

International Journal of
**ATHEROGENIC
DIABETIC DYSLIPIDEMIA**

THIS ISSUE

Original Article
Review Article

Editor-in-Chief

Dr. Prof. Subhankar Chowdhury

**VOLUME 7
ISSUE 1**



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***International Journal of ATHEROGENIC DIABETIC
DYSLIPIDEMIA***

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About the Journal

Atherogenic dyslipidemia, characterized by elevated triglycerides (TGs), raised small dense LDL (low-density lipoprotein) levels and decreased HDL (high-density lipoprotein) cholesterol levels, is the most common pattern of dyslipidemia in type 2 diabetic patients. It is characteristically seen in patients with obesity, metabolic syndrome, insulin resistance, and T2DM and has emerged as an essential marker for the increased CVD risk observed in these populations. In fact, the combined presence of dyslipidemia and diabetes escalates the CV risk by 3–4 times.

Dyslipidemia, diabetes and hypertension are all a part of the cluster that includes nonalcoholic fatty liver disease (NAFLD) too, another major CVD risk factor. As diabetic dyslipidemia is characterized by hypertriglyceridemia, the risk of pancreatitis is also high in these patients.

With the increasing burden of these conditions in the world, clinicians can struggle to keep themselves updated in the advances in research and therapy.

With this journal, we aim to keep doctors updated in the current understanding, trends in therapy and new modalities of care. Our objective is:

- ❑ To be the knowledge partner for healthcare professionals by presenting contemporary research and novel treatment options in the field of atherogenic diabetic dyslipidemia.
- ❑ To raise awareness about the latest clinical practices, for better management of the condition, thus improving on the standards of overall disease management
- ❑ To provide researchers of the field with a medium to elicit like thought processes in their peers working on similar innovations or experiments
- ❑ To provide clinicians with a platform to showcase their case studies

International Journal of Atherogenic Diabetic Dyslipidemia will contain literature encompassing all the scientific and clinical aspects that address the cause and management of atherogenic dyslipidemia. The content of the journal shall include, but not limited to subject areas like atherogenic dyslipidemia, obesity, NAFLD, acute pancreatitis, hypertriglyceridemia, pharmacological management/therapeutic options for atherogenic dyslipidemia in type 2 diabetes and new strategies for management.

We hope to provide a platform to publish interesting and informative articles on topics connected with the management of atherogenic diabetic dyslipidemia as well as encourage correspondence and participation from our readers.

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Real-world Consensus on ADD Management: Insights from an Indian Physician Survey

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Article information

Received date: 29/04/2026; **Accepted date:** 25/05/2025; **Published date:** 29/05/2025

ABSTRACT

Background: Atherogenic diabetic dyslipidemia (ADD), defined by elevated triglycerides, reduced high-density lipoprotein cholesterol, and predominance of small dense low-density lipoprotein particles, is a highly prevalent phenotype among individuals with type 2 diabetes mellitus (T2DM), particularly within South Asian populations. Despite the availability of international guidelines, significant gaps persist in the realworld diagnosis and management of atherogenic diabetic dyslipidemia in India.

Objective: To establish expert consensus recommendations for the diagnosis and management of atherogenic diabetic dyslipidemia in Indian clinical practice.

Method and Result: A structured survey was conducted between April and August 2025 among 146 Indian physicians to generate consensus statements addressing epidemiology, pathophysiology, screening, diagnostic criteria, lipid targets, lifestyle interventions, and pharmacological management of atherogenic diabetic dyslipidemia in T2DM. Predefined agreement thresholds defined consensus. Strong agreement of 66.44% was achieved on the high prevalence of atherogenic diabetic dyslipidemia in Indian patients with T2DM, the necessity of lipid assessment beyond low-density lipoprotein cholesterol (LDLC) (with emphasis on triglycerides, nonHDLC, and apolipoprotein B), and the universal role of lifestyle modification as foundational therapy. Statins were endorsed as essential for highrisk patients irrespective of baseline LDLC, with frequent recognition of the need for combination therapy to mitigate residual atherogenic risk.

Conclusion: This consensus underscores the importance of a phenotypebased, comprehensive approach to dyslipidemia management in Indian patients with diabetes. Early identification of atherogenic diabetic dyslipidemia and individualized treatment strategies are critical to reducing cardiovascular risk in this population.

Keywords: Atherogenic diabetic dyslipidemia, Type 2 diabetes mellitus, Hypertriglyceridemia, Residual cardiovascular risk, Saroglitazar

INTRODUCTION

Atherogenic diabetic dyslipidemia (ADD) is a distinct lipid phenotype that contributes substantially to residual cardiovascular risk in patients with type 2 diabetes mellitus (T2DM). Characterized by elevated triglycerides (TG) (≥ 150 mg/dL), low high-density lipoprotein cholesterol (HDL-C) (< 40 mg/dL in men, < 50 mg/dL in women), raised apolipoprotein B (apo B), and a predominance of small dense low-density lipoproteins (sd-LDL), ADD is particularly prevalent among South Asians. This pattern reflects the interplay of hyperglycemia, adipocytokine imbalance, and early, severe insulin resistance, further compounded by truncal obesity and high carbohydrate intake, making ADD both highly prevalent and clinically challenging in Indian practice.¹

Epidemiological data underscore ADD's high burden in Indian diabetics, with prevalence reaching 34% in treatment-naïve patients, 73% of whom had poor glycemic control (HbA1c $> 8\%$) and 89% of newly diagnosed cases showing dyslipidemia at presentation.² The diabetes epidemic has surged from 90 million cases in 2011 to 140 million by 2025, amplifying ADD as a primary complication and mortality in T2DM patients compared to non-diabetics.³ The Research Society for the Study of Diabetes in India (RSSDI) 2022 consensus guidelines emphasize annual screening and comprehensive profiling (including non-high-density lipoprotein [HDL]-C and apo B) for all diabetics, recognizing ADD's unique atherogenicity in South Asians versus Caucasians.

Persistent uncertainties surround ADD management in India, including optimal TG cutoffs (> 150 mg/dL for diagnosis, > 200 mg/dL for cardiovascular disease (CVD) risk intervention, > 500 mg/dL for pancreatitis prevention), fasting versus non-fasting TG reliability, and residual risk strategies beyond statins despite LDL-C control. While global guidelines predominantly prioritize LDL-C lowering as the primary strategy for CVD risk reduction, emerging evidence indicates that residual CVD risk persists despite achieving optimal LDL-C levels. Evidence also supports hypertriglyceridemia, particularly in the context of insulin resistance and sd-LDL predominance contributing to CVD risk. Lipoprotein(a) further elevates risk dose-dependently, yet population-specific thresholds remain underexplored (4).

The current study addressed these gaps through a consensus survey capturing opinions from 146 Indian physicians on ADD prevalence, diagnosis, and management in diabetic patients. Experts reviewed RSSDI guidelines alongside emerging evidence on insulin resistance-driven Very low-density lipoprotein (VLDL) overproduction, Triglyceride-Glucose (TyG) index utility, and therapies targeting residual TG risk (e.g., saroglitazar dual lipid-glycemic benefits).

This survey establishes practical, evidence-based recommendations tailored to Indian diabetics, validating RSSDI frameworks while resolving real-world ambiguities in ADD care. Near-universal consensus ($> 90\%$ in key areas) underscores the need for ADD-specific screening, multi-marker assessment, and stepwise intensification beyond LDL-C targets to mitigate India's escalating CVD burden in diabetes.

METHOD

1.1 Study design and questionnaire development

A structured survey was employed to facilitate optimal consensus among a broad panel of 146 expert physicians from diverse backgrounds. This systematic approach provided comprehensive, expert-driven opinions to ensure robust, evidence-based agreement.⁵ The expert panel comprised physicians from across India with expertise in diabetes and dyslipidemia management, including clinicians from key specialties involved in cardiometabolic care [internal medicine (n=84), endocrinology (n=39), cardiology (n=20), nephrology (n=3)], representing diverse clinical practice settings and supporting a multidisciplinary, practice-oriented consensus process. The consensus survey was conducted manually, with responses collected and compiled by the research team, ensuring broad geographic participation across India [North zone (n=24), South zone (n=37), West zone (n=25), East zone (n=60)], complete response capture, and standardized recording of all consensus items. The scientific committee, constituted based on members' extensive expertise and professional experience, collaborated with practising physicians to design the survey questionnaire. Survey development was guided by a structured literature search that prioritized systematic reviews and other critical evidence syntheses from databases such as MEDLINE, EMBASE, and PubMed, supplemented by manual review of relevant articles identified through keywords including *atherogenic dyslipidemia* and *cardiovascular risk*. Each item was drafted as a clear statement, affirmative or negative, intended to capture professional opinion or clinical recommendations and to address areas of uncertainty, debate, or practical relevance in the management

of atherogenic dyslipidemia. The final questionnaire comprised consensus statements grouped into three domains: disease prevalence (4 items), diagnosis (4 items), and disease management (8 items). The expert panel reviewed these statements (Table 1) and voted using predefined criteria (“strongly agree,” “agree,” “disagree,” “undecided,” or “not my area (NA) of expertise”), providing comments for refinement. Responses were analyzed descriptively, with consensus defined as $\geq 80\%$ respondents selecting ‘Agree’ or ‘Strongly agree’ in line with established survey methodologies. The response option “Not my area of expertise” was included to allow panellists to abstain from statements outside their clinical scope and to preserve the validity of responses. For consensus calculations, NA responses were excluded from the denominator; thus, agreement was expressed as the proportion of substantive responses selecting “Strongly agree” or “Agree” (i.e., among non-NA responses). Iterative rounds incorporated feedback, with revised statements recirculated until convergence was achieved, followed by final approval. The approved statements informed the manuscript and were endorsed by all authors.

