

Denominator bias in MENA MASLD epidemiology: A call for decision-grade surveillance

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent in the Middle East and North Africa (MENA) region, yet published estimates of prevalence and outcomes remain uncertain because the underlying denominators are inconsistently defined. This perspective argues that MENA MASLD epidemiology is systematically biased by three interacting mechanisms: distorted sampling frames, referral pathway selection, and structural undercapture of rural and displaced populations. Much of the current evidence is derived from convenience cohorts concentrated in urban, tertiary care settings where diagnostic availability and follow-up are greater than in the general population, leading to directional rather than random error. In parallel, risk stratification pathways that rely on two-step testing can funnel case detection toward specialty rich settings, overrepresenting advanced disease while missing earlier stages managed outside hepatology services. MASLD nomenclature change and incomplete alignment of coding and clinical documentation may further introduce artefactual inflection points that complicate trend interpretation. We highlight how underdiagnosis and under-recording in primary care propagate bias across downstream estimates and how validation of administrative algorithms and text-based ascertainment can quantify

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hidden disease reservoirs within routine data systems. Building on regional priority settings, we propose denominator-focused actions: probability-based sampling embedded in noncommunicable disease surveys; purposeful inclusion of rural and displaced groups; linkable data across primary care, laboratories, hospitals, and mortality registries; and harmonized coding and terminology. By decision-grade denominators, we refer to population denominators that are sufficiently representative, transparent, and linkable to support national surveillance, resource allocation, and trial-readiness decisions.

Keywords: Burden, denominator bias, epidemiology, MENA region, metabolic dysfunction-associated steatotic liver disease (MASLD), prevalence

“Not everything that can be counted counts, and not everything that counts can be counted.” (often attributed to Albert Einstein).^[1]

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a highly prevalent disease of the Middle East and North Africa (MENA) region.^[2] Yet, we still contest its true prevalence and outcomes because we rarely agree on the denominator. Recent estimates suggest a very high burden of MASLD, including pooled estimates approaching 45% in adults in the general population in the MENA and even higher among people with type 2 diabetes.^[2-5] Global meta-analyses, however, show marked heterogeneity driven as much by study design as by biology.^[6,7] In the MENA, heterogeneity is amplified by health system fragmentation, conflict-related displacement, and uneven access to diagnostics, all of which shape who is counted and who remains invisible.^[8] This correspondence argues that the region's MASLD epidemiology is systematically biased by three interacting forces: sampling frame distortion, referral pathway bias, and undercapture of rural and displaced

populations [Figure 1].^[8] These forces operate as a reinforcing cycle in which sampling bias shapes referral patterns, referral pathways magnify coding bias, and coding practices ultimately institutionalize undercapture, producing a self-perpetuating denominator gap. This matters because recent regional agendas are increasingly shifting the focus from estimating burden alone to building implementable care pathways and surveillance systems that can generate decision-grade denominators.^[9]

The best available MENA burden estimates have moved the field forward. Still, they are often interpreted as if they were direct measurements rather than model-based summaries of uneven underlying data.^[3,6] Even when methods are rigorous, the input studies can be clustered in urban tertiary settings, enriched for metabolic comorbidity, and limited by diagnostic availability, creating a biased denominator that is smaller, sicker, and more health system-connected than the actual population at risk.^[2-6] The result is not simply random error, but directional bias, because the underlying evidence is often preferentially drawn from urban, tertiary, and metabolically enriched

