD did not allow to accurately describe chronic liver disease in the context of combined metabolic and alcohol related factors, but the nomenclature remained unchanged.

In 2020, Elslam *et al* proposed a new name and definition, with a positive criteria of Metabolic Dysfunction Associated Fatty Liver Disease (MAFLD) when steatosis was detected in the presence of metabolic alterations.[29] The proposal was an attempt to solve the problems, but had inherent limitations, most notably the fact that it allowed for co-existing disease drivers to be present without appropriately acknowledging their contributively and separate roles. Also, there is increasing evidence on the role of stigma associated with the term "fatty" in some cultures.[30] Finally, the MAFLD proposal did not result from a rigorous consensus process.[31]

Recently, a large consensus process involving a wide and comprehensive range of stakeholders and following a stringent methodology, issued a new framework of terminology and definitions to settle the issues.[1] First, the term "fatty" was replaced by "steatotic" to avoid stigma. The "old" NAFLD referring to liver steatosis in the context of CMRF is now named Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD). Second, the new nomenclature introduced the overarching concept of SLD, hence with the starting point of diagnosis being the feature of steatosis, regardless of the aetiology. This concept deliberately favours a broad differential diagnosis, stressing the

potential co-existence of multiple risk factors of liver steatosis and hence supporting a holistic care. Under the SLD umbrella there are subcategories of all potential causes of liver steatosis, with alcohol and metabolic dysfunction being the two leading aetiologies. MASLD and ALD share several central pathophysiological features starting with liver steatosis that can be accompanied by hepatic inflammation (steatohepatitis), which is considered the driver of liver fibrosis and ultimately leads to cirrhosis with complications (**Figure 1**).[32,33] Furthermore, both conditions share common genetic risk factors including single nucleotide polymorphisms in *PNPLA3*, *TM6SF2* and *HSD17B13*.[34-36] Historically, MASLD and ALD have been regarded as distinct entities, but in clinical practice many individuals have risk factors for both conditions, and this overlap adversely affects prognosis.[37,38]

The SLD subcategories are based on presence of at least one CMRF and level of alcohol use (**Figure 2**). Individuals with at least one CMRF and alcohol use below 20/30 g/day are labelled MASLD. Individuals with SLD and both at least one CMRF and alcohol use above 20/30 g/day but below 50/60 g/d are labelled MetALD and bridges the gap between MASLD and ALD (**Figure 1**).[39] If alcohol use exceeds 50/60 g/d, the main diagnosis is still Alcohol-related Liver Disease (ALD), although a contribution of CMRF to disease progression is also important in these individuals.[38,40,41] Individuals without CMRF but alcohol above 20/30 g/day are also labelled ALD.

The subclassification not only mirrors the clinical phenotype of SLD more accurately but also provide positive criteria for each subclass enabling targeted clinical trials. In this framework, people combining different risk factors for SLD and chronic liver disease can be appropriately diagnosed and managed for all contributing factors. The new framework did not change the concepts of steatohepatitis (only changing NASH to Metabolic Dysfunction Associated Steatohepatitis (MASH))

nor the liver fibrosis staging. This, and the large overlap between NAFLD and MASLD also implies that the scientific data gathered so far with the "old" nomenclature are still valid.[42,43]

A particular diagnostic challenge is posed in patients who exhibit liver fibrosis but without any diagnostic modality showing steatosis and in whom presence or history of CMRF and/or alcohol use are the only aetiological clues. Alcohol-induced steatosis typically resolves with abstinence, why many patients with a history of excessive alcohol use do not present with steatosis when undergoing assessment for liver disease.[44] Furthermore, features of steatosis and steatohepatitis tend to disappear in SLD when cirrhosis progresses.[45] Therefore, steatosis is not mandatory for the diagnosis of MASLD/MASH with advanced fibrosis or cirrhosis.[1] This also applies to patients with MetALD and ALD with significant fibrosis.[1] In these cases, excluding other relevant aetiologies is key.

Panel 3: Changes in terminology to reduce stigma

Old terms	Abbreviation	**New terms**	Abbreviation
Fatty liver disease	-	Steatotic liver disease	SLD
Non-alcoholic fatty liver disease	NAFLD	Metabolic dysfunction associated steatotic liver disease	MASLD
Non-alcoholic steatohepatitis	NASH	Metabolic dysfunction associated steatohepatitis	MASH
-	-	Metabolic and alcohol-related liver disease	MetALD
Alcoholic liver disease	ALD	Alcohol-related liver disease	ALD
Alcoholic cirrhosis		Alcohol-related cirrhosis	

Alcoholic		Person with alcohol use disorder	
Alcoholic hepatitis	AH	Alcohol-related hepatitis/ Alcohol-associated hepatitis	AH
Alcoholism	-	Alcohol use disorder	AUD

1

Clinical presentation of SLD

SLD is mostly asymptomatic in the pre-cirrhotic stages, as is the case with most causes of chronic liver disease.[46] Typically, patients present either with incidentally discovered abnormal liver blood tests or with steatotic liver on an ultrasound, most commonly performed for another indication. Of incident cases of cirrhosis, 70% are first diagnosed on an acute admission with hepatic decompensation.[17] Symptoms such as dull right upper quadrant pain or fatigue are non-specific but may impact quality of life.[47] Patients with MASLD are usually overweight or obese and might have additional features of the metabolic syndrome, such as type 2 diabetes, dyslipidaemia and/or arterial hypertension. The diagnosis of an alcohol problem is best made by the history but may be hindered by underreporting. Therefore, alcohol consumption biomarkers can be useful to help reveal and quantify recent alcohol intake.[48] There is a higher prevalence of patients with SLD among individuals with lower socioeconomic status, and these individuals are at an increased risk of developing advanced liver disease.[49,50] Once cirrhosis develops, patients can exhibit spider naevi, palmar erythema, splenomegaly or experience muscle cramps. Decompensated cirrhosis presents with ascites, hepatic encephalopathy or variceal bleeding.[46] Hepatocellular cancer is a complication of cirrhosis in SLD, but can also present in patients without cirrhosis in MASLD[51]. Laboratory findings may include increased transaminases, however patients can have persistently normal liver enzymes, even with advanced fibrosis or cirrhosis.[52] An aspartate aminotransferase (AST) higher than alanine aminotransferase (ALT) can indicate either the presence of cirrhosis or alcohol as the main driver of SLD. Hyperferritinaemia with normal transferrin saturation is a common finding and does not indicate the need for venesections, but can be associated with an increased risk of liver related events.[53] Patients with ALD might exhibit macrocytosis due to the long-term toxic effect of alcohol on the bone marrow.[54]

1

Diagnostic approach

Steatosis

SLD is usually diagnosed by ultrasound, which is often performed for an unrelated indication. Ultrasound is not very sensitive, as it can be negative when steatosis is less than 20% and is operator-dependent.[55] Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) is considered the non-invasive gold standard, but is only available in specialist centres and is currently used predominantly in the context of clinical trials.[56] Laboratory-based scores such as the Fatty Liver Index can be used in population studies.[56] The controlled attenuation parameter (CAP™) value, as part of liver assessment by Fibroscan®, has emerged as an alternative way for assessing steatosis, but needs further validation, requires specific equipment and is not widely available in non-hepatology settings.[57]

Aetiology

SLD is an umbrella term, therefore the diagnosis liver steatosis should trigger a comprehensive investigation of all potential causes.[1] The presence of abnormal liver blood tests should lead to a screen for all potential causes of liver disease, even in the presence of obvious causes such as increased alcohol use or cardiometabolic comorbidities.[46] Specifically for liver steatosis, the three most common causes (*i.e.*, alcohol, metabolic dysfunction, and drug induced liver injury) should be looked for, whereas the search for more rare causes should be triggered if the findings cannot be explained or are disproportionate to the degree of alcohol use or CMRF.

The distinction between MASLD, MetALD and ALD is not always straightforward as it is mainly based in clinical history and self-reported alcohol use.[21] Accurate assessment of alcohol history is paramount for the proper classification of individuals with SLD.[31] However, self-reported alcohol use is frequently underreported, leading to diagnostic misclassification: A retrospective study of 279

patient diagnosed with chronic liver disease, showed that 161 (58%) underreported alcohol use compared to phosphatidylethanol (PEth) levels.[20] In a study of 184 consecutive patients with presumed MASLD, 28.6% had moderate to excessive ethanol consumption based on hair ethylglucuronide testing[22]. Similarly, a register-based study from Sweden among more than 15.000 patients diagnosed with MASLD found 17% of patients to have a prior or later diagnosis of an alcohol-related illness.[21] Those patients had a considerably poorer prognosis than patients with only MASLD, underlying the clinical significance of a correct diagnosis.[21,44] For the assessment of alcohol use, the Alcohol Use Disorders Identification Test-Consumption (AUDIT) tool, developed by the WHO, or its shorter version AUDIT-C, which includes the first three questions of the full questionnaire, has been validated and translated into multiple languages.[58] Biomarkers for alcohol consumption such as the carbohydrate deficient transferrin (CDT)[59] and PEth[60] can be of value. PEth is excellent for confirming low alcohol intake and abstinence with high accuracy.[61] However, both PEth and CDT are less accurate in quantifying high alcohol intake,[61] making them less useful for differentiating between MetALD and ALD.

Steatohepatitis

Steatohepatitis is considered the primary driver of liver fibrosis, making presence of steatohepatitis an inclusion criterion in the EMA and FDA guidance of designing drug trials in patients with MASLD.[62] Both agencies also recommend the histological resolution of steatohepatitis as a surrogate marker for clinical benefit in these trials on a par with the improvement of liver fibrosis. The diagnosis of steatohepatitis is based on three histological features: steatosis (lipid droplets within hepatocytes), inflammation (infiltration of inflammatory cells in the liver lobules), and hepatocyte ballooning (cellular swelling). However, there is significant intra and inter-observer variation in the histological diagnosis of steatohepatitis,[63] and

no non-invasive methods can accurately assess hepatocyte ballooning or lobular inflammation.[64] Therefore, the assessment of steatohepatitis is not part of the diagnostic framework for early detection of fibrosis in SLD (**Figure 3**), but it currently remains mandatory for inclusion in drug trials for patients with MASLD.

Fibrosis

The presence and progression of liver fibrosis is the main predictor of liver-related events across the whole spectrum of SLD,[9,10,44] therefore biomarker development and testing approaches have been focusing on staging of liver fibrosis. Fibrosis severity has traditionally been staged on liver biopsy on a 5-point semiquantitative scale from 0 to 4: F0 (no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis), and F4 (cirrhosis).[65] Scores of ≥F2 denote significant fibrosis, while ≥F3 indicates advanced fibrosis. The presence of significant and most importantly advanced fibrosis is associated with liver-related morbidity and mortality.[9,10,66] Although SLD is prevalent in up to 30% of the adult population, only a minority has advanced liver fibrosis.[3] This implies that most patients with SLD can be managed for their metabolic comorbidities and/or excessive alcohol use in primary care, community centres and/or obesity and endocrinology clinics and will not require dedicated follow up by a hepatologist. It also has important implications for identification of liver fibrosis, as it calls for a stepwise approach using non-invasive tests for case finding of liver fibrosis with the first-tier testing performed in primary care settings (**Figure 3**).