Table 1. Expert consensus levels of agreement (N = 146 experts).^a

Statements	Strongly agree (%)	Agree (%)	Disagree (%)	Strongly disagree (%)	Undecided (%)	Consensus (% SA+Agree)
Disease prevalence						
1. Indian diabetic patients with TG ≥ 150 mg/dL, low HDLC (<40 mg/dL in men, <50 mg/dL in women), and abnormal sdLDL should be classified as ADD patients	66.44	28.77	0.68	–	3.42	95.21
2. In South Asians, insulin resistance is more common and occurs earlier, contributing to the increasing ADD incidence	72.60	23.97	–	–	2.74	96.57
3. Elevated TG is more common than LDL-C in Asians; hypertriglyceridemia should be considered a significant CVD risk factor	48.63	41.10	0.68	–	8.90	89.73
4. In patients with controlled LDL-C on statins, elevated TG increases residual CVD risk	40.41	44.52	2.74	–	10.27	84.93
Diagnosis						
1. Fasting TG is more reliable than non-fasting TG, though non-fasting can be used if fasting is unavailable.	38.36	45.89	6.85	0.68	7.53	84.25
2. TG ≥ 150 mg/dL should be used as the cut-off for hypertriglyceridemia in Indian patients	36.99	41.10	5.48	–	13.70	78.09
3. Non-HDL-C and apoB should be considered secondary markers for CVD risk along with TG and LDL-C	48.63	43.84	1.37	–	5.48	92.47
4. The TyG index is a validated marker for insulin resistance and CVD and should be regularly calculated	34.25	43.84	3.42	–	17.81	78.09

Statements	Strongly agree (%)	Agree (%)	Disagree (%)	Strongly disagree (%)	Undecided (%)	Consensus (% SA+Agree)
Management						
1. Lifestyle modifications (weight reduction, diet, stress reduction) are first-line before medical therapy	78.08	15.75	1.37	–	1.37	93.83
2. Statin therapy is the first-line medication for managing dyslipidemia in diabetes	76.71	19.18	–	0.68	1.37	95.89
3. TG >200 mg/dL should be the threshold to initiate medication for CVD risk reduction	38.36	40.41	4.11	–	14.38	78.77
4. TG >500 mg/dL should be treated to prevent pancreatitis	86.30	10.27	–	–	0.68	96.57
5. In patients with controlled LDL-C post statin, if TG >200 mg/dL, non-statin agents (ezetimibe, bempedoic acid, PCSK9 inhibitors) should be added	39.04	34.93	11.64	1.37	9.59	73.97
6. In patients with controlled LDL-C on statins, if TG >200 mg/dL, TG-lowering drugs (saroglitazar, fenofibrate, icosapent ethyl, niacin) should be added	48.63	41.78	3.42	–	3.42	90.41
7. In patients with TG >500 mg/dL, TG-lowering drugs should be started (with or without statins) to prevent pancreatitis	79.45	15.07	0.68	–	0.68	94.52
8. Saroglitazar is the preferred add-on to statins for hypertriglyceridemia, given insulin-sensitizing and glycemic benefits	67.81	26.03	0.68	–	2.74	93.84

Note: ^a Responses marked as Not applicable (NA) were excluded from the analysis as they were considered analytically non-informative and did not contribute meaningfully to the assessment of consensus. The results presented include only valid responses, and consensus statements were derived based on the proportion of respondents selecting “Agree” and “Strongly agree,” which represented the predominant statements observed.

The proportion of NA responses across individual statements ranged from 0.68% to 4.11%, indicating minimal item-level abstention. ADD = atherogenic diabetic dyslipidemia; apoB = apolipoprotein B; CVD = cardiovascular disease; HDLC = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; sdLDL = small dense low-density lipoproteins; TG = triglycerides; TyG = triglyceride-glucose index.

1.2 Disease prevalence

Hyperglycemia, insulin resistance, adipocytokine imbalance, and insulin deficiency disrupt lipid metabolism in diabetes, creating a distinct profile common among South Asians.⁶ Compared to Caucasians, Indians typically exhibit only modestly elevated LDL-C levels but a higher proportion of sd-LDL particles, alongside raised fasting triglycerides (>150 mg/dL), increased apo B, and lower HDL-C, collectively defining atherogenic diabetic dyslipidemia.⁴ These features are further aggravated by abdominal adiposity (waist circumference exceeding 90 cm in men or 80 cm in women) and features of metabolic syndrome. Atherogenic diabetic dyslipidemia affects 34% of treatment-naïve Indian diabetics, with 73% exhibiting poor glycemic control (HbA1c >8%) and 89% demonstrating dyslipidemia across the studied groups.⁷

Beyond LDL-C alone, comprehensive screening with non-HDL-C, apolipoprotein B (apo B), fasting/non-fasting triglyceride profiles, and ethnicity-adjusted QRISK3 proves essential for diabetics stratified as high/very high CVD risk per RSSDI guidelines (considering comorbidities and target organ damage).⁸ Single-time lipoprotein(a) assessment merits recommendation, particularly with a family history of premature CVD.⁹ Risk enhancers that shift low or moderate-risk diabetics into higher categories, requiring stricter LDL-C targets, include triglyceride elevations above 150 mg/dL (or >175 mg/dL in the nonfasting state), intermediate lipoprotein(a) levels (20–49 mg/dL), impaired fasting glucose in the 100–125 mg/dL range, and high-sensitivity C-reactive protein values exceeding 2 mg/L.¹⁰ Additional modifiers comprise air pollution exposure, inflammatory joint disease, premature menopause, preeclampsia, gestational diabetes, polycystic ovary syndrome, elevated polygenic risk scores, and chronic infections.¹¹

High-density lipoprotein particles confer cardiovascular protection by facilitating reverse cholesterol efflux from peripheral tissues to the liver and promoting endothelium-mediated vasorelaxation, plus anti-inflammatory, antithrombotic, and antioxidant mechanisms. Diabetes markedly impairs HDL's anti-inflammatory function, making isolated HDL-C levels unreliable for CVD risk assessment.¹² The HDL concentration, composition, metabolism, and functionality diverge substantially from nondiabetic norms; type-1 diabetes mellitus (T1DM) with nephropathy or T2DM frequently displays low HDL-C, even as some T1DM cases maintain normal/elevated levels despite heightened CVD incidence from distorted cholesteryl ester/triglyceride ratios, diminished phospholipids, impaired macrophage cholesterol efflux, reduced anti-inflammatory/antioxidant capacity, and other proatherogenic traits. T2DM produces triglyceride-laden HDL prone to rapid catabolism.¹³

Lipoprotein(a), structurally akin to plasminogen, binds its receptors to heighten thrombosis and aids CVD risk reclassification among moderate/high-risk individuals.¹⁴ In patients with T2DM who develop CVD or related complications, ADD is frequently characterized by altered apolipoprotein profiles together with genetic polymorphisms that modulate lipid metabolism and amplify diabetes-associated CVD risk.¹⁵ Apolipoprotein B reveals high-risk dyslipidemia patterns overlooked by routine lipid panels, informing lipid-lowering therapy initiation to curb cardiovascular morbidity/mortality, particularly among hypertriglyceridemia or coronary heart disease (CHD) patients achieving LDL-C/non-HDL-C goals.¹⁶ The European Society of Cardiology (ESC) guidelines position apo B as superior to LDL-C for assessing atherogenic lipoprotein burden, especially in diabetes, obesity, hypertriglyceridemia, or very low LDL-C contexts.¹⁷

1.3 Diagnosis

Diagnosing ADD demands comprehensive lipid profiling that surpasses traditional LDL-C evaluation alone. This phenotype manifests through persistently low HDL-C, raised triglycerides, and a predominance of sd-LDL particles collectively forming atherogenic lipid triad typical of diabetic patients. The pattern proves especially prominent among South Asians, where unremarkable LDL-C concentrations often mask substantial loads of proatherogenic lipoproteins.¹⁸

Both fasting and non-fasting lipid assessments serve for initial screening; however, fasting profiles gain preference amid hypertriglyceridemia since triglyceride levels fluctuate markedly with meals and insulin resistance, while postprandial surges may distort LDL-C computations. Fasting triglycerides thus offer superior risk estimation, whereas apo B and non-HDL-C function as robust indicators of particle number irrespective of prandial state. Triglyceride-enriched remnants including chylomicrons and VLDL characterize hypertriglyceridemia in diabetes and metabolic syndrome, with their prolonged circulation driving atherogenesis and constituting residual risk despite optimized LDL-C.¹⁹

ApoB measurement holds particular utility in South Asian populations, precisely quantifying total atherogenic particles and associating more robustly with cardiovascular outcomes than LDL-C amid elevated triglycerides or adiposity. Advanced techniques quantifying sd-LDL subfractions, when accessible, enhance diagnostic precision, given sd-LDL enrichment as a signature of South Asian diabetic dyslipidemia.²⁰ Screening merits initiation at diabetes diagnosis, with annual repetition and accelerated intervals for suboptimal glycemic regulation, manifest CVD, or lipid-modifying treatments. Prompt phenotype recognition proves vital, frequently antedating clinical events and sustaining residual risk post-glycemic optimization, thus underscoring targeted diagnostics for effective management.²¹

Fasting ≥ 8 hours isolate predominantly hepatic lipoproteins, contrasting non-fasting profiles that incorporate intestinal remnants for a comprehensive 24-hour atherogenic exposure snapshot. Contemporary assays enable reliable non-fasting LDL-C derivation, with evidence affirming equivalent cardiovascular risk prediction across prandial states. While fasting triglycerides represent the benchmark in mild, moderate, or severe hypertriglyceridemia, permitting non-fasting evaluations

streamlines routine practice, surmounting adherence obstacles and broadening diabetic risk appraisal.²²

Accurate ADD evaluation hinges on strategic fasting/non-fasting threshold application.²³ Fasting lipid panels become imperative when non-fasting triglycerides surpass 440 mg/dL, signaling potential secondary etiologies or severe familial hypertriglyceridemia. Likewise, non-fasting non-HDL-C ≥ 220 mg/dL raises familial lipid disorder suspicion, prompting fasting confirmation, especially alongside premature cardiovascular disease family history. Fasting testing endures as the cornerstone for familial hyperlipidemia screening and monitoring.²⁴

Moderate non-fasting triglyceride elevations (~ 175 mg/dL) require no mandatory fasting verification but necessitate lifestyle guidance. Non-fasting triglycerides ≥ 200 mg/dL justify repeat fasting profiling within 2–4 weeks to validate persistence and inform intervention. Established lipid thresholds provide a practical framework for identifying heightened atherogenic burden in patients with diabetes.²⁵ Fasting triglyceride concentrations at or above 150 mg/dL, or nonfasting values ≥ 175 mg/dL, are considered abnormal and signal residual risk. NonHDL-C levels ≥ 145 mg/dL in the fasting state or ≥ 150 mg/dL when nonfasting denote excess atherogenic lipoproteins, while LDL-C values ≥ 115 mg/dL are clinically relevant for risk stratification.²⁶ Apo B concentrations ≥ 100 mg/dL further identify high-risk dyslipidemia patterns not captured by routine lipid panels. In addition, remnant cholesterol levels ≥ 30 mg/dL (fasting) or ≥ 35 mg/dL (nonfasting) reflect increased residual risk.^{16, 27} Collectively, these thresholds underscore the importance of comprehensive lipid assessment in ADD and provide a framework for intensifying therapy to reduce cardiovascular morbidity and mortality. Incorporating prandial-specific cutoffs further strengthens diagnostic workflows by balancing feasibility with accuracy, thereby ensuring that high-risk South Asian patients with diabetes are appropriately prioritized for early identification and targeted intervention.^{28, 29}

1.4 Management

Effective dyslipidemia management in diabetes requires an integrated strategy targeting lipid derangements, metabolic abnormalities, and modifiable cardiovascular risks.³⁰ Lifestyle optimization forms the foundation, particularly for hypertriglyceridemia, encompassing smoking cessation, routine exercise, structured nutrition, adequate sleep, and mental health support.³¹ Recent American Diabetes Association (ADA) guidance advises intensified lifestyle measures and glycemic control in diabetics with elevated triglycerides or low HDL-C. Alcohol intake should be restricted to ≤ 2 drinks/day in men and ≤ 1 drink/day in women when triglycerides are 150–499 mg/dL, with complete abstinence mandated at ≥ 500 mg/dL to prevent pancreatitis. Achieving 5–10% weight loss reduces triglycerides ($\sim 20\%$), enhanced by high-protein, lower-carbohydrate diets while avoiding refined sugars, high-glycemic foods, and fructose beverages ($>10\%$ energy intake). Maintain total fat at 30–35% calories (favoring monounsaturated fatty acids [MUFAs]/polyunsaturated fatty acids [PUFAs]) for mild-moderate hypertriglyceridemia, reducing to 20–25% (500–999 mg/dL) or $<5\%$ (≥ 1000 mg/dL), potentially incorporating medium-chain triglycerides. The ADA guidance prescribes at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity exercise, with recognition of variability in individual responses.

