EDITORIAL COMMENT

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From CKM to CKLM: Why the Liver may be the Missing Fourth Pillar

Mehdi Zoghi

Department of Cardiology, Ege University Faculty of Medicine, İzmir, Türkiye

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An Organ Recognized, but Not Yet Fully Integrated

When the American Heart Association (AHA) formally defined cardiovascular-kidney-metabolic (CKM) syndrome in 2023, it reframed obesity, type 2 diabetes, chronic kidney disease (CKD), and cardiovascular disease as manifestations of an interconnected pathophysiological continuum rather than four separate conditions.[1,2] The 2026 AHA/ACC/ADA/ASN guideline has taken an important further step by explicitly recognizing metabolic dysfunction-associated steatotic liver disease (MASLD) within CKM care and recommending non-invasive liver fibrosis assessment, including the Fibrosis-4 (FIB-4) index, in selected patients.[3] Yet an important conceptual question remains unresolved: Should this clinical recognition evolve into formal recognition of the liver as a fourth structural axis of CKM syndrome? The central argument is straightforward. The liver is now clinically recognized within the CKM framework, but it has not yet been formally integrated as a fourth structural axis of the syndrome.

The timing of this evolution is relevant to understanding the current CKM framework. The original CKM construct was developed before the 2023 international consensus established the contemporary MASLD/MASH nomenclature.[4] Subsequent work has increasingly emphasized the liver as an integral component of the cardiometabolic continuum, including within broader conceptualizations of CKM syndrome.[5] This temporal context may partly explain why hepatic disease was not explicitly incorporated as a distinct axis in the original CKM framework; however, it does not resolve whether the liver should now be formally integrated into the syndrome. The biological rationale for such an integration is substantial. MASLD and MASH share major pathophysiological drivers with CKM syndrome, including insulin resistance, visceral adiposity, ectopic lipid accumulation, and chronic low-grade inflammation. Moreover, liver disease is closely and bidirectionally linked to both CKD and cardiovascular disease, while increasing hepatic fibrosis is associated with adverse cardiovascular and cardiorenal outcomes.[6,7] These relationships support viewing hepatic disease not simply as a comorbidity accompanying CKM syndrome, but as part of the interconnected multisystem disease process. This concept has increasingly emerged across several recent frameworks, including MALCKS,[8] cardiovascular-renal-hepatic-metabolic syndrome,[6] cardiovascular-kidney-liver-metabolic (CKLM),[9] CKLMS,[10] and CARDIAL-MS.[11] Although these proposals differ in terminology, scope, and intended clinical application, they share a common premise: hepatic disease may warrant a more explicit and integrated position

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Address for Correspondence: Prof. Dr. Mehdi Zoghi, Department of Cardiology, Ege University
E-mail: mehdi_zoghi@hotmail.com
ORCID ID: orcid.org/0000-0002-8156-2675

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within cardiometabolic disease models. More recently, a 2026 JACC communication proposed extending the CKM framework toward CKML and emphasized the role of the liver within the cardiometabolic clinical workflow.[12] Taken together, these developments do not necessarily establish that the CKM acronym should be changed. Rather, they indicate that the transition from clinical recognition of liver disease in CKM care to its formal conceptualization as a fourth structural axis deserves careful consideration.

The CKLM Paradigm: From Clinical Recognition to Structural Integration

Nomenclature alone will not change practice. The practical task is to embed hepatic evaluation into the existing CKM staging architecture, as illustrated in Figure 1. The 2026 guideline already provides a framework for doing so.[3] Among adults with CKM syndrome and diabetes or at least two cardiometabolic risk factors, FIB-4 calculation every 1-2 years is recommended; among adults with CKM stage 1 due to prediabetes, calculation every 2-3 years is considered reasonable.[3] FIB-4 is derived from age, aspartate aminotransferase, alanine aminotransferase, and platelet count, and therefore can be incorporated into routine CKM assessment without requiring additional laboratory infrastructure. In adults aged 35-64 years, a FIB-4 below 1.3 identifies a group at low-risk for clinically significant fibrosis, whereas age-adjusted interpretation is required in adults aged 65 years or older, for whom a threshold of 2.0 is used.[3] Intermediate or high-risk results should prompt sequential assessment, commonly with vibration-controlled transient elastography or enhanced liver fibrosis testing, with specialist referral when clinically significant fibrosis is suspected.[3]

