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Perspective

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Evolving models of care in patients with metabolic dysfunction-associated steatotic liver disease, recognising its population burden and the impact of metabolic dysfunction on incident rates of hepatic and extrahepatic outcomes

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with any one of five principal traits of the metabolic syndrome. MASLD is characterised by multimorbidity with liver-related and extrahepatic complications including cardiovascular and cardiac disease, chronic kidney disease and certain extrahepatic cancers. While increasing liver fibrosis severity is well-established as a major contributor to the hepatic complications of MASLD, emerging evidence demonstrates that the severity of associated metabolic dysfunction significantly influences adverse extrahepatic clinical outcomes and all-cause mortality. Changing models of care are needed for patients with MASLD, extending the focus beyond that of liver health and optimising the inherent

(heterogeneous) cardiometabolic dysfunction. Such an approach requires multi-stakeholder and community-based engagement with improved identification and diagnosis, and better patient and healthcare provider education that also focuses on type 2 diabetes, hypertension, and obesity, to ameliorate the consequences of this highly prevalent global multisystem disease.

Keywords: Metabolic dysfunction-associated steatotic liver disease, metabolic syndrome, liver fibrosis, genetic predisposition, type 2 diabetes, major adverse liver outcomes, multisystem disease

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease, affecting an estimated 35%-40% of the global adult population[1,2]. MASLD is a multisystem disease which increases the risk of liver-related and extrahepatic complications such as hepatocellular carcinoma (HCC), cardiovascular disease (CVD), chronic kidney disease (CKD) and certain extrahepatic cancers[3]. Patients with MASLD may have only one or all five cardiometabolic traits, resulting in a highly heterogeneous cohort with substantially large metabolic dysfunction burden variance. The severity and combination of these metabolic syndrome (MetS) traits and genetic susceptibility may play a critical role in determining the risk of both hepatic and extrahepatic complications in MASLD. Despite this, the routine investigation of MetS traits and inherent genetic predisposition in patients with MASLD remains limited. In this perspective, we explore how metabolic dysfunction severity impacts the risk of MASLD complications and how models of care could evolve to recognise the importance of the metabolic dysfunction burden in MASLD.

THE IMPORTANCE OF METABOLIC DYSFUNCTION SEVERITY IN MASLD

Emerging evidence in individuals with and without SLD supports the adverse impact of increased metabolic dysfunction on the risk of both hepatic complications and extrahepatic diseases [Table 1]. The relative impact of metabolic dysfunction severity on hepatic versus extrahepatic complications in MASLD remains unclear. Hepatic disease severity may primarily "drive" major adverse liver outcomes (MALOs), while systemic metabolic dysfunction appears more influential for extrahepatic risks like CVD, and obesity-related cancers. Moreover, these findings also highlight the notion that specific MetS traits, particularly type 2 diabetes mellitus (T2DM) and hypertension, may have the most substantial relative impact on the risk of both hepatic and extrahepatic (i.e., CKD and CVD) complications, compared with other MetS traits[4].

A potential hierarchy of risk associated with each MetS trait could infer that prioritising the treatment of those traits is important. While controversial, we also consider that MetS trait hierarchy is also important in considering "*what is the most effective threshold requirement for both type and number of MetS traits, in the diagnosis and management of MASLD*". Indeed, while patients with SLD and only one MetS trait (i.e., the current MASLD diagnosis threshold) may capture individuals with minimal risk, this degree of "risk" is potentially highly heterogeneous and influenced by the type and number of specific MetS traits [Figure 1].

DIVERSE MECHANISMS CONTRIBUTE TO HEPATIC AND EXTRAHEPATIC COMPLICATIONS IN MASLD

The pathophysiological connections between MASLD, systemic metabolic dysfunction, and extrahepatic complications are complex, multifactorial, and multidirectional. It is key to note that MASLD and MetS can occur without obesity, indicating that, in some individuals, the disease is driven by primary hepatic effectors that modulate tissue crosstalk. Furthermore, even low-to-moderate alcohol consumption likely contributes to MASLD risk and disease severity and should be considered as a key amplifying MASLD risk factor[5].