Pharmacotherapy becomes necessary when lifestyle and metabolic optimization fail to meet lipid goals.³² Attaining very low LDL-C levels through statins represents the primary means to counter ADD's effects. Tailor therapy to the dominant lipid phenotype using agents with established cardiovascular outcomes benefits. Initiate high-intensity statins in high/very high CVD-risk diabetics regardless of baseline lipids.³³ Given dyslipidemia's multifactorial etiology, combination regimens often prove essential for target achievement. Statins serve as the primary pharmacologic therapy for dyslipidemia control in diabetic individuals. Their use extends beyond genetic dyslipidemias (e.g., familial hypercholesterolemia) to primary and secondary CVD prevention, with established benefits in high-risk diabetics, including those with >40 years of disease duration.³⁴ In the absence of contraindications, moderate-to-high-intensity statins are recommended as first-line therapy according to current American Association of Clinical Endocrinology (AACE) guidelines.³⁵ Despite intensive statin regimens, significant residual cardiovascular risk persists in primary prevention populations harbouring multiple risk factors. Landmark statin clinical trials enrolling substantial diabetic cohorts demonstrate clear reductions in CVD events.³⁶

Hypertriglyceridemia management primarily aims to mitigate atherosclerotic cardiovascular risk and prevent pancreatitis. Cardiovascular outcome data supporting triglyceride-lowering lags substantially behind LDL-C reduction evidence, prioritizing LDL-C target attainment for CVD prevention. Conversely, aggressive TG reduction remains essential for pancreatitis prophylaxis, as risk escalates sharply above 500 mg/dL. In statin-treated diabetics attaining LDL-C goals yet exhibiting persistent hypertriglyceridemia (≥ 200 mg/dL), therapy must distinguish LDL particle-mediated versus triglyceride-rich lipoprotein-driven residual risk. Ezetimibe, bempedoic acid, and PCSK9 inhibitors primarily target LDL-C and suit

scenarios of suboptimal LDL-C control or incremental LDL-related risk reduction; their triglyceride-lowering effects remain modest.³⁷

Ezetimibe inhibits intestinal cholesterol absorption and, combined with statins, produces additive LDL-C lowering with improved target attainment. This enables lower statin doses while maintaining efficacy and minimizing adverse effects.³⁸ Ezetimibe shows neutral or favorable glycemic effects in the long term. Guidelines recommend its addition when LDL-C goals persist despite maximal statins; the American Heart Association (AHA) endorses statin-ezetimibe for ($\geq 50\%$ LDL-C) reduction in high-risk diabetics (10-year CVD risk $\geq 20\%$).¹ Bempedoic acid, a liver-selective ATP citrate lyase inhibitor prodrug, reduces hepatic cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, ideal for statin-intolerant patients.^{39,40} PCSK9 inhibitors (alirocumab, evolocumab) achieve 55–72% LDL-C reductions in high-risk groups, including diabetic dyslipidemia, without glycemic detriment. Guidelines support their use when LDL-C (≥ 70 mg/dL) remains despite maximal statins \pm ezetimibe, demonstrating safety and superior efficacy beyond statins alone.^{41,42}

In ADD patients with several co-existing risk factors and triglyceride concentrations above 150 mg/dL on statins, icosapent ethyl provides incremental cardiovascular benefit.⁴³ For triglycerides (≥ 500 mg/dL), prioritize statins and ezetimibe as an add-on treatment, initially to avert pancreatitis before fibrates or alternatives.⁴⁴ Icosapent ethyl addresses residual risk in statin-treated patients with persistent triglycerides, alongside glycemic optimization.⁴⁶ Fenofibrate and saroglitazar (dual peroxisome proliferator-activated receptor alpha/ Gamma [PPAR- α/γ] agonist) effectively reduce triglycerides and improve atherogenic profiles in diabetic dyslipidemia, with South Asian trials confirming substantial TG lowering and good tolerability as statin add-ons.⁴⁵ Saroglitazar has demonstrated robust efficacy in both real-world and trial settings for diabetic dyslipidemia.^{48,49} Niacin lowers TG and raises HDL-C but is limited by flushing, glycemic worsening, and lack of cardiovascular benefit atop statins.⁴⁷ Agent selection considers renal function, glycemic/edema risks, interactions, and lipid phenotype, with non-HDL-C and apoB monitoring.

FINDINGS/DISCUSSION FROM CONSENSUS SURVEY

This national consensus survey provides robust, practice-oriented guidance for identifying and managing atherogenic dyslipidemia in Indian patients with diabetes, emphasizing phenotype-based strategies that move beyond traditional LDL-C-centric approaches. In this Consensus Statement, the authors report the final statements and recommendations, together with a summary of the broader literature on the prevalence, diagnosis, and pharmacological management of ADD.

2.1 Disease Prevalence

The survey demonstrated a strong and consistent expert consensus on the definition and clinical significance of ADD in Indian diabetic patients, as presented in Figure 1. Overall, 95.21% of respondents expressed consensus that the coexistence of raised triglycerides (≥ 150 mg/dL), reduced HDLC (thresholds of <40 mg/dL in men and <50 mg/dL in women), and abnormal sdLDLC levels should define patients as having ADD. This marked level of agreement establishes a clear and clinically relevant diagnostic framework for identifying this high-risk dyslipidemia phenotype in the Indian population.

Experts prodigiously recognized insulin resistance as a central pathophysiological abnormality in South Asians, with 96.57% agreeing that it is more prevalent and occurs earlier in this population. This consensus underscores the importance of considering ethnic-specific metabolic characteristics when assessing cardiovascular risk in Indian patients, as traditional lipid-centric models may inadequately capture the underlying risk driven by insulin resistance.

Hypertriglyceridaemia was widely endorsed as a major cardiovascular risk factor, with 89.73% of respondents agreeing that elevated triglycerides should be considered as clinically important as LDL-C in cardiovascular risk assessment. This reflects an evolving understanding that triglyceride-rich lipoproteins represent an independent and meaningful contributor to atherogenic risk, particularly in Asian populations characterized by higher carbohydrate consumption and greater insulin resistance.⁵¹

Importantly, 84.93% of experts agreed that elevated triglyceride levels contribute significantly to residual cardiovascular risk, even among patients who reach recommended LDL-C thresholds with statin therapy. This finding highlights the limitations of an LDL-C-driven treatment paradigm and reinforces the need for comprehensive lipid management approaches that address triglyceride abnormalities to achieve optimal cardiovascular risk reduction in Indian diabetic patients.

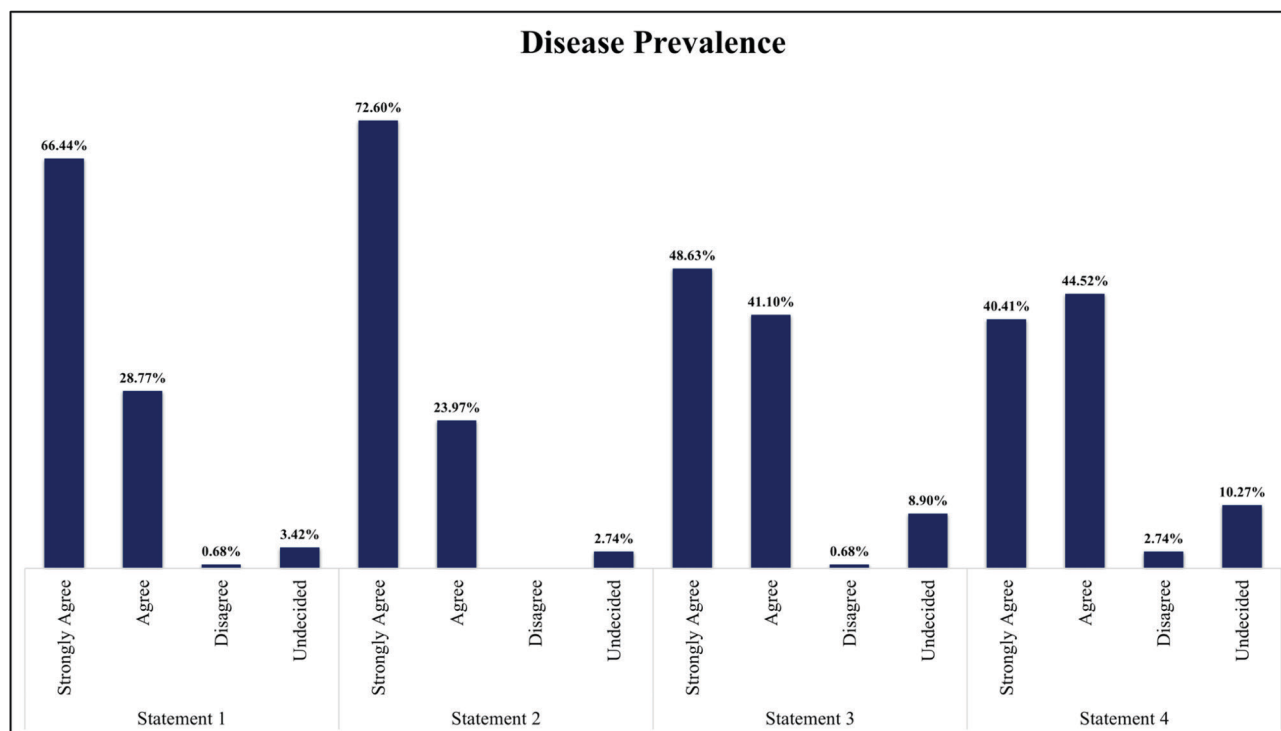


Fig 1. Disease prevalence and agreement levels on dyslipidemia-related cardiovascular risk in Indian and South Asian populations.