A range of biomarkers with varying strengths are commonly used for case-finding of liver fibrosis (**Table 1**). For first-tier testing, Fibrosis-4 (FIB-4) is the most used biomarker and recommended in leading guidelines.[67,68] It is inexpensive, easy to calculate and works as a traffic light in terms of risk stratification. A value of below 1.3 has a high sensitivity and negative predictive value for advanced

fibrosis and is associated with a very low risk of liver-related events. It can therefore serve to rule-out significant liver fibrosis and need for referral and further fibrosis testing. Patients with a FIB-4 of above 1.3 should undergo further fibrosis testing with either a serum biomarker or an elastography method, usually transient elastography.[67] The Enhanced Liver Fibrosis test (ELF®) is a proprietary serum biomarker which has been validated both in MASLD and in ALD[69,70]. A cut-off of 9.8 can be used to guide secondary care referrals, while a cut-off of 11.3 is indicative of cirrhosis[71]. Values of vibration controlled transient elastography of 8 and 12 kPa have 90% sensitivity and specificity respectively for advanced fibrosis[72]. Due to the low pre-test probability of advanced fibrosis in unselected populations, a two-tier testing system will still produce over 40% of false positive results. The use of concordant independent fibrosis tests is therefore recommended in order to reduce the need for confirmatory liver biopsies.[73] This is particularly important for the selection of patients with MASLD and fibrosis who would benefit from pharmacotherapy. Liver biopsy might be required in patients with discordant results of non-invasive fibrosis assessment or in diagnostic uncertainty.

Guidelines are moving from testing for fibrosis in patients with an established diagnosis of SLD to testing in patients with risk factors for SLD, such as those with type 2 diabetes, obesity or excessive alcohol use.[67,68,74] Such strategies have important resource implications for widespread implementation and would require a substantial increase in the biomarker testing capacity outside hepatology settings. This would also require the rationalisation of the tested population, with the exclusion from testing of individuals with significant comorbidities in which the diagnosis of advanced fibrosis would not change prognosis. Ongoing studies will provide more data on the validity of such approaches.[75]

Prognostication, monitoring and clinical follow-Up

Patients with SLD have excess non-liver related mortality, which argues for the need of multidisciplinary models of care. In unselected patients with MASLD, cardiovascular disease is the main cause of death, followed by non-liver related cancers.[76] The risk of cardiovascular disease increases with worsening fibrosis severity.[77] Among people who consume alcohol, there is an almost 20% excess risk of death from cardiovascular disease, cancers, non-medical causes and all-cause mortality for every 100 g/week higher alcohol intake.[78]

Disregarding the uncommon instances of ALD without CMRF, SLD is effectively a spectrum influenced by alcohol consumption, transitioning from MASLD over MetALD to ALD with increasing worsening of prognosis.[79] Looking at the risk of hepatic decompensation, the subclasses show a stepwise increase going from MASLD, through MetALD, to ALD, with hazard ratios escalating from 5, to 8, and then to 10, compared to patients without SLD (**Figure 4**).[44] In a prospective study of 1,773 adults with MASLD, the incidence of liver-related events was 0.99 and 2.69 per 100 persons/years in patients with F3 and F4 respectively.[10] Conversely, in a prospective cohort of 462 patients with ALD, 18% developed a liver-related event after a median of 18 months.[9] Although studies suggest that the prognosis for MetALD falls between MASLD and ALD, [1+80-82] data are still limited, and the prognosis will likely to vary across populations depending on how individuals with MetALD present in terms of socioeconomic status and the severity of cardiovascular co-morbidity.[83]

[1] Sripongpun et al " Characteristics and long-term mortality of individuals with MASLD, MetALD, and ALD, and the utility of SAFE Score" JHEP Reports 2024, In Press
https://doi.org/10.1016/j.jhepr.2024.101127

Historically, MASLD and ALD have been regarded as distinct conditions, but in clinical practice many individuals have risk factors for both conditions, and this overlap adversely affects the prognosis.[37,38] Indeed, observational studies suggest a supra-additive interaction of metabolic comorbidities and alcohol intake in terms of liver-related events.[84] In a cohort of over 50,000 patients with diabetes, the attributable fraction of alcohol to the liver burden was 55%.[85] Variations in alcohol intake[44] and the level of control of metabolic comorbidities[86] have a significant impact on liver disease progression in SLD. The profound interaction between alcohol, type 2 diabetes and obesity suggests that patients harbouring multiple risk factors require more aggressive assessment, monitoring, and treatment.[84,87,88] The presence of genetic factors, such as single nucleotide polymorphisms in *PNPLA3*, *TM6SF2*, *MBOAT7* and *HSD17B13*, can influence the progression of fibrosis and the development of hepatocellular carcinoma (HCC).[89] The combination of these polymorphisms with clinical characteristics in polygenic risk scores has the potential to offer personalised monitoring strategies in the near future.[90] **Figure 5** summarizes the multiple factors that need to be taken into account when assessing patients with SLD in specialised liver units.

The level of alcohol use strongly correlates with the risk of disease progression and prognosis at any stage of SLD.[9,44,91,92] A study involving 461 individuals with a history of alcohol use and early-stage ALD demonstrated a 15% lower risk of liver-related events after 5 years among those who ceased drinking.[9] Similar findings were observed in advanced stages of ALD with decompensated disease.[91] Changes in alcohol intake can also strongly affect hypertension and dyslipidaemia, necessitating reassessment when patients alter their alcohol use.

The intensity and setting (primary *vs.* secondary care) of monitoring depends on the burden of cardiometabolic comorbidities and the presence and severity of liver fibrosis. Patients with minimal or no fibrosis can be managed in alcohol services in the presence of alcohol use disorder and/or

primary care/endocrinology settings with a focus on cardiometabolic risk in MASLD. If there is significant liver fibrosis, patients should be also managed by a hepatologist with the aim of monitoring liver disease progression, treating liver fibrosis and screening for complications of cirrhosis. Non-invasive fibrosis tests can also be used for risk stratification and longitudinal monitoring.[67] These tests including FIB-4, transient elastography and ELF also have prognostic information in SLD.[9,93] A FIB-4 < 1.3 is associated with very low risk of liver-related events. Scores specifically developed to predict the risk of liver-related events are emerging to reduce the false positive rates associated with use of current diagnostic fibrosis biomarkers.[94-96] The LiverRisk score was recently developed in a general population cohort and independently validated against clinical outcomes and can stratify people across four risk categories for predicting the liver-related prognosis.[97] Similarly, the MAF-5 score, comprising of waist circumference, BMI, diabetes, AST and platelets, was developed in the general population and validated in multiple cohorts, and also predicts the liver-related prognosis.[98] The Baveno rule-of-5 (elastography values of >5, >10, >15 and >20 KPa) can be used to stratify patients at different risks of hepatic decompenstaion.[99] Changes (improvement or worsening) in the results of non-invasive tests may be used for monitoring of the disease as they indicate improved or worsening prognosis.[100,101]

Current management of SLD

The SLD concept subsequently implies that if multiple risk factors for steatosis are present, management of all these causes is required. However, for patients with newly diagnosed SLD, initiating the treatment of all risk factors at once can be extensive and overwhelming. Therefore, it is essential to conduct a risk assessment to prioritise care, bearing in mind that the goal of any treatment is to achieve a clinically meaningful benefit (**Figure 5**). In case of a combination of both alcohol and metabolic dysfunction as causes, it can be argued that, if a combined approach is not feasible, priority is given to manage the excessive alcohol use and to tackle the cardiometabolic disease drivers as a second step. Patients with SLD who are identified with significant fibrosis should be offered a more intensive liver-directed management by a hepatologist. To date, for MASLD, these benefits have been defined by histological response, both for practice guideline recommendations and for drug development: resolution of MASH and/or improvement of fibrosis.[62] Although plausible, whether these surrogates truly result in better outcomes, still needs to be validated as only one study so far could demonstrate, in a cohort of cirrhotic patients, that fibrosis regression indeed reduces the risk of liver-related events.[102]

Body composition and weight loss

The cornerstone of treating the metabolic dysfunction associated component of SLD, whether isolated or combined with other risk factors for chronic liver disease, is the control of the CMRF as drivers of disease (**Figure 5**).[86,103] As adipose tissue dysfunction is a crucial aetiological factor, weight loss, resulting in improved adipose tissue function, improves the liver condition. Studies with paired biopsy have shown that patients need achieve 7-10% of body weight loss in order to achieve fibrosis improvement.[103] It is currently unclear whether the strategy to obtain weight (*e.g.*, caloric

restriction and increased physical activity, bariatric/metabolic surgery or weight lowering treatments) adds to the amount of weight loss. Weight lowering drugs such as glucagon-like protein 1 (GLP1) receptor agonists have been best documented, with semaglutide showing an effect size (for a subcutaneous dose of 0.4 mg) of 42% over placebo in terms of MASH resolution in non-cirrhotic patients in phase II.[104] However, eighteen months of treatment with semaglutide did not result in fibrosis regression, illustrating that a pure metabolic approach tackling the extrahepatic disease drivers is not enough to achieve fibrosis regression in such time period. Furthermore, in patients with MASH cirrhosis, despite weight loss and cardiometabolic improvement, there was no benefit in terms of fibrosis improvement.[105] However, reports from post bariatric surgery series of up to 5 years do show the possibility of fibrosis improvement by weight loss,[106] but long term maintenance of the weight loss seems necessary and does not occur in all patients.[107]

Dual and triple GLP1 receptor agonists, glucagon receptor and glucose-dependent insulinotropic polypeptide, are all being tested as specific MASH treatments and some of them are approved already for diabetes and/or obesity. Data on non-invasive markers, in particular liver steatosis content by MRI-PDFF, show promising results but data on histology have not been published yet and[108] whether they have a benefit beyond the induced weight loss remains to be established. The same holds true for Sodium Glucose Co-Transporter 2-inhibitors (SGLT2i).[109] Some guidelines recommend that these drugs can be used in for MASH in individuals meeting the criteria of the approved indications, and an associated benefit on MASH is likely,[74] but the impact on long term outcomes still needs to be established.

Pioglitazone, a peroxisome proliferator-activated receptor (PPAR) gamma agonist has Phase 2 and 4 data showing histological benefit on NASH resolution (but not fibrosis regression) and can also be used within its approved indication.[110,111] It improves overall atherosclerotic cardiovascular events

and outcomes, but caution is warranted in patients with reduced cardiac function (New York Heart Association (NYHA) class I and II heart failure) and contraindicated in NYHA class III or IV heart failure.[112]

Other CMRF treatments

Other drugs used to treat the CMRF also might have some benefit for the treatment of MASLD. Statins might slow down disease evolution towards decompensation and HCC, probably due to the vascular effect which is considered an important pathophysiological mechanism for MASH disease progression.[113,114] Aspirin and other anti-platelet treatment may have the same beneficial effect.[115] Physicians should therefore be informed and encouraged to prescribe statins and aspirin in SLD when indicated for primary or secondary prophylaxis of cardiovascular events, as these could have additional benefits of preventing liver disease progression and development of HCC.[116,117]. Besides a potential beneficial role of angiotensin-converting enzyme inhibitors[118,119] there are little or no data on the potential liver benefit of antihypertensive treatment.

Licensed anti-MASH treatments

Finally, the thyroid hormone receptor (TRH) beta agonist resmetirom has shown beneficial effect on both NASH resolution (effect size 20% for the 100 mg arm) and fibrosis regression (12% effect size for the highest dose) in phase III[120] and is the first drug to have obtained U.S. food and drug administration (FDA) accelerated approval (March 2024) for the treatment of patients with MASH and fibrosis consistent with F2-F3 and therefore likely to bring it to the market. It is hence the first drug for MASH as a formal indication. No other drugs currently are licensed for indication of MASH.

Alcohol

Any reduction in alcohol use leads to improved outcomes and should be actively pursued. Behavioural interventions and relapse prevention medications, either alone or in combination, represent the first line treatment. Screening for alcohol use, providing information, and referring patients to local addiction services are imperative. Brief motivational interventions, feasible for most clinicians, have been demonstrated to reduce alcohol consumption in a meta-analysis (mean difference −20 g/week, CI, −29 to −12).[121,122] Pharmacotherapy should be considered in all people with harmful alcohol use who cannot reduce intake with behavioural approaches. Drugs include acamprosate that reduces craving and has shown efficacy in supporting abstinence compared to placebo in a meta-analysis (risk reduction = 0.83, 95% CI 0.77 to 0.88), and naltrexone for preventing relapse (risk reduction = 0.83, 95% CI 0.75 to 0.91).[123,124] Disulfiram is not recommended due to the risk of liver toxicity and limited efficacy.