Table 1. Evidence indicating the impact of increasing numbers of MetS traits on hepatic and extrahepatic complications commonly associated with SLD

Study (Participants)	MetS traits	Outcomes	Key findings
Guzder *et al*. (2006)[33] (562 patients with newly diagnosed T2DM)	Defined according to NCEP 2001 criteria[34] - Overweight - Hypertension - Hypertriglyceridemia - Low HDL-C - Hyperglycaemia	Prevalent CVD and CHD (113 cases of CVD and 80 cases of CHD)	Compared to participants without MetS (≤ 2 traits), the presence of the MetS (> 2 traits) increased the risk of prevalent CVD (aOR: 2.54; 95%CI: 1.31-4.93) and prevalent CHD (aOR: 4.06; 95%CI: 1.66-9.92)
		Incident cardiovascular (98 events over a median follow-up of 5 years)	Compared to participants without MetS, the presence of the MetS increased the risk of incident CVD (aHR: 2.05; 95%CI: 1.13-3.74) and showed a trend for increased incident CHD risk (aHR: 1.94; 95%CI: 0.92-4.09)
		Incident CHD (60 events over a median follow-up of 5 years)	There was a fivefold increase in the risk of CVD in participants with all five traits compared to those with only T2DM and the risk of CVD increased linearly with the increasing presence of MetS traits
Kanwal *et al*. (2018)[35] (271,906 patients with NAFLD)	- Obesity - T2DM - Hypertension - Dyslipidaemia (hypertriglyceridemia and/or low HDL-C)	Incident HCC (253 events over a median follow-up of 9.3 years) Incident liver cirrhosis (22,794 events over a median follow-up of 9.3 years)	Compared to patients with one or no traits, the risk of progression to the composite outcome (Either incident HCC or incident liver cirrhosis) increased as the number of MetS traits increased aHR (95%CIs) for risk of incident composite outcome were: 1.33 (1.26-1.40), 1.61 (1.53-1.69), and 2.03 (1.93-2.13) in those with 2, 3, and 4 MetS traits, respectively When considering individual traits, the presence of hypertension had the greatest impact on the risk of all incident outcomes and this risk was further increased by the presence of T2DM
Shang *et al*. (2024)[14] (230,993 patients with T2DM)	Defined according to WHO 1998 criteria[36] - T2DM - Hypertension - Obesity - Hypertriglyceridemia - Low HDL-C -Albuminuria	Incident MALO (3,215 events over a median follow-up of 9.9 years)	Compared to patients with only T2DM, the risk of incident MALO increased as the number of MetS traits increased aHR (95%CIs) for risk of incident MALO were: 1.55 (1.01-2,38), 2.35 (1.54-3.59), 2.69 (1.76-4.11), 3.42 (2.22-5.27), and 4.09 (2.50-6.68) in those with 2, 3, 4, 5, and 6 MetS traits, respectively When considering individual traits, hypertension consistently had the strongest association with incident MALOs
Bilson *et al*. (2024)[37] [234,488 participants with (HSI > 36) or without (HSI < 30) SLD]	Defined according to MASLD criteria[2] - Dysglycaemia/T2DM - Hypertension - Overweight/central obesity - Hypertriglyceridemia - Low HDL-C	Prevalent CKD (10,232 cases in those with or without SLD) Incident ESRD (229 events over a median follow-up of 13.6 years)	Compared to participants with no SLD and no MetS traits, the risk of prevalent CKD increased as the number of MetS traits increased aOR (95%CIs) for prevalent CKD were: 1.10 (0.94-1.31), 1.53 (1.35-1.74), 2.06 (1.83-2.33), 3.11 (2.76-3.51), and 5.83 (5.11-6.65) in those with SLD and 1, 2, 3, 4, and 5 MetS traits respectively When exploring individual traits, only hypertension and dysglycaemia/T2DM were associated with an increased risk of prevalent CKD An analysis of the incident ESRD as the outcome was done by comparing the risk of outcome between those with SLD with vs without the MetS (i.e., > 3 traits). The presence of the MetS (≥ 3 traits) in participants with SLD significantly increased the risk of incident ESRD (aHR: 1.70; 95%CI: 1.19-2.43) compared to those with SLD but without the MetS (i.e., < 3 traits)
Henney *et al*, (2024)[13] 163, 301 patients with MASLD based on ICD-10 code or positive modified HSI	Defined according to MASLD/Alberti *et al*.'s (2009) criteria[38] - Insulin resistance/Dysglycaemia/T2DM - Hypertension - Overweight/central obesity	Primary outcome: Time-to-incident composite micro- and macrovascular disease Secondary outcomes: Time-to-incident	Compared with a reference arm of adults without any MetS components or hepatic steatosis: MASLD, defined by hepatic steatosis and insulin resistance (n = 15,937), carried the highest risk of microvascular disease [HR:13.93 (95%CI: 8.55-22.68)]