Consensus Statements

1. Indian diabetic patients with elevated triglycerides 150 mg/dL, low HDL-C (40 and 50 mg/dL for male and female, respectively) and abnormal sd-LDL levels should be considered as ADD patients.
2. In the South Asian population, insulin resistance is more common and occurs at an earlier age. It is one of the root causes contributing to the increasing incidence of ADD in India.
3. Considering the Asian population has higher insulin resistance and greater carbohydrate consumption, elevated TG is more common than elevated LDL-C. So, like LDL-C, hypertriglyceridemia should be considered a significant CVD risk factor.
4. In patients with controlled LDL-C on statin therapy, elevated triglycerides play a crucial role in increasing residual CVD risk.

2.2 Diagnostic Considerations

The diagnostic component of the survey demonstrated a strong yet pragmatic consensus among experts as presented in Figure 2. Fasting triglyceride measurements were considered more reliable by 84.25% of respondents; however, there was clear acknowledgment of the clinical utility of non-fasting triglyceride values when fasting samples are not feasible, reflecting a balance between diagnostic accuracy and real-world applicability. A triglyceride threshold of ≥ 150 mg/dL for defining hypertriglyceridemia in Indian patients achieved 78.09% agreement, indicating broad acceptance while also highlighting ongoing discussion regarding population-specific cut-off values. There was robust support (92.47%) for incorporating non-HDL-C and apo B as ancillary determinants of cardiovascular risk alongside LDL-C and triglycerides, consistent with a comprehensive, multi-marker approach to atherogenic risk assessment in diabetic dyslipidaemia.⁵² Additionally, the TyG was endorsed by 78.09% of respondents acting as a surrogate measure for insulin resistance and cardiovascular risk, although the relatively higher proportion of undecided responses suggests that its routine clinical adoption remains an evolving practice.

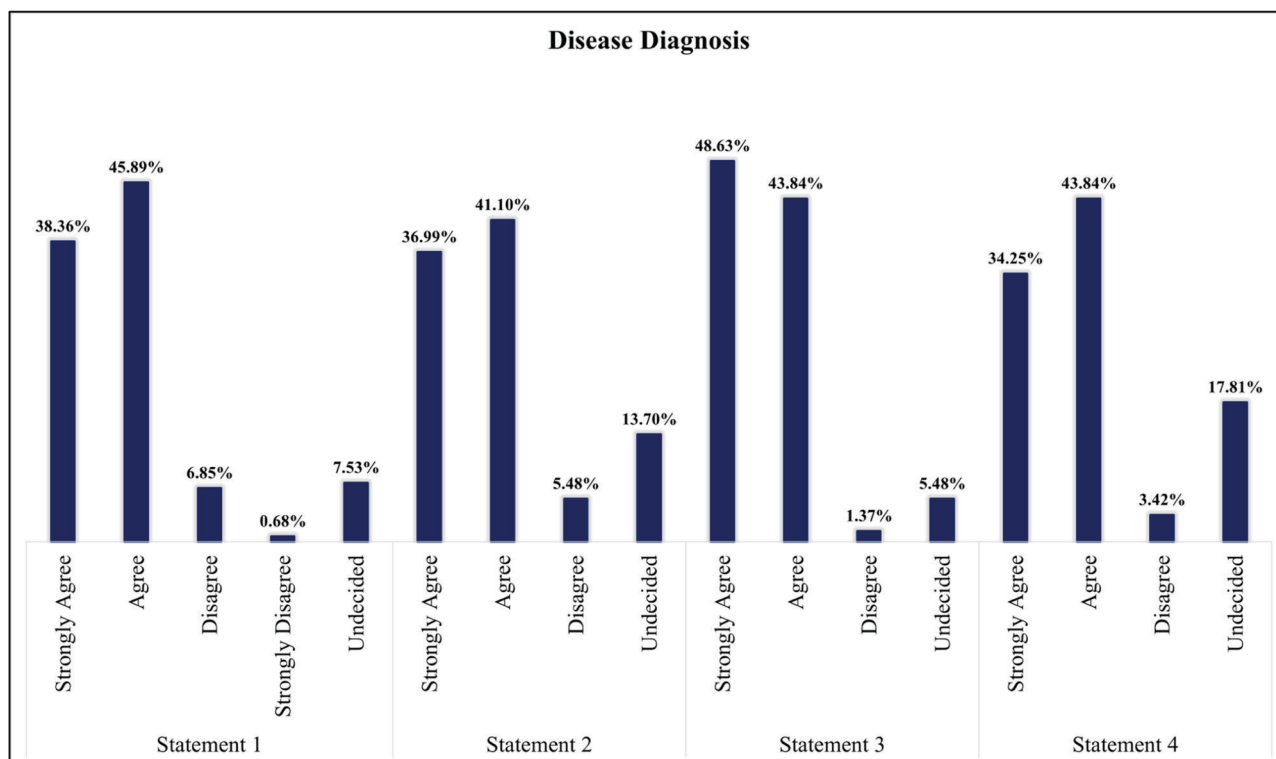


Fig 2. Agreement levels on diagnostic approaches and biomarkers for dyslipidemia and cardiovascular risk assessment in Indian patients.

Consensus Statements

1. Fasting TG should be considered more reliable than non-fasting TG for detecting dyslipidaemia. However, if fasting TG is not available, non-fasting TG can be used as an alternative.
2. Given that elevated TG plays a key role in CVD risk, TG levels above 150 mg/dL should be used as the cut-off for defining hypertriglyceridemia in Indian patients.
3. In Indian diabetic patients, non-HDL-C and Apo B should be considered as secondary markers for CVD risk assessment, along with TG and LDL-C.
4. The TyG is a validated marker for predicting insulin resistance and CVD. It should be regularly calculated in Indian diabetic patients suffering from dyslipidaemia.

2.3 Management Strategies

The therapeutic management section demonstrated the strongest consensus as presented in Figure 3. An overwhelming 93.83% of respondents endorsed lifestyle modifications as first-line therapy, with 78.08% expressing strong agreement. This reflects evidence-based prioritization of non-pharmacological interventions before initiating medical management. Statin therapy as first-line pharmacological management achieved near-universal acceptance at 95.89%, consistent with global guidelines and extensive clinical trial evidence supporting statins in diabetic populations. Treatment thresholds for hypertriglyceridemia showed interesting patterns. For initiating medication to reduce CVD risk, 78.77% agreed with a threshold of >200 mg/dL, while extreme hypertriglyceridemia (>500 mg/dL) requiring treatment to prevent pancreatitis achieved the highest consensus in the entire survey at 96.57%. This clear differentiation between cardiovascular risk reduction and acute pancreatitis prevention reflects evidence-based threshold distinctions (53). The add-on therapy section revealed more nuanced perspectives. When LDL-C is controlled, but triglycerides remain elevated (>200 mg/dL), 73.97% supported adding TG-lowering drugs (saroglitazar, fenofibrate, icosapent ethyl, niacin) along with statins.

In contrast, a similar proportion (73.97%) supported non-statin agents (ezetimibe, bempedoic acid, PCSK9 inhibitors), but with notably higher disagreement (13.01%) compared with TG-lowering drugs. This suggests greater clinical confidence in agents with specific triglyceride-lowering mechanisms rather than primarily LDL-lowering agents for managing hypertriglyceridemia. For severe hypertriglyceridemia (>500 mg/dL), 94.52% agreed that TG-lowering drugs should be initiated regardless of statin use, prioritizing acute pancreatitis prevention. Saroglitazar achieved exceptional endorsement (93.84%) as the preferred add-on option for managing hypertriglyceridemia in diabetic patients. This strong preference reflects the drug’s dual benefits of insulin sensitization and glycaemic control alongside triglyceride reduction, making it particularly suitable for the diabetic dyslipidaemia phenotype prevalent in Indian patients.

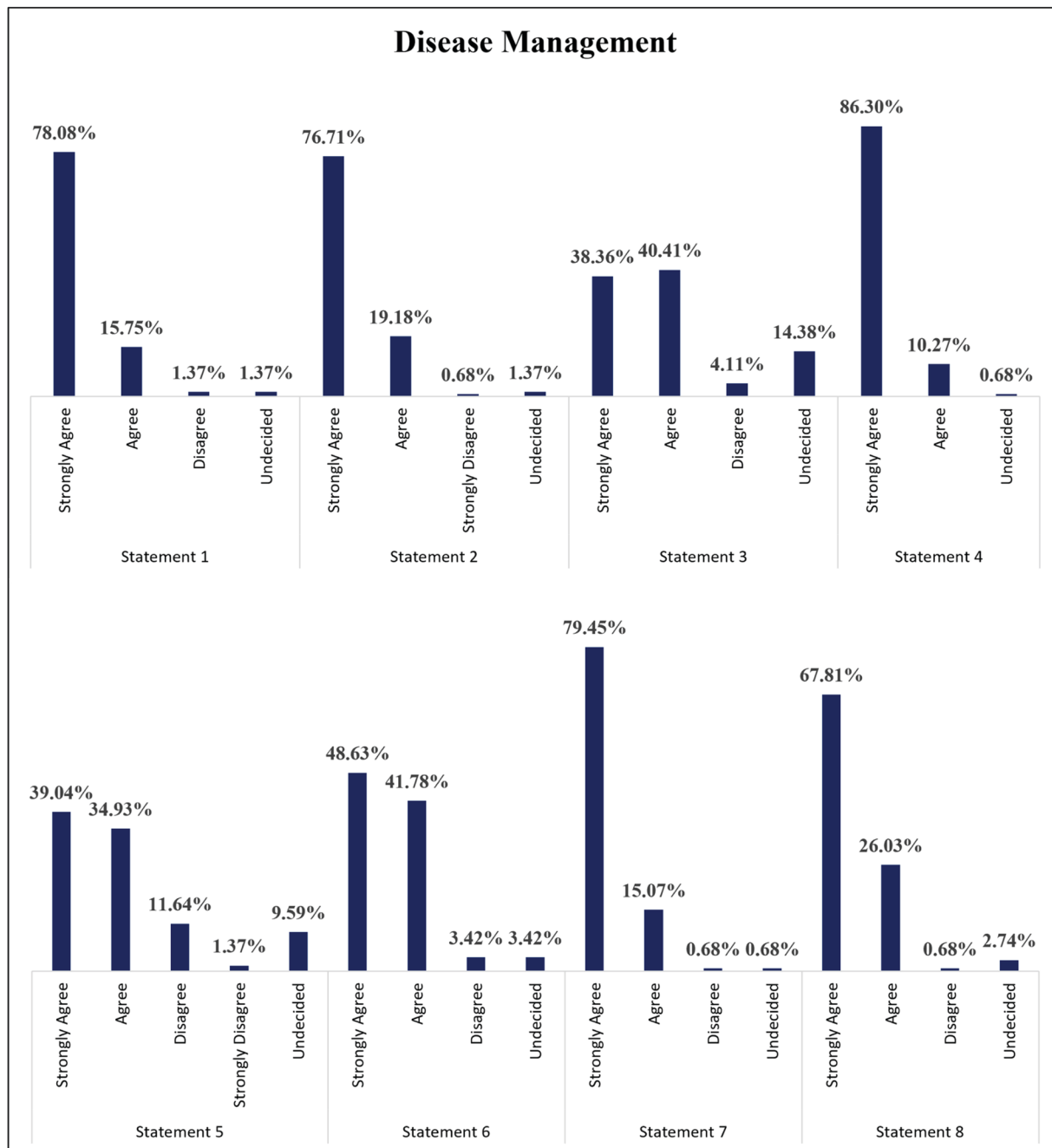


Fig 3. Agreement levels on therapeutic strategies for the management of diabetic dyslipidemia and hypertriglyceridemia in Indian patients.