A subset of patients suffering from SLD may present with addiction to either food or alcohol, necessitating specialized treatments tailored to address conditions such as alcohol use disorder, alcohol dependence, or eating disorders. However, the majority of patients can significantly mitigate their behaviour-related risk factors through interventions readily implemented in most clinical settings.[125] Recent research involving nearly 5000 individuals revealed that providing specific information regarding liver damage, coupled with appropriate advice, led to notable improvements in behaviours related to alcohol use (excessive drinking reduced from 46% to 32%), 35% improved diet, 13% lost body weight, and 22% increased exercise.[126]

Holistic & multidisciplinary management

Management of SLD needs a holistic and multidisciplinary approach to adequately address all risk factors and associated conditions.[127] The practical implementation hereof is still maturing, and several models of care can be envisioned, tailored to local resources and organisation of health care systems.[128] Depending on the health care system, the management of cardiometabolic risk factors typically takes place with primary care physicians, but it can also occur in clinics specialising in the management of cardiometabolic risk factors and alcohol services. Such a multidisciplinary approach has, in an observational study, shown that patients with MASLD benefit from lifestyle advice, signposting to weight loss services, and pharmacological treatment of diabetes and cardiovascular risk factors, which improved both cardiovascular and liver-related parameters.[129] Another example from UK community alcohol services showed that the introduction of liver stiffness assessment for patients with alcohol problems improved their engagement and retention and also suggested that it could support the reduction in alcohol intake.[125]

Multidisciplinary care models should become the standard of care in order to tackle the multiple comorbidities of SLD and should be combined with preventive measures at a societal and individual level.[130,131]

1

Panel 4: **Standard treatments for cardiometabolic risk factors and alcohol use**

Overweight / obesity: Target is at least 7-10% weight loss through a staged approach. Start with counselling for lifestyle modification diet and exercise. Consider GLP1 receptor agonists or dual agonists or bariatric surgery if lifestyle modifications are unsuccessful in patients who fulfil the criteria for these treatments (e.g., weight lowering drugs usually BMI>30 kg/m^2 or >35 kg/m^2 with comorbidities, and surgery BMI>40 kg/m^2 or >35 kg/m^2 and comorbidities).

Type 2 diabetes: Preference for drugs that might impact on liver inflammation and/or liver fibrosis, such as GLP1 receptor agonists, SGLT2i and pioglitazone. Choice depends on BMI and comorbidities.

Hyperlipidaemia: Offer statins for primary or secondary prevention of cardiovascular events according to guidelines and treatment thresholds.

Hypertension: Start on treatment if blood pressure above 140/90 mm Hg or 130/80 mm Hg in patients with type 2 diabetes at higher cardiovascular risk. No preference for a particular drug class.

Smoking: Encourage smoking cessation and offer pharmacotherapy if required.

Sleep apnoea: Evaluate for sleep apnoea and offer continuous positive airway pressure (CPAP) if required.

Alcohol use: Any reduction at any stage of disease improves outcomes**.** Advise complete abstinence in patients with advanced fibrosis or cirrhosis. Advise avoiding binge drinking. Combination of behavioural motivational modalities and relapse prevention medication such as acamprosate or naltrexone is recommended. Individuals with AUD should be referred to specialised community programs.

2

Drug Development Across the SLD Spectrum

New therapeutic modalities for SLD are developed along the lines of the underlying aetiologies, mainly referring to MASLD [132] or ALD. MetALD represents a novel target population for drug development, with a rapidly growing interest of drug developers in this specific population that target both causes cardiometabolic and alcohol-related drivers.[132]

Novel treatments for MASLD focus mainly on endoscopic procedures and on drugs. Therapeutical targets can conceptually be separated into primarily metabolic pathways, mechanisms of cell stress and apoptosis, inflammation, fibrogenesis and genetic targets[110,133] some of them being common with MetALD and ALD (**Figure 6**). Many approaches have combined effects directly on several targets.

Many drugs are under investigation targeting MASH (**Table 2**). As mentioned, resmetirom is now licensed by the FDA for patients with MASH and moderate (F2) or severe (F3) fibrosis, but not yet in cirrhosis for which the phase III trial is ongoing. The other drugs tested in phase III are the GLP1RA semaglutide, the panPPAR agonist lanifibranor, the fibroblast growth factor 21 analogues efruxifermin and pegozafermin and the fatty acid synthase inhibitor denifanstat. The phase 2b trial of lanifibranor showed an effect size of 19% for fibrosis regression and 27% for MASH resolution after six months of treatment.[134] There were no major safety issues, and the drug was generally well tolerated, some weight gain was noted attributable most probably to the peroxisome proliferator-activated receptor gamma activity. Two studies with Fibroblast growth factor 21 (FGF21) analogues have shown positive results in phase II. The highest doses pegozafermin showed an effect size of 20% for fibrosis regression and 24% for MASH resolution after 6 months of treatment.[135] Efruxifermin showed an effect size of 21% for fibrosis regression and 61% for MASH resolution after 24 weeks of treatment.[136] However, the effect size of the trials cannot be compared due to

substantial differences in trial design and primary analysis presented. Side effects were mainly gastrointestinal in nature, sometimes leading to treatment discontinuation. Denifanstat showed an effect size of 23% for fibrosis regression and 24% for MASH resolution after 52 weeks of treatment (company announcement). Side effects were mainly gastrointestinal and dermatological.

A plethora of drugs with many different modes of action are currently under investigations, including genetic target, e.g., an siRNA lowering the mRNA expression of *PNPLA3* and a siRNA directly reducing hepatic Hydroxysteroid 17β dehydrogenase 13 *(HSD17B13)* expression.[110] The gut-liver axis can be target at several steps preventing translocation of microbial products from gut to the liver and hereby reduce liver inflammation and fibrosis progression, e.g., a gut-specific antibiotic, rifaximin-α, that is considered to improve the gut barrier might reduce progression of liver fibrosis in patients with ALD.[137]

Many drug trials primarily involve non-cirrhotic patients, a trend arisen by repeated failures in trials involving cirrhotic subjects. Such failures may stem from the disparity between drug targets and the varied disease drivers spanning the disease severity (see **Figure 6**). The prevailing model for drug approval necessitates trials in cirrhosis patients with clinical endpoints, as conducting outcome studies in earlier stages is challenging due to the slow and unpredictable progression of disease. Acknowledging this challenge, several phase III compounds are concurrently undergoing separate trials targeting cirrhotic patients. Non-invasive disease markers have been insufficiently validated as substitutes for histology or clinical outcomes to be accepted by the regulatory authorities for both accelerated/conditional and final approvals. Resmetirom nevertheless secured FDA approval without explicitly necessitating a liver biopsy, suggesting potential shifts in regulatory positions.

The group of MetALD patients represents a new important target group for clinical trials, as these patients have previously been excluded from MASH trials and as the cardiometabolic disease drivers have largely been neglected in ALD. Furthermore, there is the substantial overlap in pathophysiological, behavioural, metabolic, and genetic risk factors among MASH, MetALD and ALD (**Figure 5 and 6**) opening a promising opportunity to evaluate numerous drugs currently in development for MASH in patients with MetALD and ALD.[132,138] Preclinical evidence indicates that GLP-1 analogues and the hormone FGF21 can mitigate alcohol consumption through central neurotransmission pathways.[139,140] Clinical observations further suggest that FGF21 attenuated alcohol use individuals with SLD.[141] Semaglutide and tirzepatide have been shown to reduce the intake of alcohol additionally to inducing weight loss in people with obesity,[142] and are therefore potentially attractive in MetALD patients.

Challenges and controversies

The evolving landscape of liver disease and implementation of the SLD nomenclature as a spectrum from MASLD and MASH to ALD, presents a complex array of challenges and potential controversies that must be addressed going forward. This shift in terminology is not just semantic; it reflects a deeper understanding of the multifactorial nature of liver disease. However, it also introduces several uncertainties and research questions.

The criterium for alcohol use critically needs specificity in defining the timeframe for current and historical alcohol use to ensure correct subclassification of SLD.[44] Determining when alcohol ceases to be a primary disease driver is essential, as it influences the transition between subclasses. This is particularly significant in clinical trials, where accurate classification impacts both treatment strategies and outcome assessment. Moreover, the reliability of self-reported alcohol use is problematic due to the inaccuracies imposing a high risk of misclassification.[21,22] While biomarkers like PEth and CDT can rule out alcohol use, they are less effective in quantifying alcohol use needed for SLD subclassifcation.[59,60] Furthermore, the fluctuating nature of alcohol use over time adds another diagnostic challenge in case of absence of steatosis at the time of liver assessment. Approximately 40% of individuals show no signs of liver steatosis yet they may be at high risk of hepatic decompensation.[143] This raises the question of which fibrosis thresholds should be used.

Since the introduction of the SLD nomenclature, studies have demonstrated that almost all individuals with a current excessive alcohol use also present with CMRF. In the NHANES cohort 0.08% (95% CI 0.04–0.22) presented with ALD without CMRF.[42] In a Danish cohort of individuals with a history of excessive alcohol use, only one in 446 (0.2%) individuals presented with ALD without CMRF.[44] This shows that excessive alcohol use is closely associated with CMRF indicating that ALD without CMRF is a subgroup that will rarely be seen.

The importance of the individual CMRF is also contentious. While conditions like type 2 diabetes and obesity are strongly associated with risk of liver-related mortality, other factors like hypertension and dyslipidaemia are less. Yet, according to the SLD criteria each CMRF weight equally, which may not accurately reflect their relative importance.

Monitoring treatment responses in clinical practice, particularly using non-invasive tests, is crucial to minimize the need for liver biopsies. This approach could enhance patient comfort and reduce healthcare costs. Resmetirom, a drug for treatment of MASLD, recently secured FDA approval without explicitly necessitating a liver biopsy, suggesting potential shifts in regulatory positions.

Additionally, screening asymptomatic individuals with risk factors for liver fibrosis presents dilemmas about whom to test, the frequency of testing, and the methods employed.[144] Finally, the patient journey through the healthcare system, from home to primary care, to secondary care, and back to managing a chronic disease, is a critical aspect. The role of self-monitoring and artificial intelligence (AI) tools in managing liver disease is an emerging field that promises to revolutionise patient care. While the SLD nomenclature and diagnostic framework reflect a more nuanced understanding of liver disease, it also presents several new questions and challenges that necessitate careful consideration, consensus-building, and ongoing research.

Increasing awareness on steatotic liver disease to improve global liver health

There is a growing focus on advancing liver health through awareness and policy measures led by the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Disease (AASLD), the Lancet and the WHO.[145,146] The overall aim is to combat SLD through prevention and early detection and to inform policy measures to mitigate the structural determinants of poor liver health. Therefore, SLD should be included as part of the WHO programme on fighting non-communicable diseases.[24,145,147]

A key aspect for improving global liver health will be to change the dialogue around liver diseases to reduce stigma by shifting the narrative and adopting terminology that more accurately represents their multifactorial nature, recognising that factors beyond CMRF and alcohol contribute to SLD and promoting more open discussions about this.[30] In line with this is the aim to foster a deeper understanding of SLD among healthcare professionals, patients, and the broader public.[130] On a structural level, there is a need for a unified global effort to integrate liver health into broader health policy frameworks. This includes prevention and enhancing early diagnosis and treatment access.[24] Such structural improvements should aim to address not only liver health but also related metabolic and alcohol use disorders as part of a comprehensive approach to reduce non-communicable diseases on a broader scale.

Contributors

All authors contributed equally to both the writing and critical review of various sections of the Seminar, and all have given their approval for the final version to be submitted.