- Hypertriglyceridemia - Low HDL-C	individual micro- and macrovascular disease components	MASLD, defined by hepatic steatosis and hypertension (*n* = 53 028), carried the highest risk of macrovascular disease [7.23 (6.45-8.13)] MASLD with all MetS components carried the greatest risk of both micro- [31.20 (28.88-33.70) (*n* = 462,789)] and macrovascular [8.04 (7.33-8.82) (*n* = 336 010)] disease

MetS: Metabolic syndrome; T2DM: type 2 diabetes mellitus; HDL-C: high-density lipoprotein-cholesterol; NCEP: national cholesterol education program; CVD: cardiovascular disease; CHD: coronary heart disease; aOR: adjusted odds ratio; CI: confidence interval; aHR: adjusted hazard ratio; NAFLD: non-alcoholic fatty liver disease; HCC: hepatocellular carcinoma; MALO: major adverse liver outcomes; MASLD: metabolic dysfunction-associated steatotic liver disease; SLD: steatotic liver disease; HIS: hepatic steatosis index; CKD: chronic kidney disease; ESRD: end-stage renal disease; ICD-10: international classification of diseases, 10th revision.

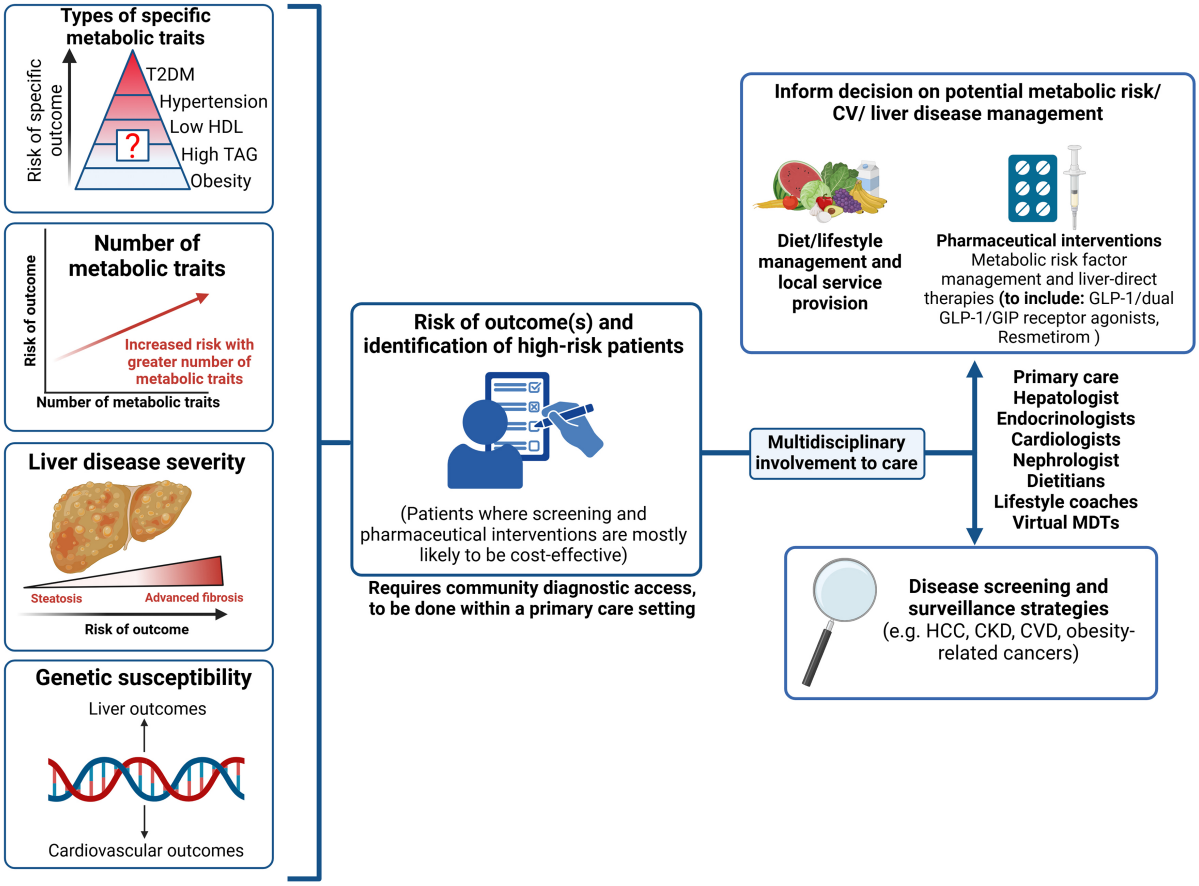

Figure 1. Consideration of type and number of metabolic syndrome traits along with hepatic disease severity and genetic susceptibility to inform clinical decision making in patients with MASLD. Figure was made using BioRender (https://BioRender.com/e3uqzr1). T2DM: Type 2 diabetes mellitus; HDL: high-density lipoprotein; TAG: triacylglycerol; CV: cardiovascular; GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulinotropic polypeptide; MDTs: multidisciplinary teams; HCC: hepatocellular carcinoma; CKD: chronic kidney disease; CVD: cardiovascular disease; MASLD: metabolic dysfunction-associated steatotic liver disease.