Consensus Statements

1. In the management of diabetic dyslipidemia, lifestyle modifications like weight reduction, low-calorie intake, meditation, and stress reduction are always considered as a first-line therapy before considering medical management.
2. Statin therapy is the first-line medication for managing dyslipidaemia in diabetes patients.
3. In India, the ideal threshold level for TG should be 200 mg/dL to initiate medication to reduce the risk of CVD.
4. If TG levels exceed 500 mg/dL, they should be treated with appropriate medication to prevent the risk of pancreatitis.
5. In patients with controlled LDL-C post statin therapy, if TG is >200 mg/dL, non-statin agents (ezetimibe, bempedoic acid, PCSK9 inhibitors) should be added to reduce TG level along with statin.
6. In patients with controlled LDL-C on statin therapy, if TG is >200 mg/dL, a TG-lowering drug (Saroglitazar, Fenofibrate, Icosapent ethyl, Niacin) should be added along with statin.
7. In patients with TG levels >500 mg/dL, TG-lowering drugs should be started (with or without statin) to prevent acute pancreatitis.
8. Saroglitazar is the preferred add-on option to statin therapy for managing hypertriglyceridemia, as it has insulin-sensitizing properties and improves glycemic control along with a reduction in TG in diabetic dyslipidaemia patients.

This consensus survey represents expert opinion requiring prospective validation; it does not provide empirical evidence from interventional or outcomes-based studies. The panel may not fully represent all Indian clinicians, particularly those practising in resource-limited settings. Findings are specific to the Indian/South Asian context and may not be directly generalizable to other populations. Recommendations are based on the current evidence base and should be periodically updated as new data emerge.

CONCLUSION

Consensus expert physicians recognized ADD as a major determinant of residual cardiovascular risk in Indian and broader South Asian patients with T2DM. The panel endorsed a phenotype-driven approach for diagnosis and management, emphasizing early identification and targeted treatment of hypertriglyceridemia in conjunction with LDL-C reduction, and acknowledged non-HDL-C and apo B as complementary indicators. Practical guidance on therapeutic sequencing and intervention thresholds supports integrated metabolic risk management tailored to ethnicspecific metabolic characteristics and real-world clinical practice, with lifestyle measures prioritized, statins as first-line pharmacotherapy, and TG-lowering agents added when triglycerides remain elevated. Consensus further highlighted saroglitazar as a preferred adjunct in patients with persistent hypertriglyceridemia despite statin therapy, reflecting evidence of improvements in triglycerides, glycemic parameters, and insulin sensitivity, and reinforcing its role in cardiovascular risk reduction in ADD.

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MASLD and Hepatic & Extrahepatic Malignancies: Epidemiology, Mechanisms, and Clinical Implications

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Article information

Received date: 27/04/2026; **Accepted date:** 25/05/2026; **Published date:** 29/05/2026

ABSTRACT

Background: Early-onset cancers are increasingly associated with metabolic risk factors and unhealthy lifestyle patterns. Metabolic dysfunction–associated steatotic liver disease (MASLD), a common chronic liver condition linked to metabolic syndrome, is associated with metabolic and inflammatory alterations linked to carcinogenesis and is associated with both hepatic and extrahepatic malignancies, highlighting its growing public health significance.

Materials and Method: This narrative review summarizes current evidence on MASLD and cancer, focusing on epidemiology and mechanisms. Literature from 2024–2026 was identified through major databases and qualitatively synthesized to provide an integrated overview.

Conclusion: Metabolic dysfunction–associated steatotic liver disease (MASLD) is increasingly associated with both hepatic and extrahepatic malignancies. Its association with hepatocellular carcinoma (HCC) and multiple systemic cancers is driven by interconnected metabolic, inflammatory, and genetic mechanisms. Early risk stratification and appropriate surveillance strategies are essential to improve clinical outcomes.

Keywords: MASLD, Cancer, HCC, Extrahepatic malignancies, Cancer surveillance

INTRODUCTION

Early-onset cancers are increasingly reported and have been linked to unhealthy lifestyle patterns and the rising burden of “diabesity,” the coexistence of obesity and type 2 diabetes. Diabesity contributes to carcinogenesis through metabolic imbalance, persistent cellular stress, and influences from early-life environmental and microbiome-related exposures. The growing incidence of these cancers carries significant personal, social, and economic consequences, as survivors often experience long-term complications such as infertility, cardiovascular disease, and secondary malignancies.¹

Metabolic dysfunction–associated steatotic liver disease (MASLD) is defined by hepatic steatosis in the presence of at least one cardiometabolic risk factor, reflecting its systemic metabolic basis rather than an isolated liver condition. Epidemiological studies have linked MASLD with an increased risk of overall and site-specific cancers among younger adults. MASLD is associated with metabolic and inflammatory alterations, including insulin resistance, chronic low-grade inflammation, and oxidative stress, which may contribute to a pro-tumorigenic environment promoting cell proliferation and genomic instability.¹

MASLD is one of the most common chronic liver diseases in developed regions and encompasses a spectrum ranging from simple steatosis to metabolic dysfunction–associated steatohepatitis (MASH), previously termed non-alcoholic steatohepatitis (NASH). Its increasing prevalence parallels the rising incidence of metabolic syndrome components, including obesity, insulin resistance, and dyslipidaemia, highlighting its importance as a major public health concern with systemic implications.²

Progression of MASLD may lead to cirrhosis, a severe condition associated with significant complications, including hepatocellular carcinoma, the most common form of primary liver cancer (LC), often requiring liver transplantation.² The most

commonly reported extrahepatic malignancies in individuals with MASLD include endometrial, breast, prostate, colorectal, and lung cancers. While advancing fibrosis and cirrhosis are well-established risk factors for hepatocellular carcinoma (HCC), the association between fibrosis severity and extrahepatic malignancies remains less consistent across studies. With the anticipated rise in MASLD prevalence over the coming decades, the burden of these associated malignancies is also expected to increase.³

MATERIALS AND METHOD

This narrative review summarizes current evidence on MASLD and cancer, with a focus on epidemiology, pathophysiological mechanisms, and clinical associations. A literature search was conducted using databases and publisher platforms, including PubMed, Scopus, Google Scholar, ScienceDirect, Wiley Online Library, Taylor & Francis, and MDPI. Search terms included “MASLD,” “MASH,” “cancer,” “early-onset cancer,” “insulin resistance,” “inflammation,” and “hepatocellular carcinoma.” Studies published between 2024 and 2026 were prioritized.

Peer-reviewed English-language articles relevant to MASLD and its association with cancer were included. Sources were selected based on relevance to epidemiology, disease mechanisms, and clinical outcomes. Data from the selected literature were reviewed and synthesized qualitatively to provide a structured overview of the current understanding of the relationship between MASLD and cancer.

DISCUSSION

Epidemiology of MASLD

The rising incidence of MASLD parallels the global increase in obesity, which has nearly tripled over recent decades. A meta-analysis reports that MASLD affects approximately 30% of the global population, with the highest prevalence observed in Latin America (44%), followed by Western Europe (25.1%). Current evidence also indicates that 98–99% of individuals previously diagnosed with non-alcoholic fatty liver disease (NAFLD) meet the diagnostic criteria for MASLD.³

It is the most common chronic liver disease worldwide and is increasingly recognized as a contributor to HCC, a major cause of cancer-related mortality.⁴ Hepatocellular carcinoma accounts for 75–85% of all primary liver cancers and is the fourth leading cause of cancer-related deaths globally. The majority of patients with HCC, up to 90%, have underlying cirrhosis. While viral hepatitis and alcohol-related liver disease (ALD) remain leading causes of cirrhosis and HCC in Europe, MASLD has emerged as the fastest-growing cause of HCC in several regions, including the United States, China, and the United Kingdom. It is estimated that up to 35% of global HCC cases are attributable to MASLD. Notably, nearly 40% of MASLD-related HCC cases occur in the absence of cirrhosis, complicating early detection, as routine surveillance is not recommended for non-cirrhotic MASLD populations.⁴

Data from the Global Burden of Disease 2019 study reported approximately 170,000 new cases of liver cancer associated with MASLD worldwide, accounting for 6.6% of all liver cancer cases related to chronic liver diseases. In the same year, 168,969 deaths were attributed to MASLD-related liver cancer, representing 8.6% of liver cancer mortality from chronic liver diseases. Regional analysis showed that Asia contributed 48.3% of incident cases and 46.2% of deaths, while the Middle East and North Africa (MENA) region accounted for 8.9% of cases and 8.6% of deaths related to MASLD-associated liver cancer.⁵

MASLD affects approximately 38.6% of adults in India, with a markedly higher prevalence of 68.2% among individuals with type 2 diabetes. This burden is associated with increasing obesity, sedentary behaviour, and dietary changes, and MASLD is emerging as a significant cause of cirrhosis and MASLD-related HCC in the Indian population.⁵

A meta-analysis covering the period from 1997 to 2023 reported that the prevalence of MASLD in children (≤ 18 years) was 13% in the general population, including 15% in males and 10% in females, and 47% among children with obesity, with higher rates observed in males. Studies from Asia reported higher prevalence rates compared to non-Asian regions, with 15% versus 11% in the general population and 53% versus 39% among obese children. The prevalence of MASLD increased with age, irrespective of obesity status, although the highest rates were consistently observed in individuals with obesity, with prevalence rising in parallel with increasing body weight.⁵

These findings indicate a substantial and increasing global burden of MASLD, with particularly high prevalence in Asia. As the incidence of hepatitis B virus (HBV)-related mortality declines due to improved prevention and treatment, mortality

related to MASLD and hepatitis C virus (HCV) is increasing. In parallel, MASLD-related liver cancer continues to rise, with Asia contributing the largest share of incident cases and associated deaths.⁵