This sequential approach also illustrates why the liver could be conceptualized as a parallel axis rather than an ancillary component. The analogy with the kidney is instructive: epidermal growth factor receptor and albuminuria provide organ-specific information that is integrated into CKM risk assessment without replacing the broader syndrome framework.[1-3] FIB-4 is useful, but it is not a definitive diagnostic test and has important limitations. Its prognostic value has been demonstrated in populations with obesity and/or type 2 diabetes, while discordance with elastography can occur and may be clinically relevant.[13,14] In selected patients, elastography and, when appropriate, magnetic resonance imaging (MRI)-based techniques can refine fibrosis assessment.[14,15] MRI-based techniques should be interpreted according to their

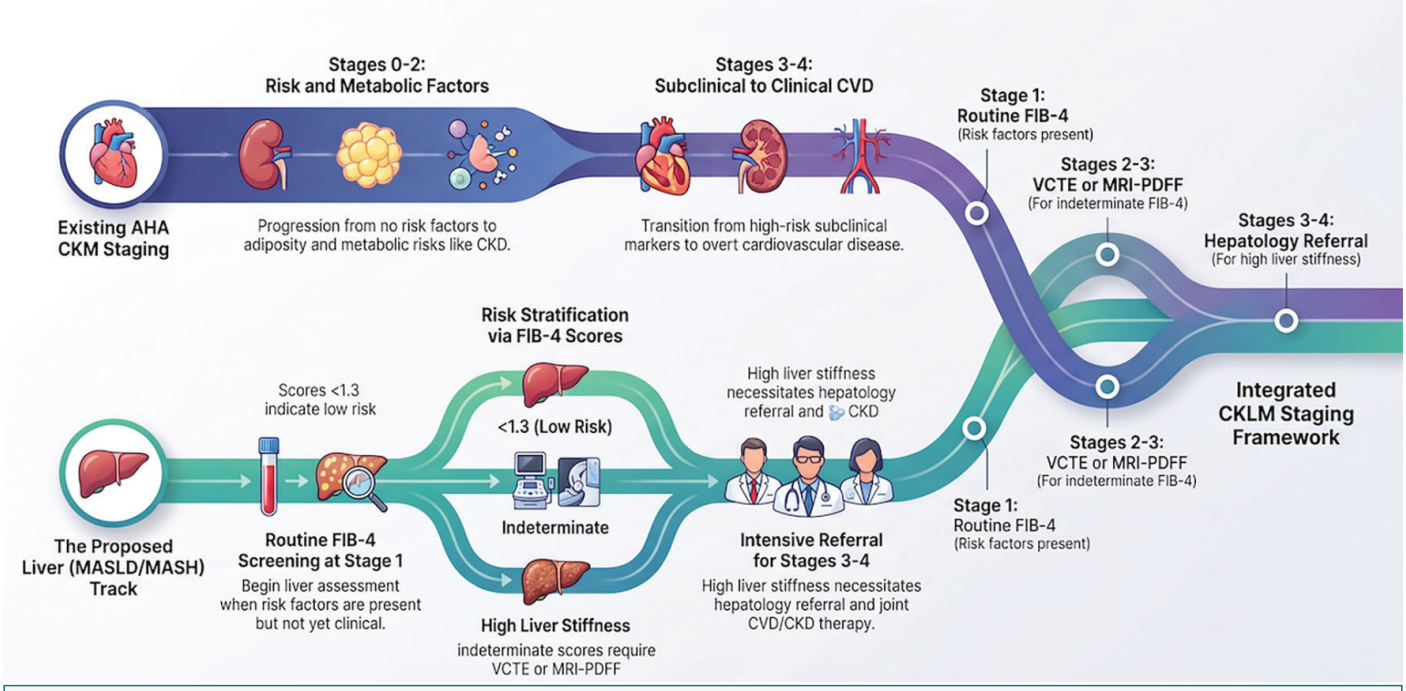

Figure 1. FIB-4 and sequential non-invasive liver assessment layered onto existing CKM stages to illustrate a practical CKLM pathway, running parallel to rather than replacing the established CKM framework

FIB-4: Fibrosis-4, CKLM: Cardiovascular-kidney-liver-metabolic, MRI: Magnetic resonance imaging, CKM: Cardiovascular-kidney-metabolic, CKD: Chronic kidney disease, MRI: Magnetic resonance imaging, CVD: Cardiovascular disease

specific purpose: magnetic resonance elastography provides an imaging-based assessment of liver stiffness and fibrosis, whereas MRI-based proton density fat fraction is primarily used to quantify hepatic steatosis.[15] The appropriate response is therefore a structured, sequential assessment rather than exclusion of the liver.