During the preparation of this work the authors used AI (ChatGTP version 4 and 4o) in order to improve language and readability. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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ET has served as a speaker for Abbvie, Dr Falk, Echosens, Novo Nordisk and Orphalan and participated in advisory boards for Alexion, Boehringer, Siemens, Merck Sharp & Dome, Novo Nordisk, Pfizer, Orphalan and Univar.

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Figures, Tables and Boxes

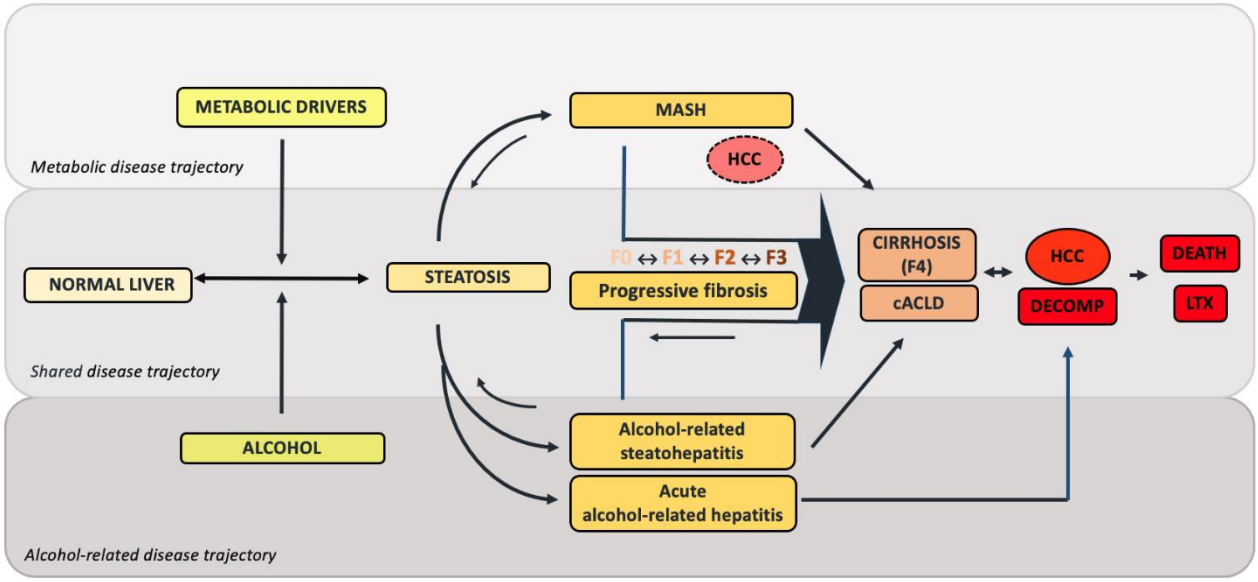

Figure 1: The natural history of SLD: In MASLD only, starting from a normal liver and depending on the balance between metabolo-inflammatory drivers and defence mechanisms, steatosis will be accompanied by steatohepatitis, which can result in progressive fibrosis ultimately leading to cirrhosis and the complications hereof.[32,33] Given the disease continuum and some intrahepatic heterogeneity, the concept of cACLD probably reflects better the transition from advanced fibrosis/F3 to cirrhosis/F4, as this is a gradual shift in severity. HCC can develop at any stage, although the risk is probably the highest in the cirrhotic stage and ill-defined in earlier stages.[148] At any stage, disease regression is possible pending improvements in the cardiometabolic milieu. Alcohol exposure induces steatosis and various degrees of hepatocyte damage depending on several risk factors.[149] Continuous exposure in susceptible people will lead to progressive fibrosis, the pattern of which might be somewhat different from MASLD but uses the same staging system. Episodes of acute severe alcohol-related hepatitis can accelerate disease progression or even lead by itself to liver decompensation. The occurrence of HCC is usually restricted to the cirrhotic stage. The natural history of people combining risk factors for MASLD and alcohol consumption is ill-defined, but they likely reinforce each other with an accelerated disease course and an increased risk of complications.
MASLD, Metabolic Dysfunction Associated Steatotic Liver Disease; MASH, Metabolic Dysfunction Associated Steatohepatitis; cACLD, compensated Advanced Chronic Liver Disease; HCC, hepatocellular carcinoma; LTX, liver transplantation.

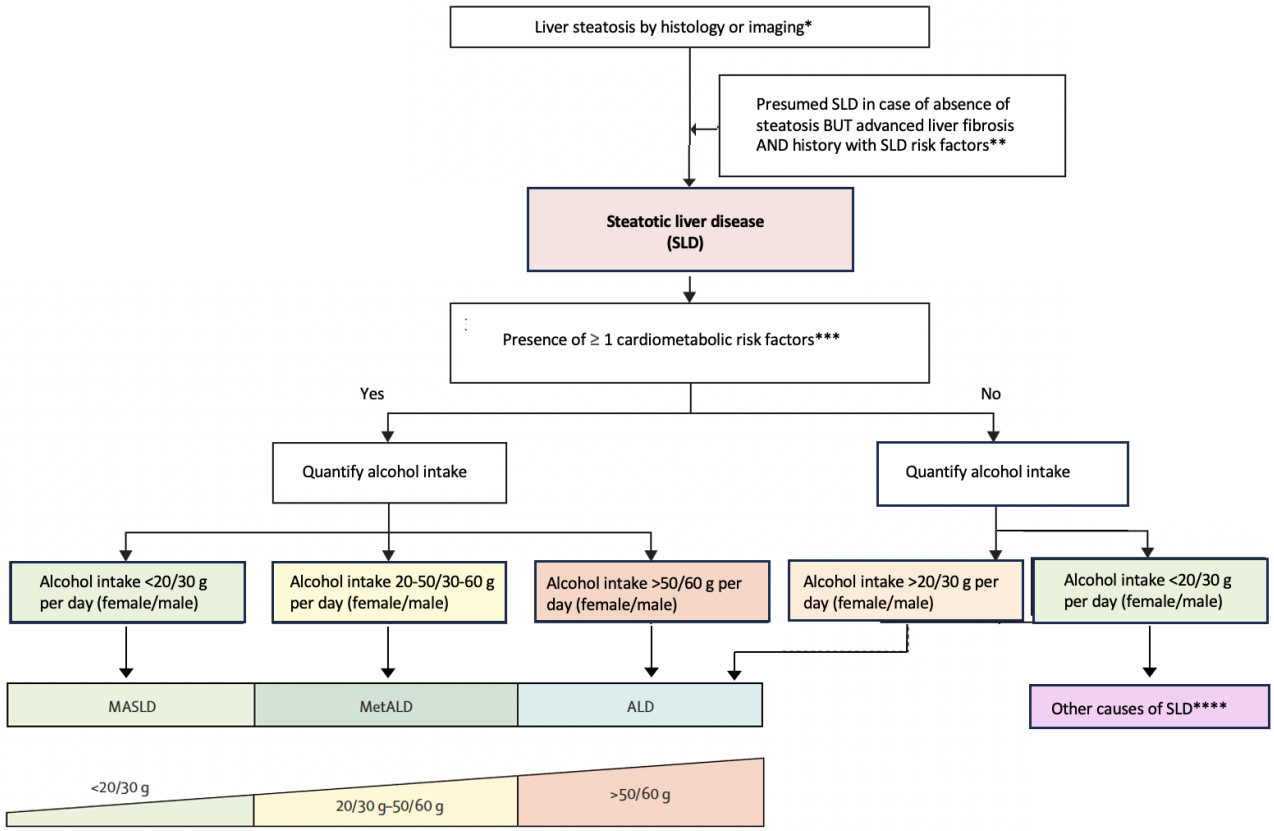

Figure 2: Flowchart showing classification and subclassification of steatotic liver disease. Based on the diagnostic criteria for steatotic liver disease nomenclature as established by the multisociety Delphi consensus statement in 2023. [1]

Specification of criteria:

* Liver steatosis is defined histologically as the presence of fat laden vacuoles in ≥ 5% of the hepatocytes.[65] Imaging including standard ultrasound and magnetic resonance imaging-proton density fat fraction can be used as non-invasive assessments for steatosis.

** Absence of steatosis may be observed if SLD risk factors are eliminated or reduced, or when extensive liver fibrosis is predominant in some cases of severe cirrhosis. However, other lesions, particularly fibrosis, are less dynamic and can persist. In cases of fibrosis without steatosis, a history of prior SLD risk factors could justify a diagnosis of presumed SLD. This includes cases with histologically confirmed advanced fibrosis (stages F3 and F4), or a corresponding liver stiffness measurement (transient elastography >12 kPa). In these cases, other causes of chronic liver disease should be carefully considered.

*** The criteria for cardiometabolic risk factors used in the definition of SLD: (1) BMI of ≥25 kg/m² (adjusted based on ethnicity), or a waist circumference ≥80 cm for women and ≥94 cm for men; (2) fasting serum glucose levels of ≥5.6 mmol/L (100 mg/dL), 2-hour post-load glucose concentrations of ≥7.8 mmol/L (140 mg/dL), glycated haemoglobin of ≥5.7% (39 mmol/mol), presence of type 2 diabetes, or treatment for type 2 diabetes; (3) blood pressure of ≥130/85 mm Hg, or the use of specific antihypertensive drugs; (4) plasma triglycerides of ≥1.70 mmol/L (150 mg/dL), or undergoing lipid-lowering treatment; and (5) plasma HDL-cholesterol levels of ≤1.3 mmol/L (40 mg/dL) for women and ≤1.0 mmol/L (50 mg/dL) for men, or receiving lipid-lowering treatment.

**** Drug-induced liver injury, monogenic diseases (Lysosomal Acid Lipase Deficiency (LALD), Wilson's disease, hypobetalipoproteinaemia, inborn errors of metabolism and miscellaneous liver disease (*e.g.*, genotype 3 Hepatitis C Virus (HCV) infection, malnutrition, celiac disease, and Human Immunodeficiency Virus (HIV) infection).

ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related liver disease; SLD, steatotic liver disease.