Biological Mechanisms Linking MASLD and Cancer

Metabolic dysfunction–associated steatotic liver disease (MASLD) is an established risk factor for HCC. Approximately 20% of individuals with MASH progress to cirrhosis, a major determinant of HCC development, with an estimated annual progression rate to HCC of about 2%. Primary liver cancer ranks as the sixth most commonly diagnosed cancer and the third leading cause of cancer-related mortality worldwide.⁶ MASH-related HCC exhibits distinct molecular and immune features and may arise in the presence or absence of cirrhosis, influenced by genetic alterations, environmental exposures, and the immune microenvironment.⁷

The pathogenesis of MASLD-related carcinogenesis involves a complex interaction of metabolic, inflammatory, genetic, and environmental factors, contributing to both hepatic and extrahepatic malignancies.⁶ (Fig. 1)

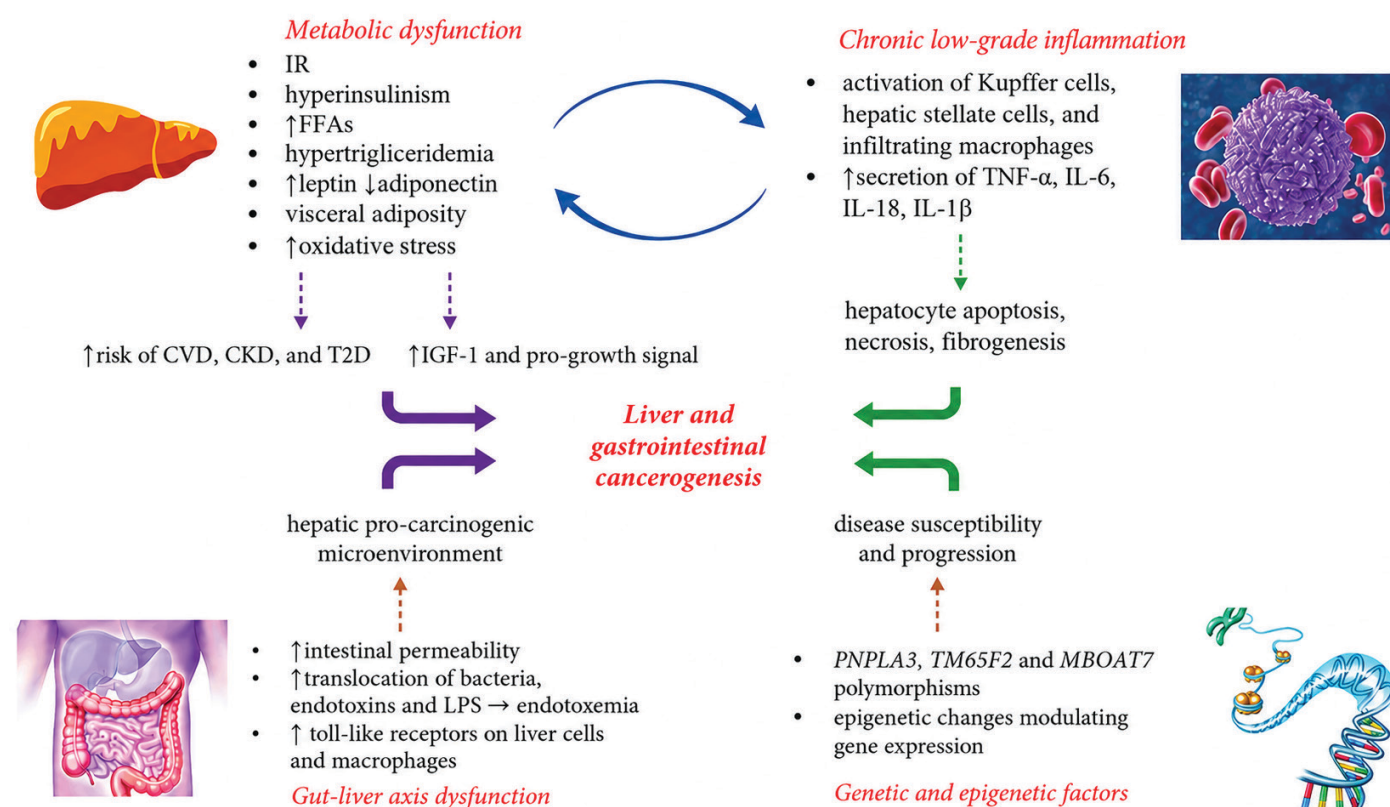


Fig 1. Interplay of metabolic, inflammatory, genetic, epigenetic, and environmental pathophysiological mechanisms linking MASLD to oncogenesis.⁸

Chronic inflammation and oxidative stress

Chronic inflammation is a central driver in the progression of MASLD from steatosis to MASH, cirrhosis, and HCC. Hepatic lipid accumulation leads to immune cell infiltration and activation, with Kupffer cells, neutrophils, macrophages, and lymphocytes releasing pro-inflammatory cytokines that perpetuate liver injury.⁶ Activation of hepatic stellate cells (HSCs), mediated by signals such as damage-associated molecular patterns (DAMPs), transforming growth factor- β (TGF- β), and inflammasome activation, promotes fibrosis and architectural distortion of the liver.⁶

Excessive accumulation of free fatty acids (FFAs) results in lipotoxicity, increasing the production of ceramides, sphingolipids, and cholesterol, all of which contribute to cellular stress. Oxidative stress leads to mitochondrial dysfunction, DNA damage, and impaired DNA repair mechanisms, facilitating oncogenic transformation.⁶ Chronic inflammation and fibrosis create a microenvironment that supports tumour initiation and progression through pathways such as signal transducer and activator of transcription 3 (STAT3) activation.⁶

During progression to HCC, inflammatory mediators including tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) promote oncogenic signalling. Accumulation of genetic mutations, including those involving telomerase reverse transcriptase, β -catenin, and TP53, further contributes to malignant transformation. The patatin-like phospholipase domain-containing 3 (PNPLA3) variant is strongly associated with increased susceptibility to MASH-related HCC.⁶

MASH-related HCC develops within a pro-inflammatory environment in early stages, which later transitions to an immunosuppressive tumour microenvironment characterized by pro-tumorigenic immune cells and reduced immune surveillance. This distinct immune profile has implications for therapeutic response.⁸

Insulin resistance and hyperinsulinemia

Insulin resistance (IR) is a central feature of MASLD and drives increased lipolysis, resulting in elevated free fatty acid flux to the liver and subsequent hepatic steatosis.⁸ Progressive fat accumulation promotes oxidative stress and triggers inflammatory cascades involving cytokines such as TNF- α , IL-6, interleukin-1 β (IL-1 β), and interleukin-18 (IL-18), leading to hepatocyte injury, apoptosis, and fibrosis.⁸

IR also activates intracellular signalling pathways, including phosphoinositide 3-kinase (PI3K)/Akt and mammalian target of rapamycin (mTOR), contributing to metabolic dysregulation, inflammation, and carcinogenesis.⁹ The coexistence of IR and MASLD amplifies pro-inflammatory and pro-fibrotic pathways, accelerating progression to HCC and contributing to distinct metabolic characteristics in MASLD-related HCC.⁹

Visceral adipose tissue dysfunction further contributes to disease progression through the release of pro-inflammatory adipokines. Altered adipokine profiles, including increased leptin and reduced adiponectin, promote cell proliferation, insulin resistance, and tumour development.⁸

Gut–liver axis disruption also contributes to carcinogenesis, with increased intestinal permeability allowing translocation of endotoxins such as lipopolysaccharides, which enhance hepatic inflammation and fibrosis.³ Genetic and epigenetic factors, including variants in PNPLA3, Transmembrane 6 Superfamily Member 2 (TM6SF2), and Membrane-Bound O-Acyltransferase Domain-Containing Protein (MBOAT7), influence susceptibility to MASLD progression and HCC development.³

Lipotoxicity and metabolic dysregulation

Lipotoxicity plays a critical role in MASLD progression. Hepatocyte injury results in the release of DAMPs, which activate the NLR family, pyrin domain-containing 3 (NLRP3) inflammasome in Kupffer cells and promote the release of pro-inflammatory cytokines.⁶ Nuclear factor- κ B (NF- κ B) signalling further amplifies inflammation and recruits immune cells, sustaining hepatic injury.⁶

Oxidative stress induced by lipotoxicity leads to mitochondrial dysfunction and increased susceptibility to cell death. This process contributes to fibrosis and chronic liver inflammation, extending beyond the liver to systemic inflammation and increasing the risk of neoplasia.³

Fibrosis and cirrhosis-mediated oncogenesis

Fibrosis and cirrhosis are major drivers of oncogenesis in MASLD, creating a persistent pro-inflammatory and pro-fibrotic environment that promotes HCC development. Although cirrhosis remains the strongest risk factor, HCC can develop in earlier stages of fibrosis or in non-cirrhotic MASLD.¹⁰

Hepatic stellate cell activation is central to fibrosis development, driven by hepatocyte injury, immune dysregulation, and metabolic stress. Progressive fibrosis results from sustained inflammatory signalling and cellular injury, ultimately altering liver architecture and function.¹⁰ (Fig. 2)

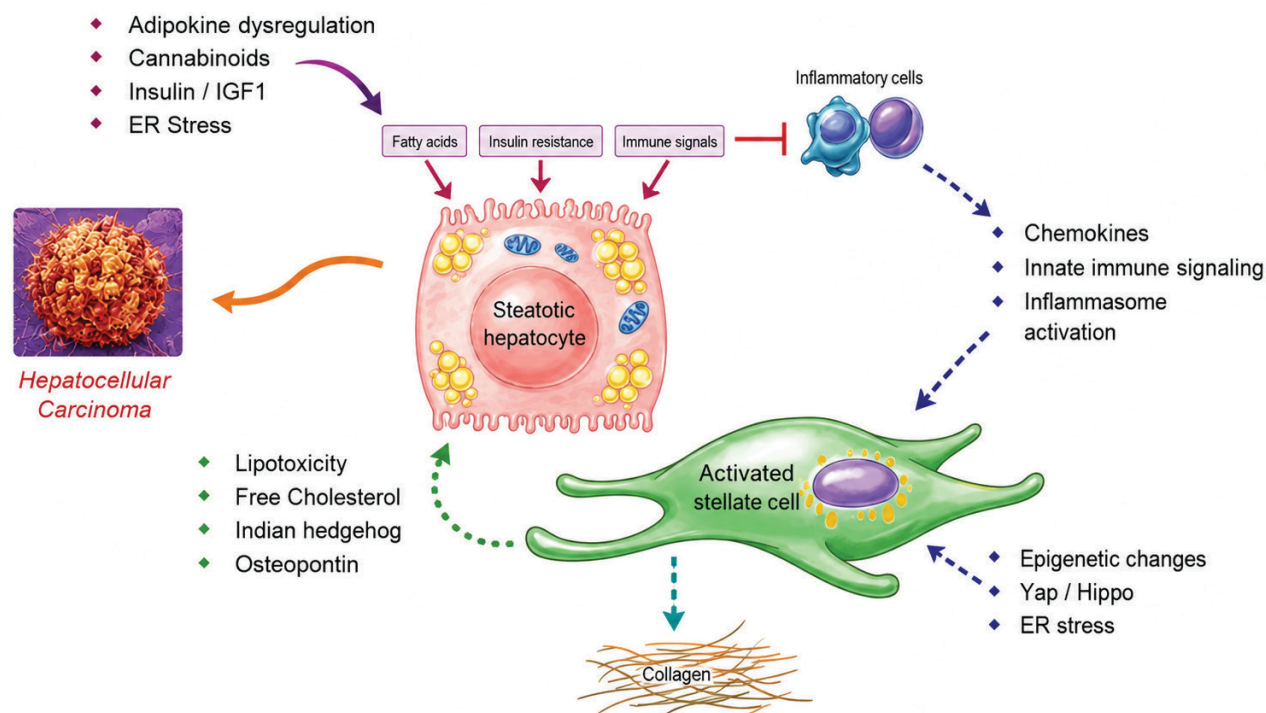


Fig 2. Hepatic drivers of MASLD and fibrosis.¹⁰

Type 2 diabetes mellitus is a major risk factor for MASLD progression and fibrosis, with strong clinical associations supporting routine screening for MASLD in affected individuals using non-invasive assessment tools. Improved metabolic control has been associated with beneficial effects on disease progression.¹⁰