Genetic factors also contribute to mechanisms, metabolic dysfunction, and risk of complications in MASLD. Through using partitioned polygenic risk scores, emerging evidence suggests that there are two distinct types of MASLD, one confined to the liver and resulting in a more severe hepatic phenotype and the other appearing to be influenced by metabolic dysfunction and leading to a greater risk of cardiometabolic disease[6]. These findings highlight the modulatory role that genetic risk factors may have on the development of MASLD and associated extrahepatic complications. Combining genetic screening and

metabolic burden assessment along with hepatic disease severity in MASLD risk frameworks could facilitate personalised and more effective clinical management strategies [Figure 1]. A detailed discussion of the mechanisms underlying MASLD and its associated complications is beyond this perspective but is reviewed elsewhere[3,7].

HOW MAY THE NEW INFORMATION ON METABOLIC DYSFUNCTION IN MASLD INFORM PATIENT CARE?

The data discussed above illustrate that a combination of inter-related factors, including polygenic risk, associated metabolic dysfunction and fibrosis severity, influence hepatic and extrahepatic outcomes. The new information regarding the prognostic relevance of the extent/severity of metabolic dysfunction necessitates a shift in our care models of these patients from considering MASLD as a liver disease, solely being within the remit of hepatologists with the focus on liver-related outcomes, to its consideration as a systemic, metabolic disease with associated multisystem (particularly cardiovascular and malignant) complications. This new perspective requires true multidisciplinary expertise with a much greater emphasis on community-based management, considering the population burden[8].