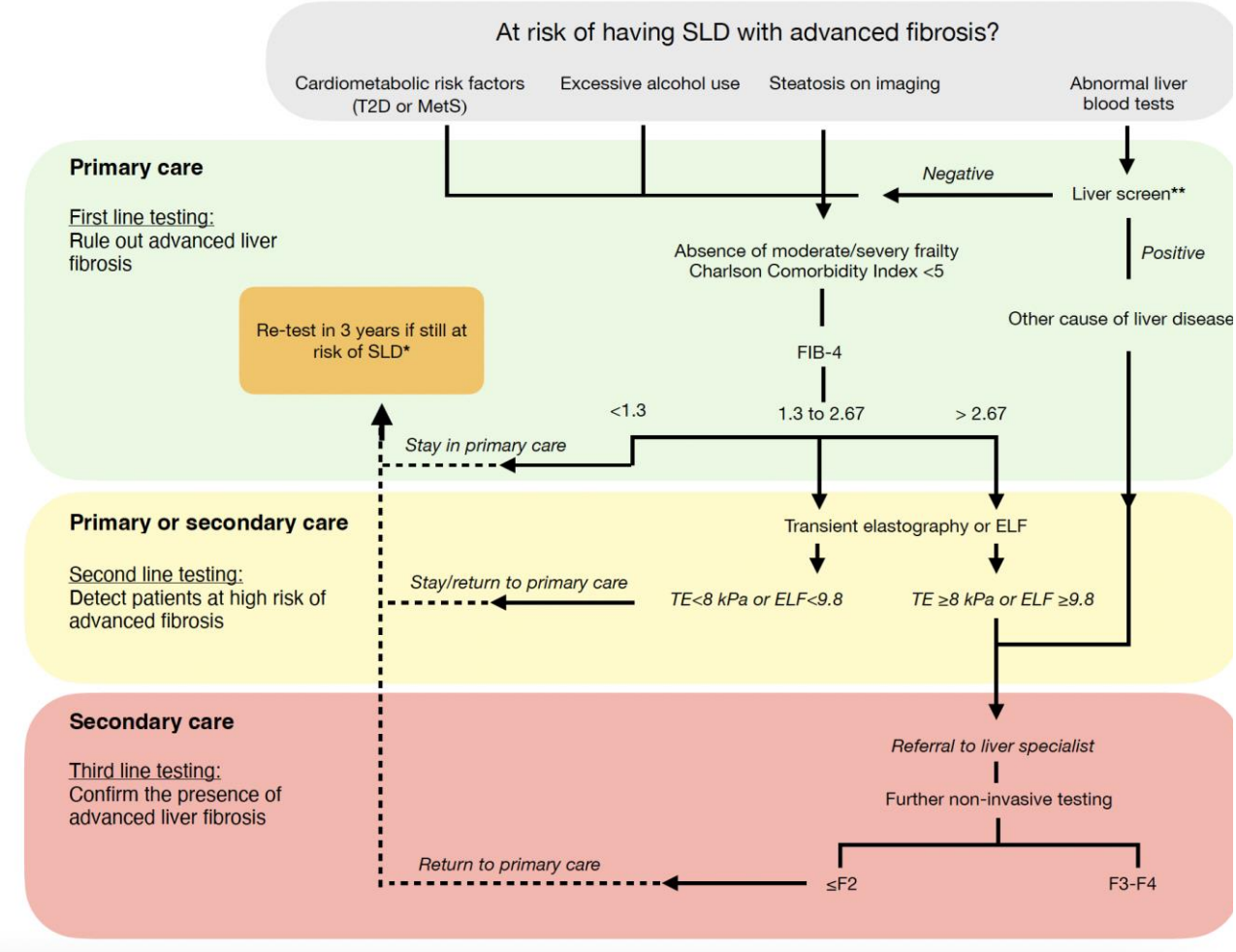

Figure 3: Diagnostic framework for early detection of advanced liver fibrosis in steatotic liver disease. The framework is validated[150] and structured around a three-tier testing process,[67] each with its specific purpose.

First-line Testing: Utilizes affordable, accessible index tests (*e.g.*, FIB-4) in primary care to rule out advanced liver fibrosis, emphasizing a high sensitivity and negative predictive value to limit further testing. Second-line Testing: Conducted in primary or secondary care depending on the healthcare system's structure. This more costly, specialized tests (*e.g.*, transient elastography or ELF) aim to detect patients at high risk of advanced fibrosis. Third-line Testing: Performed by liver specialists to confirm the presence of advanced liver fibrosis and plan a treatment strategy. This can involve further non-invasive testing or a liver biopsy, particularly in cases of discordant non-invasive test results.

In this diagnostic framework, ~~W~~we propose ways to rationalize testing and reduce the burden for healthcare systems, by using the frailty and the Charlson comorbidity index to select people who would benefit most.[151]

Although significant fibrosis would be a reasonable target, the diagnostic accuracy of existing non-invasive tests is suboptimal and we therefore focus on advanced liver fibrosis.[56,67]

~~Patients who are classified as not having advanced fibrosis should be re-tested in 3 years if they still have risk factors for SLD. Re-testing may be omitted in patients with MASLD who are older than 65 years, due to the relatively slow fibrosis progression in MASLD~~.

*Patients who are classified as not having advanced fibrosis should return to primary care and/or their already ongoing non-hepatology specialised care. Risk factors for SLD should be managed at these levels according to standard guidelines (see Panel 4). If risk factors for SLD persist, patients should be re-tested after 3 years. Due to the relatively slow fibrosis progression in MASLD, re-testing may be omitted in patients with MASLD who are older than 65 years, as the ten-year risk of developing decompensated liver disease or hepatocellular carcinoma is less than 0.5% in patients with MASLD without advanced fibrosis.[10]

**Liver screen refers to the recommended investigation of an individual with prolonged abnormal liver blood tests.[152] In adults, a standard liver aetiology screen should include an abdominal ultrasound scan (USS), hepatitis B surface antigen, hepatitis C antibody (with follow-on polymerase chain reaction (PCR) if positive), anti-mitochondrial antibody, anti-smooth muscle antibody, antinuclear antibody, serum immunoglobulins, ceruloplasmin levels in people <40 years, alpha 1-antitrypsin levels and simultaneous serum ferritin and transferrin saturation. In this context, a negative liver screen means that no other cause for the abnormal liver blood tests has been identified other than the risk factors for ~~steatotic liver disease (~~SLD~~)~~. In the case of a negative liver screen, patients should be evaluated for liver fibrosis according to the recommended algorithm. A positive liver screen indicates that another cause for the abnormal liver blood tests has been found, and individuals should be referred directly to a liver specialist.

~~First-line Testing: Utilizes affordable, accessible index tests (*e.g.*, FIB-4) in primary care to rule out advanced liver fibrosis, emphasizing a high sensitivity and negative predictive value to limit further testing.~~
~~Second-line Testing: Conducted in primary or secondary care depending on the healthcare system's structure. This more costly, specialized tests (*e.g.*, transient elastography or ELF) aim to detect patients at high risk of advanced fibrosis.~~
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ELF, enhanced liver fibrosis (test); F2, significant (moderate) fibrosis; F3, Advanced (severe) fibrosis; F4, cirrhosis; FIB4, Fibrosis-4 score; MetS, metabolic syndrome; SLD, steatotic liver disease; T2D, type 2 diabetes; TE, transient elastography.

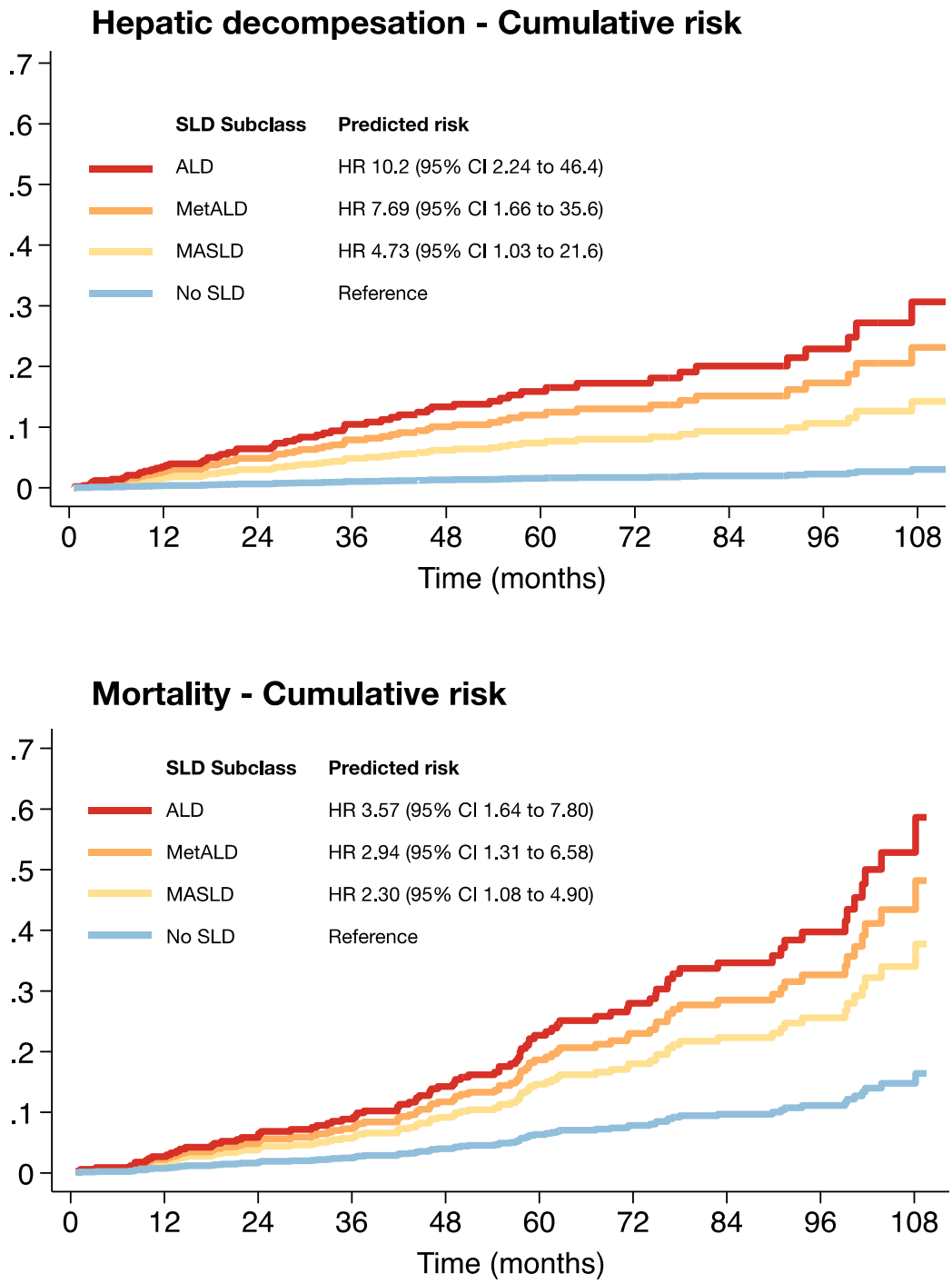

Figure 4: Predicted cumulative hazard risk curves showing distinct prognoses for the common subclasses of SLD. Models are adjusted for age, sex, and liver stiffness and based on data from[44].

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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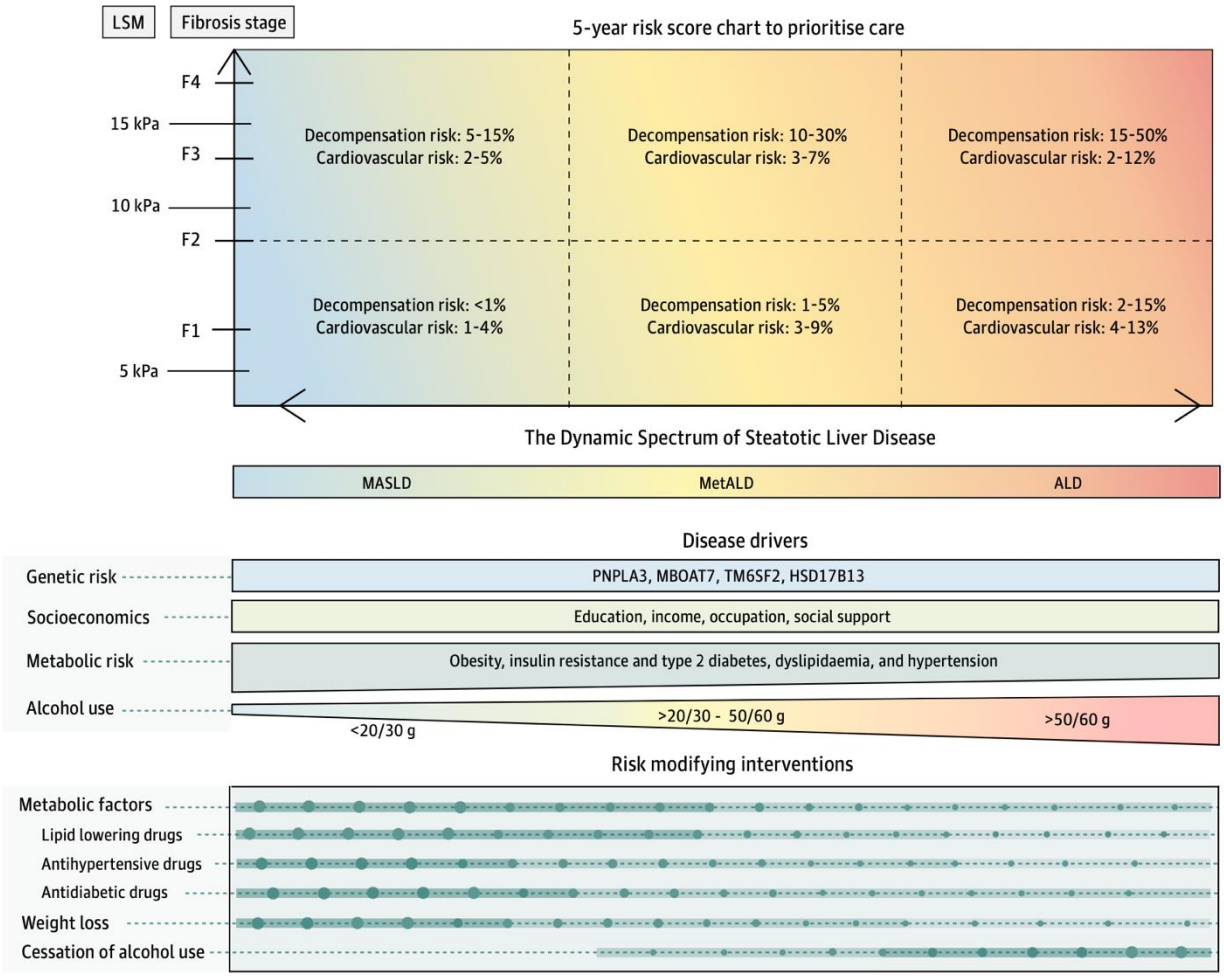