Fibrosis severity remains a key determinant of clinical outcomes in MASH, reflecting the cumulative effects of metabolic dysfunction, chronic inflammation, and sustained hepatocellular injury.¹⁰

Hepatic Malignancies Associated with MASLD

Primary liver cancer includes HCC, which accounts for approximately 80% of cases, and intrahepatic cholangiocarcinoma, representing around 15%.⁶ MASLD is increasingly recognized as a major contributor to HCC development, although the precise etiopathogenic mechanisms remain incompletely defined.³

Insulin resistance and related metabolic dysregulation contribute to hepatocarcinogenesis through proliferative and pro-inflammatory signalling pathways.³ Oxidative stress contributes to MASLD-related hepatocarcinogenesis through reactive oxygen species (ROS)-mediated lipid peroxidation, mitochondrial dysfunction, inflammation, and fibrogenesis. Hyperinsulinemia and altered iron metabolism may further enhance oxidative injury and promote tumour development.³ Gut microbiota alterations and disruption of the gut–liver axis may further contribute to hepatic inflammation and hepatocarcinogenesis.³ Genetic susceptibility variants such as PNPLA3 have also been associated with increased HCC risk in MASLD.³

Epidemiology

Primary liver cancer is the sixth most common cancer globally and the third leading cause of cancer-related mortality. HCC accounts for 75–85% of these cases, with the highest incidence reported in Asia and Africa, where viral hepatitis remains a major etiological factor.³

Among individuals with MASLD, approximately 20–30% progress to metabolic dysfunction–associated steatohepatitis (MASH), and 10–20% of these individuals develop cirrhosis. In MASLD-related cirrhosis, the annual incidence of HCC ranges from 0.5% to 2.6%. With the global rise in MASLD prevalence, HCC attributable to MASLD is increasing, while cases related to viral hepatitis are declining due to improved preventive and therapeutic strategies.³

Cirrhosis remains the primary risk factor for HCC in MASLD, although HCC can occur in non-cirrhotic individuals. The risk is higher in patients with decompensated cirrhosis. Metabolic syndrome components, particularly central obesity and type 2 diabetes mellitus, are strongly associated with increased HCC risk through persistent inflammation and oxidative stress. Duration of diabetes further influences risk, with a higher incidence observed over time.³

A prospective study comparing individuals with steatosis due to MASLD, metabolic dysfunction–associated alcohol-related liver disease (MetALD), and alcohol-related liver disease with those without steatosis demonstrated a higher risk of HCC in patients with steatosis, particularly in MetALD.³ (Fig. 3)

Fibrosis severity has been consistently associated with increased risk of HCC, with higher fibrosis-4 (FIB-4) index values correlating with a greater likelihood of cirrhosis and HCC development, supporting its role in hepatic cancer risk stratification.²

MASLD has also been associated with other hepatobiliary and systemic malignancies. Evidence indicates its role as a risk factor for biliary tract cancers, particularly in the presence of coexisting metabolic conditions such as diabetes. In addition, associations with metastatic liver involvement, including colorectal cancer metastases, have been reported, reflecting the broader systemic impact of MASLD.²

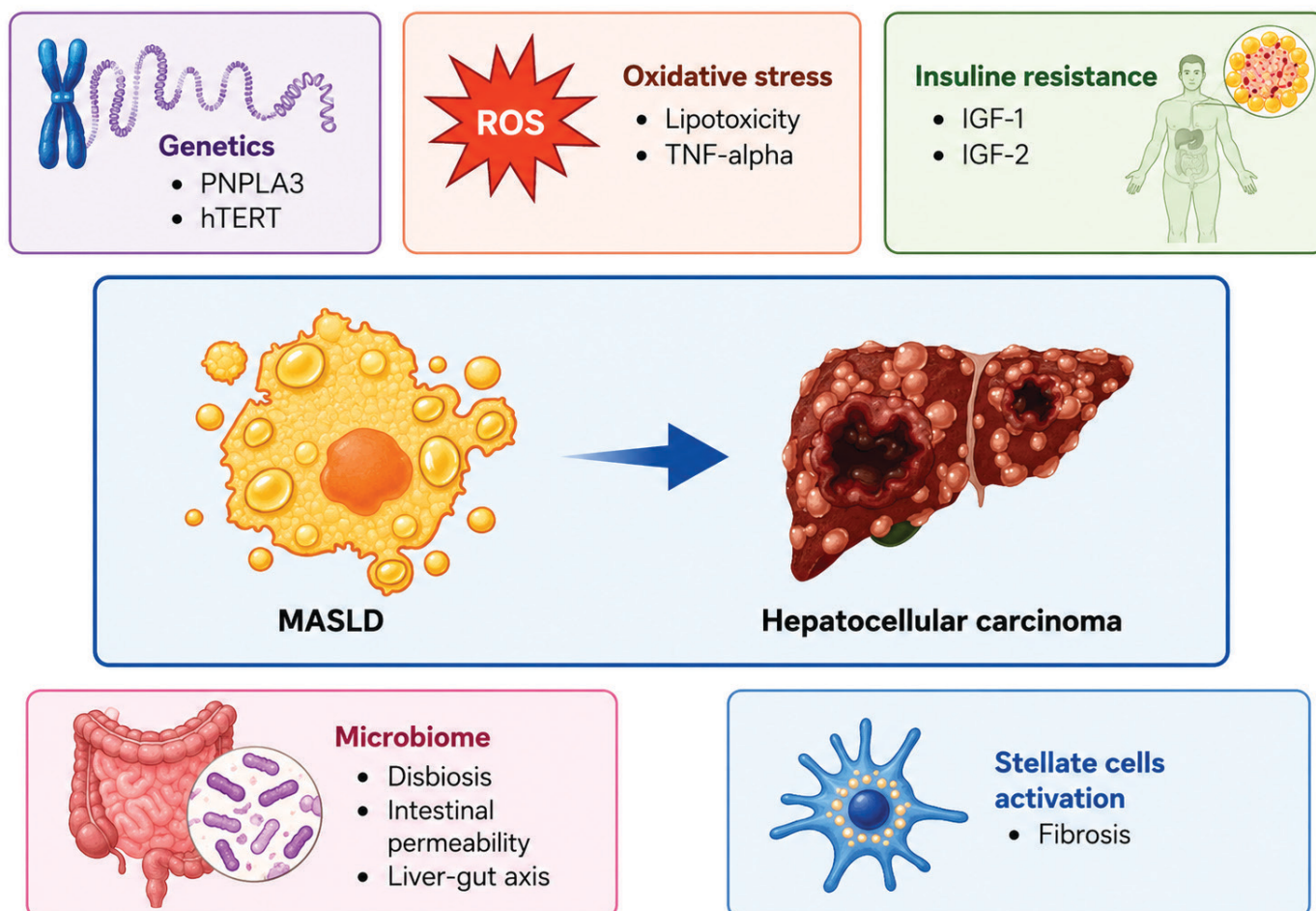


Fig 3. Etiopathogenic pathways from hepatocellular carcinoma (HCC) to MASLD.³

The incidence of MASLD-related HCC varies across populations. In Western cohorts, the annual incidence of MASH-related cirrhosis is approximately 2.6%, whereas higher rates of up to 11.3% have been reported in Asian populations.²

Population-based data indicate a rising contribution of MASLD to HCC burden. In a large European cohort, MASLD-related HCC incidence increased substantially over time, becoming a leading cause of HCC, while cases related to viral hepatitis declined. Patients with MASLD-related HCC were typically older, had a higher burden of metabolic comorbidities, and were less likely to have cirrhosis compared to other etiologies.⁴

Age-specific trends show a higher incidence in older populations, particularly those aged 70 years and above. Overall incidence rates remain lower in certain European regions compared to global averages, although the proportion of MASLD-related HCC continues to increase.⁴

Extrahepatic Malignancies Associated with MASLD

Evidence from cohort studies indicates an increased risk of multiple cancers in individuals with persistent MASLD. The most commonly reported extrahepatic malignancies include endometrial, breast, prostate, colorectal, and lung cancers. With the rising prevalence of MASLD, the burden of these associated malignancies is also increasing.³

Colorectal cancer is the most extensively studied extrahepatic malignancy in MASLD. Insulin resistance and chronic low-grade inflammation play central roles in its pathogenesis by promoting cellular proliferation and inhibiting apoptosis. Several studies have reported an increased prevalence of adenomas and colorectal cancer in individuals with MASLD, with MASLD identified as an independent risk factor for the development of colonic polyps. The risk of adenomatous polyps has been reported to be approximately threefold higher compared to the general population, with a higher likelihood of multiple lesions, right-sided distribution, and high-grade dysplasia. Cohort and prospective studies have demonstrated an association between MASLD and increased risk of colorectal cancer and adenomatous polyps.³

The association between MASLD and other malignancies involves similar metabolic and inflammatory pathways. Insulin resistance and hyperinsulinemia lead to elevated levels of insulin-like growth factor-1, which promotes cell proliferation and inhibits apoptosis. Increased levels of insulin-like growth factor-1 have been associated with cancers of the prostate, colorectal region, lung, and breast. Alterations in gut microbiota and dysbiosis have also been implicated in carcinogenesis. A meta-analysis of cohort studies reported that MASLD is associated with a 1.5–2-fold increased risk of gastrointestinal cancers and a 2.5-fold increased risk of thyroid cancer, along with a modest increase in the risk of breast, lung, urinary, and gynaecological malignancies. Obesity, a key component of MASLD, is also associated with cancers of the oesophagus, pancreas, breast, and thyroid.³