Metabolic risk factors influence outcomes and implications for screening and risk stratification

The prognostic impact of metabolic risk factors on hepatic and extrahepatic outcomes has significant implications for screening, risk stratification, and establishing a clinical care pathway/novel model of care for patients with MASLD. This "expanded" model of care aligns more closely with other diseases (e.g., coronary heart disease, type 1 and type 2 diabetes) where clinical assessment extends beyond the single organ to address the inherent risk of complications linked to diabetes. In the same way, for patients living with proven MASLD, new care models must focus on cardiovascular risk factor management and metabolic health optimisation to reduce rates of adverse hepatic and extrahepatic (cardiovascular and malignant) outcomes. T2DM and hypertension seem to have a disproportionate impact, compared with other metabolic risk factors, and therefore, should assume greater prioritisation for management.

Changing the focus of the treatment aims

Metabolic health treatment strategies must meaningfully consider non-pharmacological approaches with lifestyle interventions involving diet/weight loss and increased physical activity to reduce metabolic substrate delivery to the liver[9]. To achieve and maintain weight loss, patients need support from publicly focussed services (facilitating access to leisure centres/weight management classes) and access to primary care and secondary care weight management services where indicated. Physical activity has an important effect on liver health and should be promoted where possible, utilising the expertise of lifestyle coaches and exercise physiologists[10,11].

New guidelines place importance on the interaction of metabolic risk factors with alcohol, reflected in the nomenclature "MASLD and increased alcohol intake", characterised by MASLD combined with modest levels of alcohol intake (defined as 140-350 and 210-420 g/week for women and men, respectively)[2,12]. Individuals with SLD, particularly those with moderate or high alcohol intake, should be discouraged from consuming alcohol, while complete abstinence from alcohol should be encouraged in individuals with advanced fibrosis or cirrhosis. Pharmacological approaches must: (i) assess and optimise cardiometabolic multimorbidity with aggressive blood pressure lowering and treatment of dyslipidaemia and increased cardiovascular risk, given that CVD is the leading cause of death for people with MASLD; and (ii) consider and treat aggressively associated obesity and dysglycaemia with T2DM, knowing their disproportionate impacts, on all these of risks.

Risk stratification and screening of high-risk groups in the general population

Knowing the interconnectedness of obesity and T2DM with MASLD and their respective complications[13,14], and considering the importance of T2DM as arguably the metabolic risk factor of greatest importance[15], such patients' management must be prioritised. Indeed, stratified management of MASLD is supported by recent meta-analyses and large-scale cohort studies demonstrating that increasing metabolic burden severity and liver fibrosis severity are strongly linked to higher risks of CVD, incident diabetes, and all-cause mortality[16-19]. This is important from the perspective of considering liver disease and obesity-related and T2DM complication rates. Early detection of asymptomatic fibrosis via targeted screening of at-risk groups is needed to intervene and prevent progression to cirrhosis and its complications and primary liver cancer. Targeted screening for MASLD fibrosis is performed variably throughout the UK, particularly in those with T2DM[20], as we currently lack robust evidence regarding whether this is cost-effective[21].

Current studies aim to assess the feasibility and acceptability of a primary care liver fibrosis testing pathway that could be centred on aspects of the diabetes annual review[21,22]. Reflex testing of fibrosis-4 (FIB-4) as part of screening has been shown to be effective[23] and ongoing studies are exploring the cost-effectiveness of vibration-controlled transient elastography screening in a primary care setting[21]. T2DM treatment guidelines should emphasise novel glucose-lowering and weight loss therapies such as sodium-glucose linked transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dual GLP-1 and gastric inhibitory peptide (GIP) receptor agonists, that potentially reduce liver fat/fibroinflammation, improve glycaemic control, lower body weight significantly, and treat multiple MetS traits simultaneously. These drug classes should be introduced earlier in glucose-lowering treatment algorithms for those with T2DM.

Establishing models of delivery of care with multidisciplinary involvement

A multidisciplinary approach to the management of MASLD is associated with improvement in markers of both liver and cardio-metabolic health and proven cost-effectiveness[24]. Effective disease management requires setting up multidisciplinary teams with nursing teams and multiple specialists working collaboratively within primary care, internal medicine physicians including diabetologists, lipidologists, cardiologists, nutritionists and metabolic physicians, bariatric surgeons, and providers with expertise in lifestyle management[7]. Beyond the physician, the role of nursing input ranging from health care assistant to clinical nurse specialists, alongside other critical allied health care professionals including nutrition and physical activity experts, provides patient education, lifestyle intervention support, and multidisciplinary care coordination[25-28].