Figure 5: How to evaluate patients with steatotic liver disease in specialised liver units.
Based on the primary evaluation of a patient with SLD, the five-year risk of progression to clinically significant hepatic and cardiovascular disease can be estimated. This estimation should be considered when planning follow-up care for each individual patient with SLD in alignment with current guidelines.[64,68,153,154] The specified values for liver stiffness measurement (LSM) refer to measurements conducted with FibroScan®. *Inspired by*[138] *with an expansion on risk modifying interventions across the spectrum of SLD and data on cardiovascular risk for patients with SLD.*[31]

Risk estimates for hepatic decompensation are based on the following references.[9,10,44,155]
Risk estimates for cardiovascular risk are based on the following references.[156-160]

ALD, alcohol-related liver disease; LS, liver stiffness; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related liver disease; SLD, steatotic liver disease

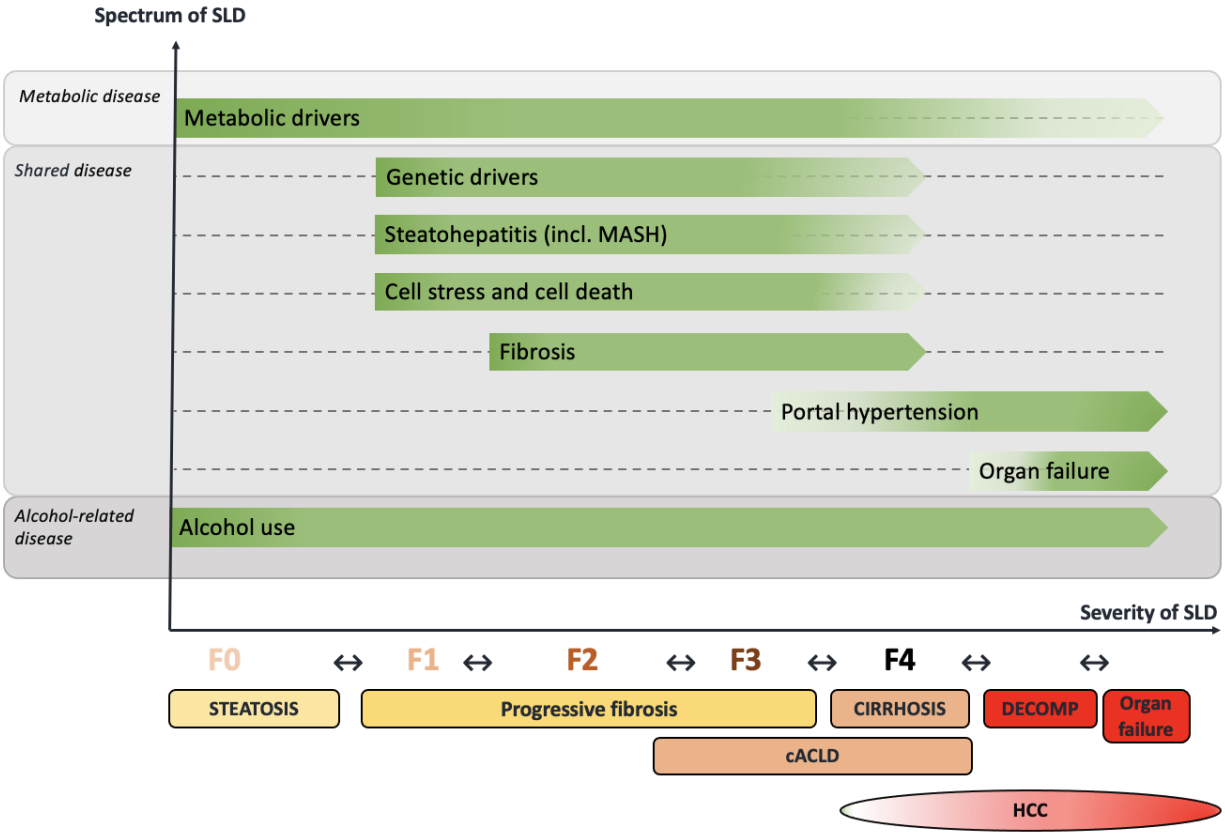

Figure 6: **Drug targets along the spectrum and severity of SLD:** Along the spectrum and severity of SLD, the role and target of different factors contributing to disease progression. The alcohol-related damage is a driver of at all severity stages of SLD. For metabolic disease (MASLD), the metabolic drivers play a dominant role. Across the spectrum of SLD, metabolic drivers and alcohol lead to steatosis and steatohepatitis. The steatohepatitis has its own intrahepatic mechanisms and drives fibrogenesis and progression towards advanced chronic liver disease and portal hypertension, and ultimately organ failure.[13] Although in more advanced disease stages and even in cirrhosis and portal hypertension, metabolic factors and intrahepatic mechanisms of cell damage and inflammation, cell stress and cell death may still play a role, even though they tend to diminish and disappear, and portal hypertension becomes a predominant driver of disease. **The green arrows** illustrate where drug targets are relevant along the spectrum and severity of SLD. Less colour intensity of the arrows symbolises less relevance of a given drug target. Drugs targeting metabolic drivers and/or intrahepatic mechanisms are more relevant at earlier time points in the disease severity and are less likely to be very efficacious in the advanced stages, where drugs tackling fibrogenesis and the (vascular) mechanisms underlying portal hypertension are more likely to be of clinical benefit.[161]* Changing the lifestyle is crucial at all stages and might be supported by pharmacotherapy in the context of addiction management.

cACLD, compensated Advanced Chronic Liver Disease; DECOMP, (hepatic) decompensation; HCC, hepatocellular carcinoma; MASH, Metabolic Dysfunction Associated Steatohepatitis.

~~***Accepted for publication**, not yet online Juan Pericàs, Quentin Anstee, Salvador Augustin, Ramon Bataller, Annalisa Berzigotti, Andreea Ciudin, Sven Francque, Juan Albraldes, Virginia Hernández-Gea, Mònica Pons, Thomas Reiberger, Ian Rowe, Peter Rydqvist, Elmer Schabel, Frank Tacke, Emmanuel Tsochatzis, and Joan Genescà. A roadmap for clinical trials in MASH-related compensated cirrhosis. NRGH 2024~~

Biomarker	Components	Setting	Cut-offs	Diagnostic accuracy for advanced fibrosis	Prognostic discrimination	Comments
LiverRisk score	Age, sex, glucose, cholesterol, AST, ALT, GGT, platelet count	First line testing	6, 10, 15	NA	HR 471 for the high-risk group	Derived in the general population.
FIB-4	Age, AST, ALT, platelet count	First line testing	<1.3, >2.67	AUROC 0.76	HR 18.76 for high cut-off	Not useful in <35 years. Age adjusted cut-off proposed for >65 years
NAFLD fibrosis score	Age, BMI, AST, ALT, type 2 diabetes, platelet count, albumin	First line testing	<-1.5, >0.67	AUROC 0.73	HR 18.51 for high cut-off	Only validated in MASLD. Performs worse than FIB-4.
ELF test	TIMP-1, PIIINP, hyaluronic acid	Second line testing	9.8	AUROC 0.83	HR 16.94 for >10.5 in ALD	Also increased in extra-hepatic fibrotic conditions. Influenced by age.
ADAPT	Pro-C3 (N-terminal type III collagen propeptide), age, diabetes and platelet count	Second line testing	6.32	AUROC 0.85	NA	Less well validated in SLD.
Transient elastography	Imaging	Second line testing	<8 KPa, >12 KPa	AUROC 0.85	HR 10.65 for >20 KPa	Needs to be performed in fasting state. Requires trained operator.
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MR elastography	Imaging	Second/third line testing	3.5 KPa	AUROC 0.92	NA	Not widely available.

Table 1: The most commonly used biomarkers for fibrosis assessment and prognostication in SLD. The diagnostic accuracy and prognostic discrimination data presented derive from [9,69,93,97,162-165]. The diagnostic accuracy data refer to the diagnosis of advanced fibrosis. The prognostic discrimination refers to liver-related mortality. When dual cut-offs are presented, the low cut-off is used to rule out and the high cut-off to diagnose advanced fibrosis. Values for cut-offs, diagnostic accuracy, and prognostic discrimination are based on data from meta-analyses or studies with validation.

AUROC. Area under the receiver operating curve, GGT, gamma glutamyl transpeptidase; TIPM-1, Tissue inhibitor of metalloproteinases 1; PIIINP, aminoterminal propeptide of type III procollagen

Diagnostic accuracy refers to fibrosis stage ≥F3 (advanced fibrosis). Prognostic discrimination refers to the development of liver-related events.

Drug	Mode of action	Estimated patient enrolment	Fibrosis stage	Study duration	Endpoints	Sponsor	Clinical trial number
Semaglutide	GLP-1 receptor agonist	1200	F2-F3	Up to 5 years, interim analysis at 72 weeks	Clinical outcomes; histological for interim analysis	Novo Nordisk	NCT04822181
Resmetirom*	THRb agonist	1759 (actual)	F2-F3	Up to 5 years, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Madrigal Pharmaceuticals	NCT03900429
Resmetirom	THRb agonist	700	F4		Clinical outcomes	Madrigal Pharmaceuticals	NCT05500222
Lanifibranor	Pan-PPAR agonist	1000	F2-F3	72 weeks, with a further 48 week follow up for safety	Histological	Inventiva	NCT04849728
Pegozafermin	FGF21 analogue	1050	F2-F3	88 weeks, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	89Bio	NCT06318169
Efruxifermin	FGF21 analogue	1000	F2-F3	Unknown, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Akero Therapeutics	NCT06215716
Efruxifermin	FGF21 analogue	600	MASLD/MASH based on biopsy or non-invasive testing	52 weeks	Safety and tolerability	Akero Therapeutics	NCT06161571
Denifanstat	FASN inhibitor	TBC	TBC	TBC	TBC	Sagimet	TBC**

Table 2: Current phase III drug trials in MASLD.