Conclusion

Among the proposed names, I favor CKLM over the alternative ordering, CKML, recently proposed in JACC.[12] Both formulations recognize the liver alongside the cardiovascular and renal axes. CKLM, however, preserves the cardiovascular-kidney sequence established by the original CKM construct while introducing the liver as the newly emphasized organ axis and retaining the metabolic domain as a central driver of the syndrome.

The original CKM framework was built around systemic interconnection rather than isolated organ silos.[1,2] The 2026 guideline has now taken an important clinical step by explicitly recognizing MASLD and incorporating FIB-4-based liver fibrosis assessment into CKM care.[3] The next question is whether this clinical recognition should evolve into structural recognition of the liver as a fourth axis of the syndrome. Future AHA scientific statements and international consensus documents should consider whether MASLD/MASH and liver fibrosis warrant formal incorporation into CKM nomenclature and staging, with prospective evaluation of how liver status modifies cardiovascular and kidney risk prediction, therapeutic decisions, and multiorgan clinical trial design.[9,10,12] The goal should not be to create another acronym for its own sake but to develop a more complete disease model in which cardiovascular, kidney, liver, and metabolic diseases are assessed as interconnected manifestations of systemic cardiometabolic disease (Figure 2).

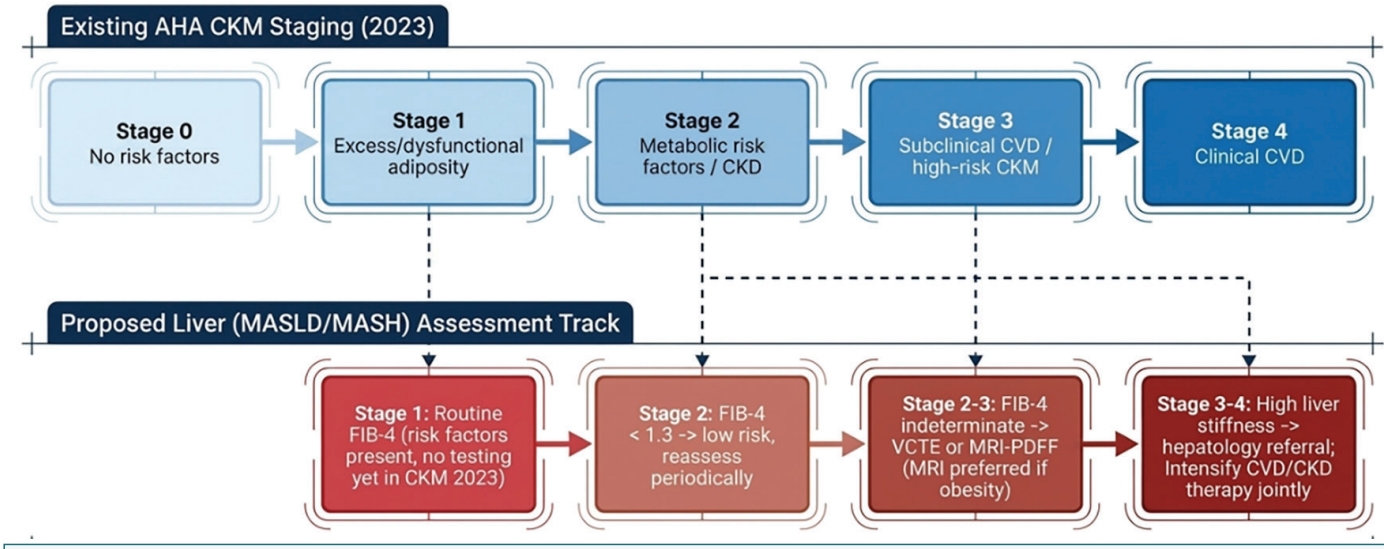

Figure 2. Proposed integration of non-invasive liver fibrosis assessment into existing AHA CKM syndrome staging, illustrating the conceptual basis of a CKLM framework

AHA: American Heart Association, CKM: Cardiovascular-kidney-metabolic, CKLM: Cardiovascular-kidney-liver-metabolic, CKD: Chronic kidney disease, FIB-4: Fibrosis-4, CVD: Cardiovascular disease

Footnotes

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