Such community-based models of care may be delivered virtually. This may consist of monthly (e.g., Microsoft Teams style) meetings with large volumes of clinical cases reviewed and discussed with suggestions for optimal disease management so that best practice can be implemented without the patient needing to attend for face-to-face review and management plans implemented by single, local practitioners. In selected cases where face-to-face review is required, the co-location of specialists in the same clinic allows a "one-stop-shop". The inclusion of standardised lifestyle assessment and intervention, including counselling on diet, affordable cooking, exercise, sleep hygiene, alcohol, and smoking cessation, is also relevant, either in person or using digital platforms (web or patient-directed apps).

Future strategies must also incorporate better public health engagement with a need to improve population-wide patient education and support for healthy behaviours, particularly in regions of high deprivation.

Transition of place of care to the community

Currently, although most cases of MASLD are managed in primary care, selected "high-risk" cases are referred to secondary care, usually hepatologists, whose focus is the assessment of liver fibrosis risk, considering that this has the greatest impact on liver-related and all-cause mortality. Fibrosis risk is evaluated using biomarkers such as FIB-4, with those at intermediate or high risk undergoing further evaluation with second-tier tests such as transient elastography or enhanced liver function (ELF). Pending these results, patients may require referral to a hepatologist. The hepatologists' primary role at present is surveillance and management of HCC and oesophageal varices and treatment of decompensated liver cirrhosis in high-risk individuals[29], but their role will inevitably extend in the near future to the use of specific (and expensive) liver-specific drugs targeting liver fibrosis. Given the high prevalence and complexity of MASLD extending beyond the liver, the new norm must be that MASLD services are concentrated in primary care utilising community diagnostic hubs with access to community-based equipment and better education of health care practitioners (medical/nursing staff including upskilling of health care assistants). Effective local management accelerates diagnosis and treatment, helping to further reduce pressure on hospitals and enhancing patient and GP satisfaction[30]. Transient elastography should be widely available in the community, not only to streamline services and facilitate referral to specialist hepatologists but also to promote lifestyle changes considering the concept of biofeedback where knowledge of disease states influences physical activity and drinking patterns[31,32].

CONCLUSION

Risk stratification and subsequent management of MASLD should consider genetic susceptibility, lifestyle patterns, liver disease severity/fibrosis risk, and importantly, the number and nature of associated MetS traits. While all approaches must be underpinned by reinforcing lifestyle changes, specific liver-directed therapies are becoming available to prevent or reverse steatosis or fibroinflammation. In parallel, the new and emerging GLP-1/incretin-based therapies used in the management of obesity and T2DM are becoming particularly relevant not only for their known efficacy in treating T2DM and reversing/improving liver fibroinflammation, but also for their impact on multiple cardiometabolic risk factors. Risk stratification should consider MetS traits together with liver fibrosis and focus attention on cardiometabolic risk factor management. Reversing MetS traits, especially with aggressive management of T2DM, hypertension, and obesity, is potentially important for improving patient outcomes and well-being with MASLD. Finally, community-based, multidisciplinary teams with access to relevant diagnostic (blood- and imaging-based) tools are imperative and will facilitate the integration of primary and secondary care services for identifying and treating this highly prevalent multisystem disease.

DECLARATIONS

Authors' contributions

Contributed equally to writing the first draft, editing and reviewing the final version of the manuscript: Bilson J, Cuthbertson DJ, Byrne CD

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Bilson J is a Junior Editorial Board member and Byrne CD is an Honorary Editor-in-Chief of the journal *Metabolism and Target Organ Damage*. Bilson J and Byrne CD were not involved in any steps of editorial

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Not applicable.

Consent for publication

Not applicable.

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