*Results have been reported[120], **Phase III study has been announced, details to be confirmed

FASN; fatty acid synthase, FGF21, Fibroblast growth factor 21; GLP-1, glucagon-like peptide 1; MASLD: metabolic dysfunction associated steatotic liver disease; MASH, Metabolic Dysfunction Associated Steatohepatitis; PPAR, peroxisome proliferator-activated receptor, THRb: Thyroid hormone receptor b; TBC: to be confirmed

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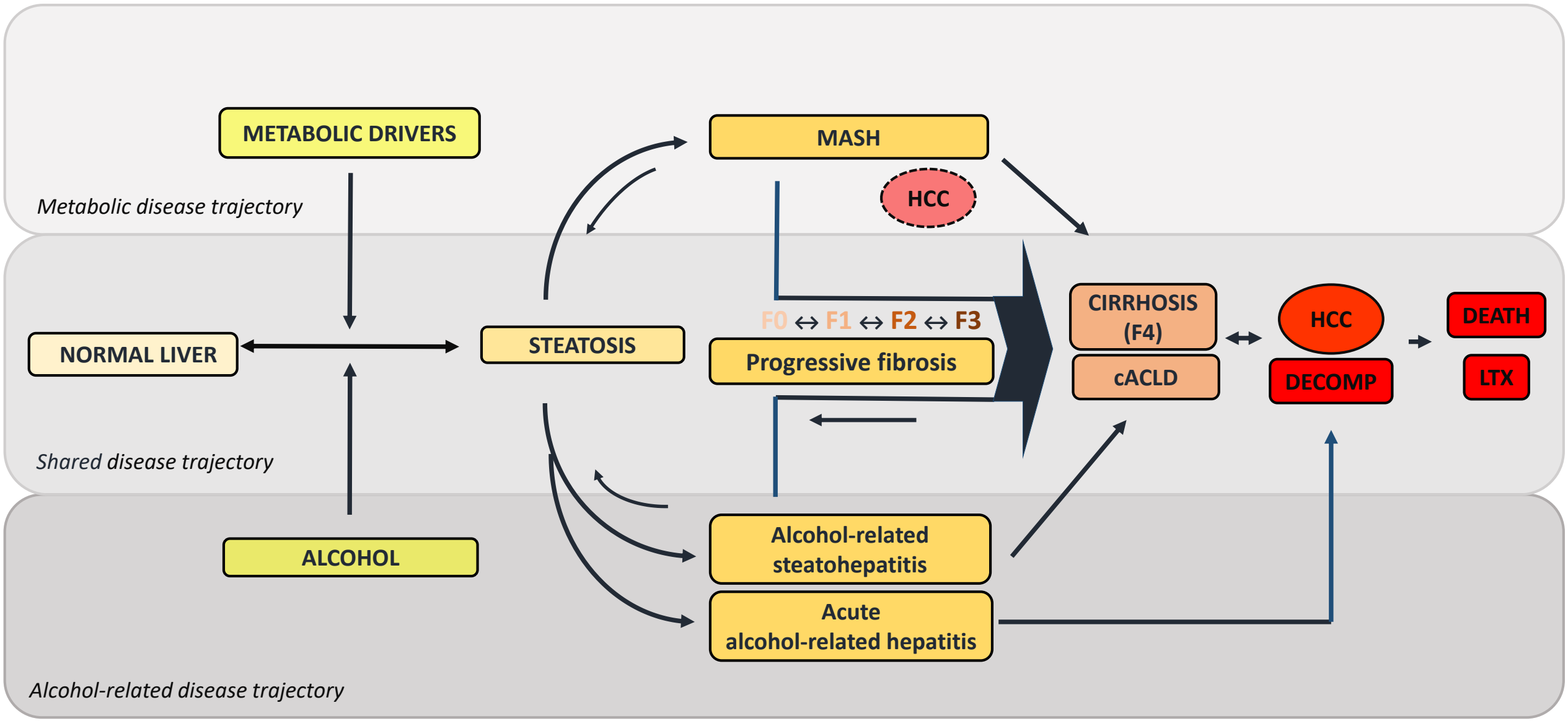

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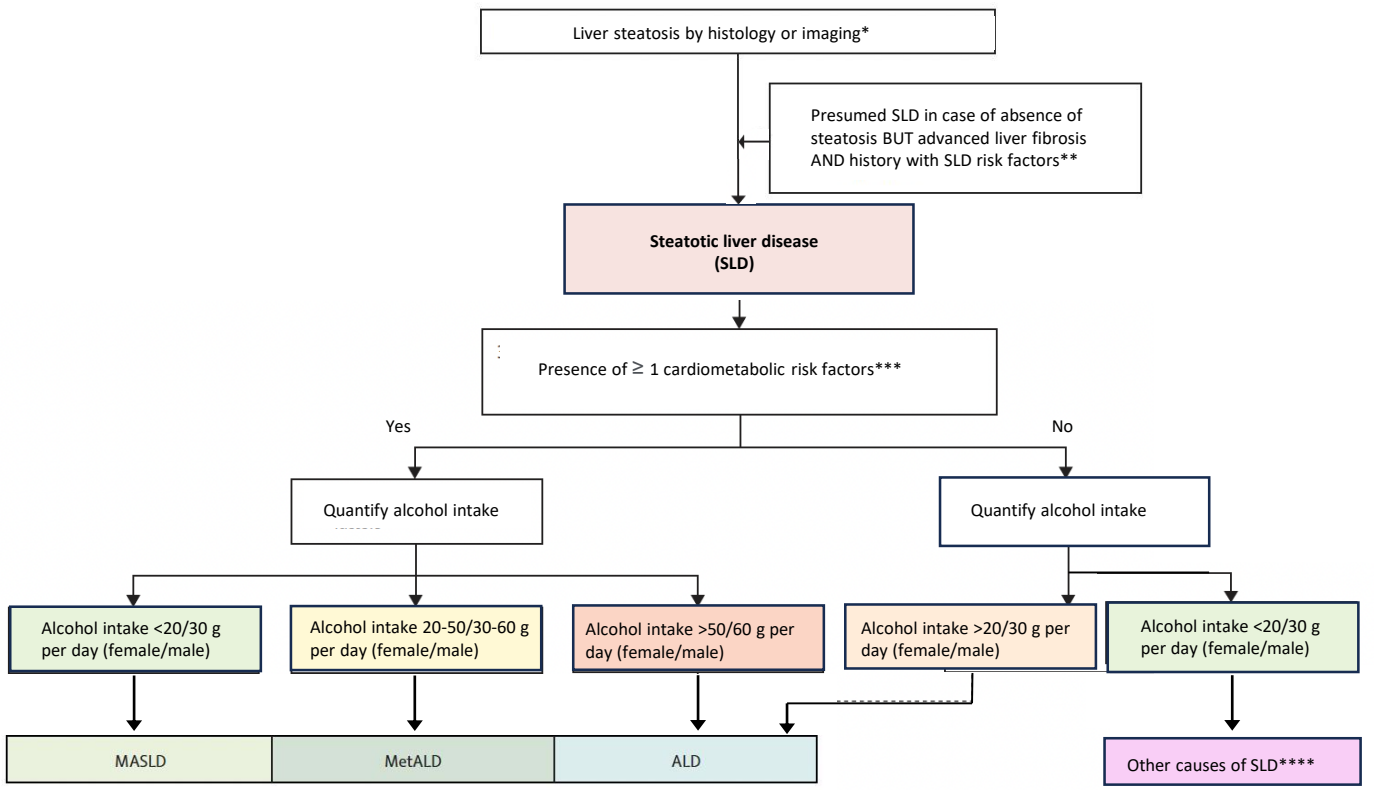

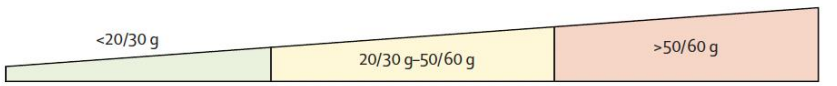

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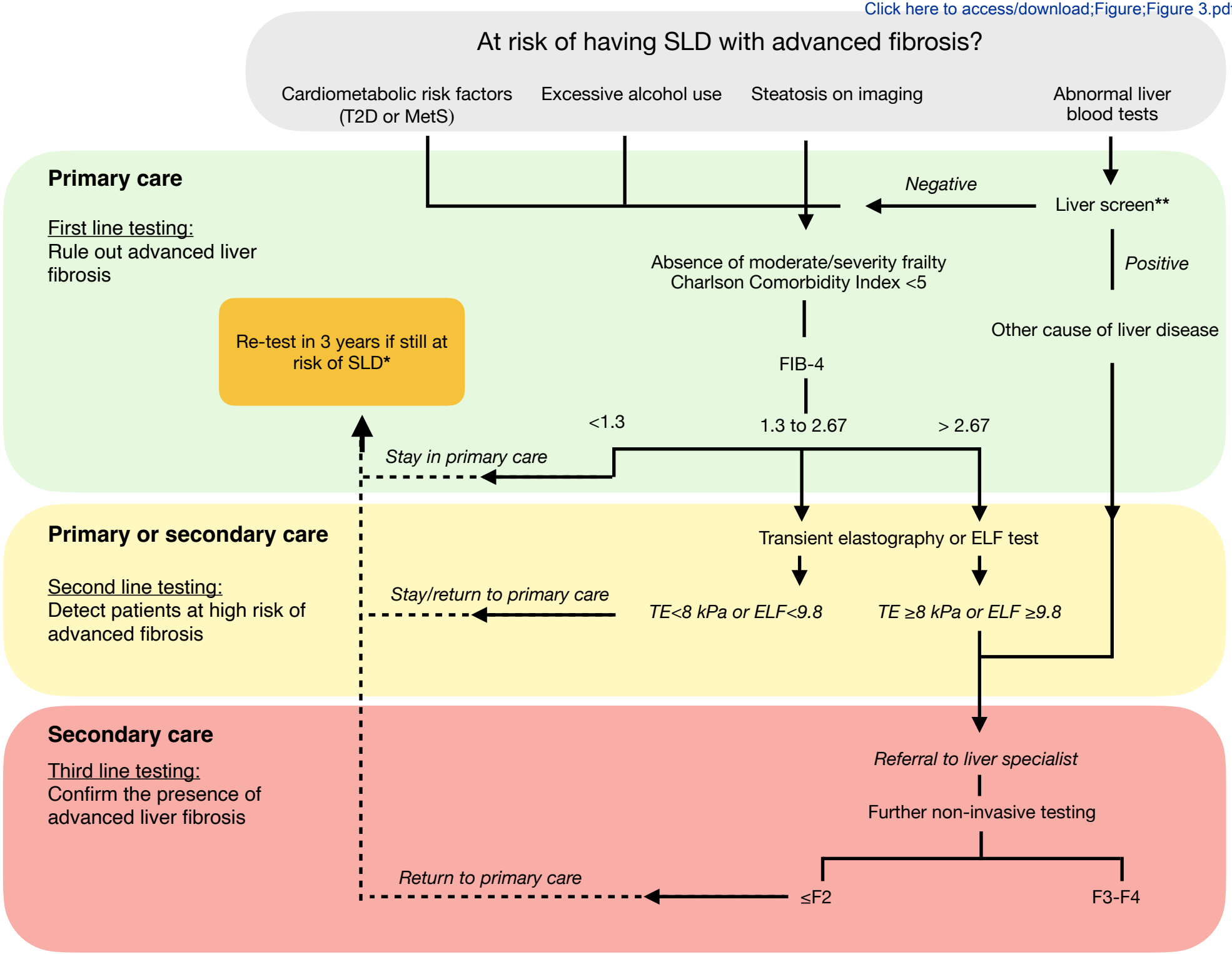