Persistent MASLD has also been linked to increased risk of site-specific cancers, including hepatic, pancreatic, renal, colorectal, biliary, and gynaecologic malignancies. A meta-analysis including multiple cohort studies demonstrated increased risks of gastric, colorectal, pancreatic, biliary tract, thyroid, urinary system, breast, and female genital cancers in individuals with MASLD. Advanced fibrosis is a recognized determinant of hepatic malignancy risk, particularly HCC. However, the association between fibrosis severity and extrahepatic malignancies remains inconsistent across studies. A cohort study conducted in the United States reported that MASLD was associated with a significantly higher overall cancer risk compared to matched controls, while extrahepatic cancer and cardiovascular mortality were more pronounced in individuals with MASLD-related cirrhosis compared to those without cirrhosis.¹¹

Sex-Specific Differences in MASLD-Related Cancer Risk

Sex-related differences influence the development and progression of MASLD and its associated malignancies. These differences are mediated by hormonal, genetic, and metabolic factors that affect fat distribution, insulin sensitivity, and oxidative stress.¹²

Men have a higher overall risk of HCC, while women exhibit a comparatively lower risk during reproductive years. This difference is partly explained by hormonal and immunological factors. In contrast, postmenopausal women demonstrate accelerated progression of fibrosis and increased susceptibility to HCC, along with reduced therapeutic response, highlighting the influence of hormonal changes on disease progression.¹²

Sex-specific variations are also observed in cancer risk patterns. In MASLD populations, the relative risk of liver cancer is higher in men compared to women, whereas the risk of extrahepatic cancers is higher in women. Reported relative risks for liver cancer are 3.16 in males and 1.25 in females, while for extrahepatic cancers, the relative risks are 1.01 in males and 1.44 in females. These findings indicate a comparatively greater predisposition to extrahepatic malignancies in women with MASLD.¹²

Sex hormones play a central role in these differences. Estrogens regulate glucose and lipid metabolism, reduce inflammation, and support hepatocellular regeneration. Loss of estrogen after menopause is associated with an increased prevalence of MASLD and a higher risk of fibrosis, with risk correlating with the duration of estrogen deficiency.¹²

Androgens also influence hepatic metabolism. Reduced androgen levels in men are associated with increased risk of MASLD and metabolic dysfunction, while excess androgens in women contribute to disease progression. These hormonal imbalances affect lipid metabolism and insulin sensitivity, thereby influencing MASLD severity and associated cancer risk.¹²

Genetic and chromosomal factors further contribute to sex-based differences. Variations in sex chromosome composition and hormone levels influence metabolic regulation and susceptibility to liver disease.¹²

Sex-based differences are also evident in clinical outcomes. Women have a higher incidence of cirrhosis, whereas men have higher rates of hepatic decompensation, HCC, cardiovascular disease, chronic kidney disease, and non-sex-specific cancers. Specifically, women have a 9% higher risk of cirrhosis, while men have an 11% higher risk of hepatic decompensation and more than double the risk of HCC. Additionally, men have increased risks of cardiovascular disease, chronic kidney disease, and overall cancer incidence compared to women.¹³

Cancer surveillance strategies in MASLD

Cancer surveillance in MASLD primarily focuses on early detection of HCC in high-risk individuals, particularly those with cirrhosis. Current strategies recommend biannual abdominal ultrasound, with or without alpha-fetoprotein (AFP) measurement.¹⁴

Given the increasing recognition of HCC risk in non-cirrhotic individuals with advanced fibrosis, risk-stratified surveillance approaches are being considered. Non-invasive scoring systems such as fibrosis-4 (FIB-4) are used to identify individuals at higher risk. Clinical guidelines support this approach, with recommendations suggesting that selected non-cirrhotic patients with advanced fibrosis may be considered for surveillance based on individualized risk assessment. Cost-effectiveness analyses indicate that surveillance is most appropriate in populations with an annual HCC incidence of approximately 1% or higher, a threshold not consistently reached in non-cirrhotic MASLD populations.¹⁴

Ultrasound-based surveillance has limitations in MASLD, particularly in individuals with obesity, where increased subcutaneous fat reduces image quality and sensitivity. Studies report that ultrasound may miss a substantial proportion of HCC cases in this population.¹⁴

Alternative imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), provide improved detection but are limited by cost, accessibility, and contrast-related concerns. Abbreviated MRI protocols have demonstrated improved detection rates compared to ultrasound, including in patients with hepatic steatosis. However, current guidelines do not recommend CT or MRI as first-line surveillance tools, reserving them for cases where ultrasound is inadequate.¹⁴

Biomarkers for Early Detection

Several biomarkers have been evaluated to improve the early detection of HCC. Due to the heterogeneity of HCC, single biomarkers have limited sensitivity, and combined biomarker approaches are increasingly utilized. The GALAD score, which incorporates age, sex, AFP, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3), and des-gamma-carboxy prothrombin (DCP), has demonstrated high accuracy for early HCC detection in MASLD populations, including those without cirrhosis.¹⁴

Circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) have also been investigated as potential diagnostic tools. Methylation-based marker panels have shown high sensitivity and specificity for early-stage HCC detection in clinical studies. However, these approaches require further validation, particularly in MASLD-specific cohorts.¹⁴

Risk stratification and screening approaches

Risk prediction models have been developed to identify individuals at higher risk of HCC. The Toronto HCC Risk Index (THRI) and age-male sex-ALBI (Albumin-bilirubin)-platelets (aMAP) score incorporate clinical and laboratory parameters to stratify patients into different risk categories. Additional models integrating liver stiffness measurements and biochemical markers have demonstrated moderate predictive performance in MASLD populations.¹⁴

Emerging approaches include genetic and molecular risk stratification. Polygenic risk scores incorporating variants such as PNPLA3, TM6SF2, MBOAT7, and Glucokinase Regulatory Protein (GCKR) have been associated with increased HCC risk. Gene expression signatures have also shown potential in predicting long-term HCC development, although further validation is required before clinical application.¹⁴

Multidisciplinary management

HCC remains a major cause of cancer-related mortality, with MASLD increasingly recognized as a contributing etiology. Early detection and accurate risk assessment are essential for improving clinical outcomes.¹⁵

Management strategies for MASLD-related HCC follow established staging systems such as the Barcelona Clinic Liver Cancer (BCLC) classification. Early-stage disease (BCLC 0 and A) may be managed with curative approaches, including surgical resection, liver transplantation, or ablation. Advanced stages require systemic therapies based on disease extent and patient factors. (Fig. 4) Treatment approaches are not currently differentiated based on underlying etiology, including MASLD.¹⁵

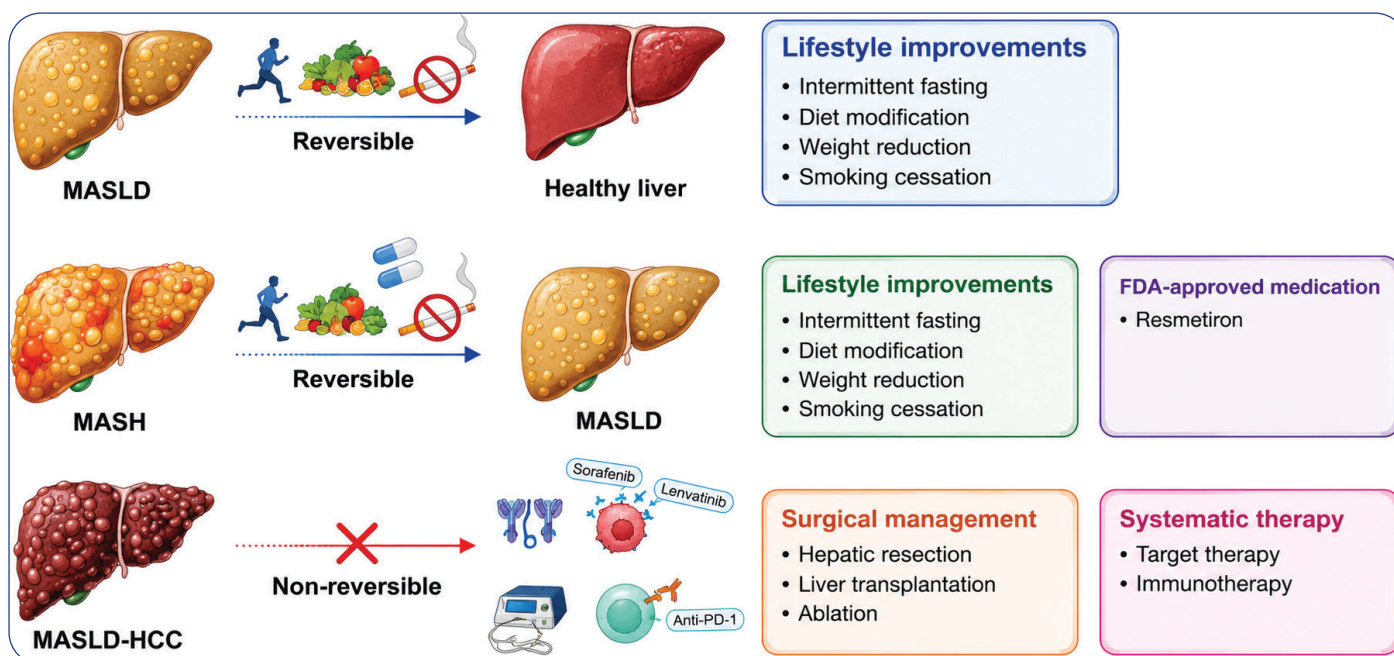


Fig 4. Clinical management for MASLD/MASLD-HCC patients.¹⁵

CONCLUSION

Metabolic dysfunction–associated steatotic liver disease represents a significant and growing contributor to the global cancer burden, particularly HCC, while also being associated with a spectrum of extrahepatic malignancies.

The association between MASLD and malignancy is linked to metabolic and inflammatory alterations, including insulin resistance, chronic inflammation, oxidative stress, gut–liver axis alterations, and genetic susceptibility.

Disease progression, especially the development of fibrosis and cirrhosis, remains a key determinant of cancer risk, although malignancies may also arise in non-cirrhotic stages. Sex-specific differences further influence disease patterns and outcomes.

Given the rising prevalence of MASLD, there is an increasing need for effective risk stratification, improved surveillance tools, and early detection strategies. A multidisciplinary approach integrating clinical, biochemical, and emerging molecular markers is essential for optimizing management and reducing MASLD-related cancer morbidity and mortality.

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