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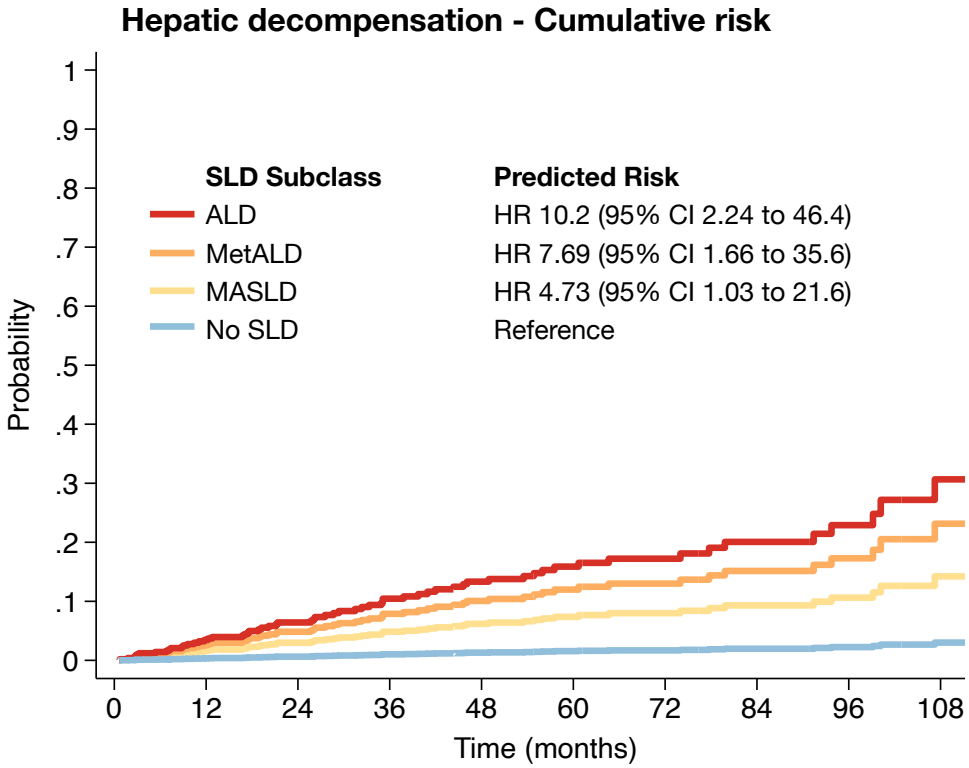

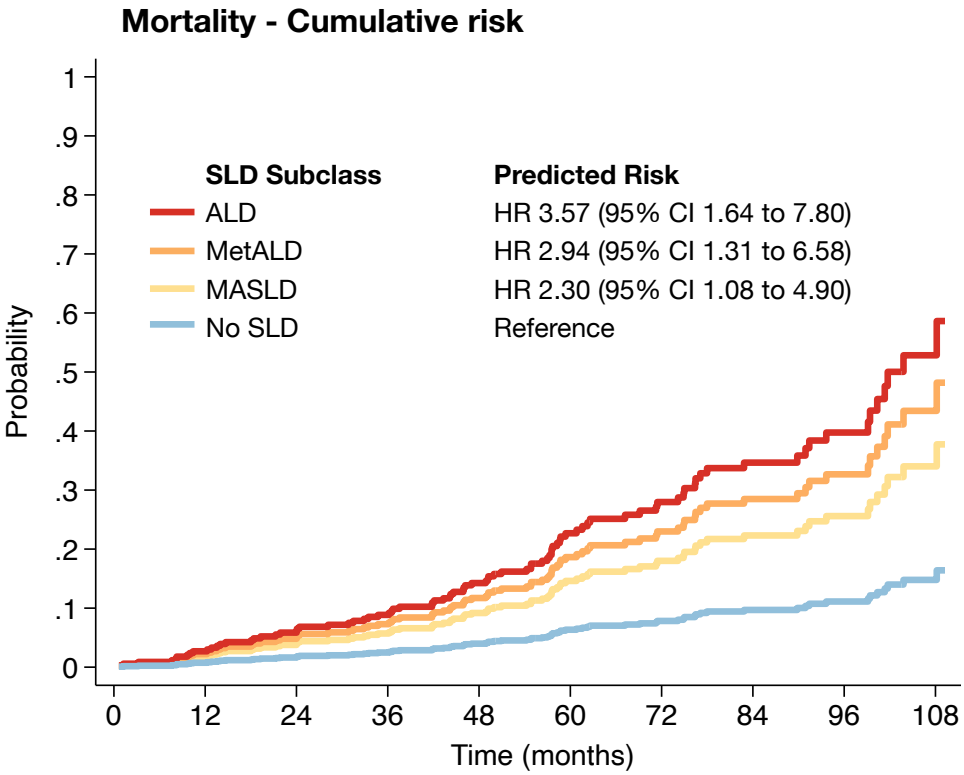

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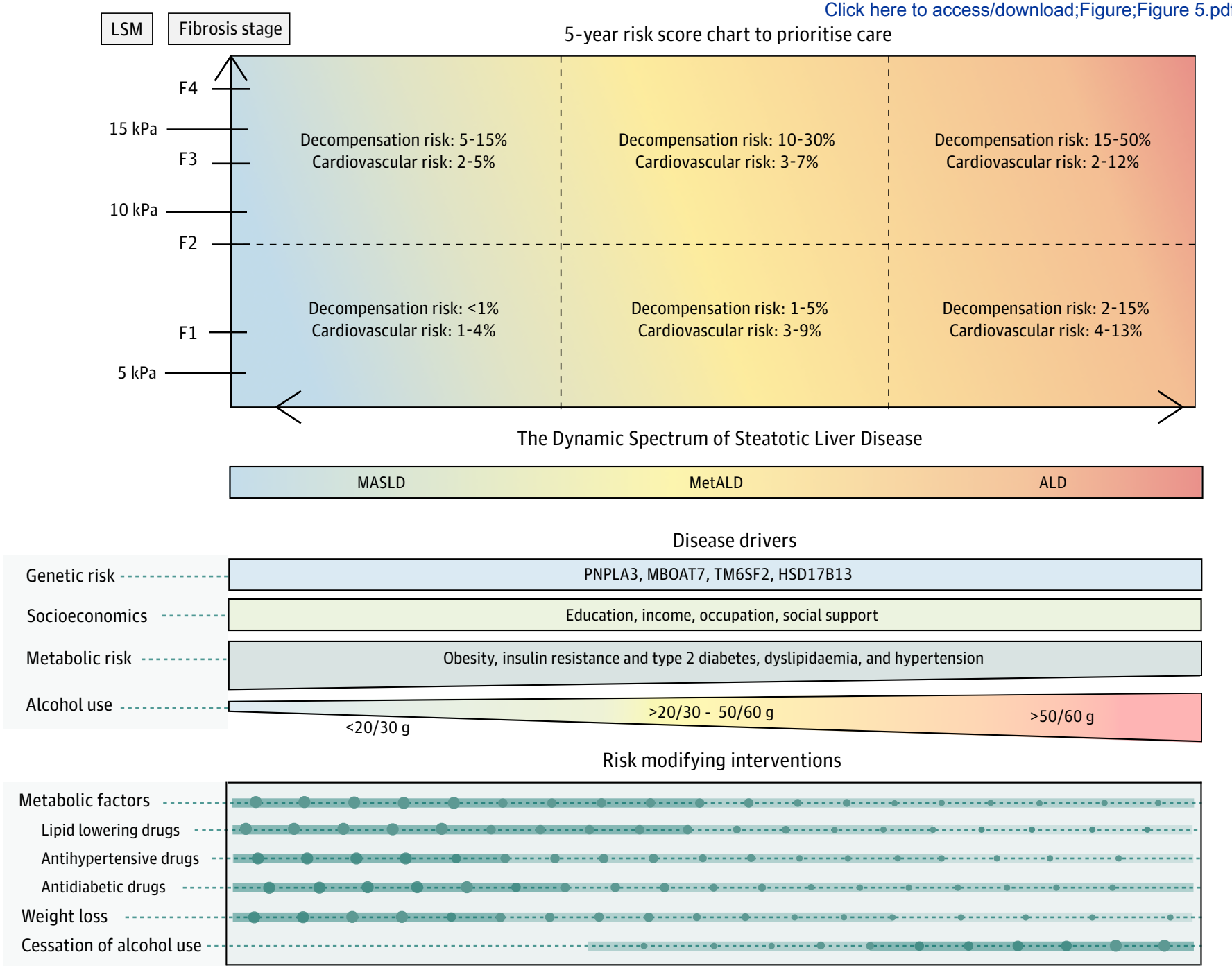

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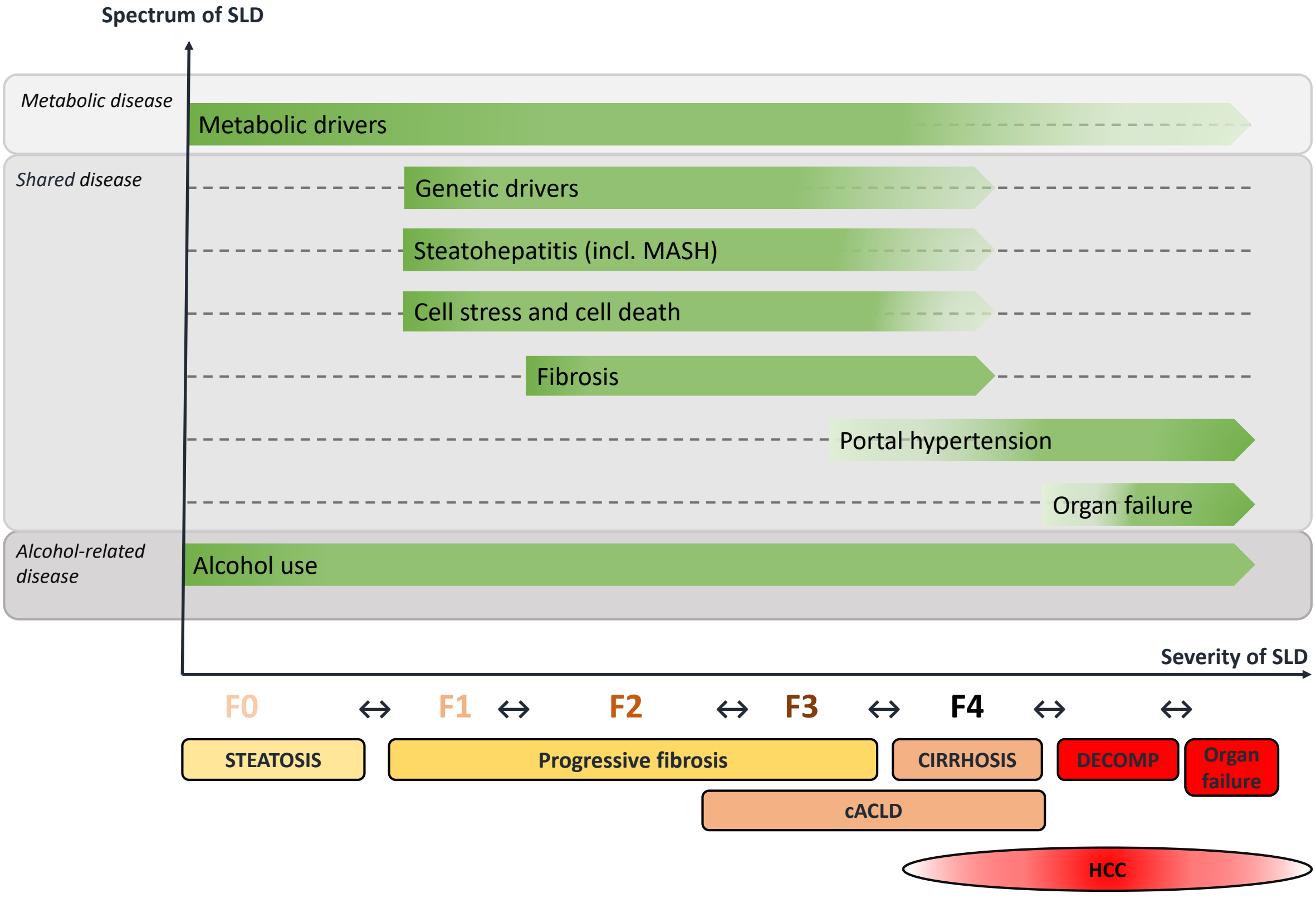

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