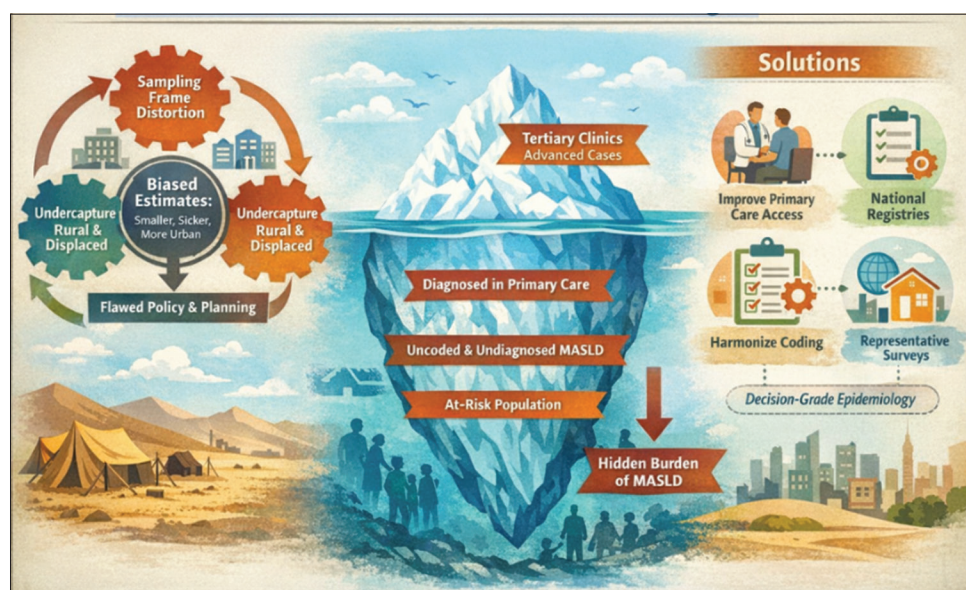


Figure 1: The self-reinforcing cycle of denominator bias in MASLD epidemiology (MENA region)

cohorts where diagnostic access and follow-up are better than in the general population, which can inflate apparent prevalence while simultaneously distorting the prevalence of advanced disease and outcomes. A simple sensitivity scenario illustrates the scale of this problem. If a country has an adult MASLD prevalence of 40% in the population, but one third of adults live in rural or displaced settings where diagnostic access captures only half as many cases as urban services, the recorded prevalence would fall to approximately 33% despite unchanged underlying disease frequency. Conversely, if the available evidence is drawn mainly from tertiary or metabolically enriched cohorts with a prevalence of 55%, the same country may appear to have a substantially higher burden. These illustrative estimates are not intended as country-specific measurements, but they demonstrate how plausible differences in ascertainment and sampling can shift apparent prevalence by several percentage points and create directional rather than random error.

First, sampling frames in the MENA are frequently defined by convenience rather than by population representativeness.^[3,6] Many prevalence studies draw participants from hospitals, clinics, employer-based health checks, or urban communities where ultrasound access and laboratory testing are routinely available, while rural communities are sparsely sampled or excluded.^[3] The issue is that this entails an untested leap from “this cohort” to “the country” without a defensible sampling frame.^[10] A global meta-analysis shows how prevalence estimates shift substantially across diagnostic modalities and inclusion criteria, reinforcing the idea that study design can be a stronger determinant of the estimate than the underlying disease frequency.^[6] For the MENA region, where within-country variation in obesity, diabetes, and healthcare access is substantial, this design sensitivity becomes a central threat to inference.^[3,5] The MASLD nomenclature

transition adds a further layer of measurement instability by changing how populations are defined and, therefore, how denominators are constructed.^[11,12] Historically, changes in disease nomenclature have produced artificial inflection points in surveillance trends, as seen with ICD revisions,^[13] and early MASLD trend analyses should therefore be interpreted cautiously. MASLD criteria are intentionally inclusive of metabolic dysfunction, but their operationalization varies substantially across datasets. This variation is amplified because many administrative systems have not yet aligned coding and reporting structures with the updated terminology.^[14] This misalignment affects both the numerator and denominator because it determines which patients are labeled, coded, and retrievable for surveillance.^[14,15] When coding and clinical labels lag behind nomenclature, apparent trends can reflect documentation artifacts rather than genuine epidemiologic shifts.^[15,16]

Second, referral bias distorts both prevalence and outcomes when speciality pathways serve as the gateway to diagnosis.^[17] Major guidelines now encourage structured case finding and risk stratification using noninvasive tools, often operationalized as a two-step pathway in which a first-line fibrosis score is followed by a second test or specialist referral for those at higher risk.^[18,19] This approach is clinically sensible, but it also concentrates the measured disease burden within the subset of patients who reach testing, and within the facilities capable of implementing the pathway.^[20,21] Prognostic evaluations of two-step pathways demonstrate intense discrimination for liver-related outcomes, but they are typically generated in systems with mature diagnostics and reliable longitudinal capture.^[18,21] In many MENA settings, the pathway is arbitrarily applied, and referrals are shaped by insurance status, geography, and clinician awareness, creating a selection funnel that preferentially captures advanced disease and systematically misses earlier stages.^[8] Referral bias also affects outcome estimates by enriching cohorts for comorbidity and by conditioning follow-up on health system engagement.^[17,20] If advanced cases are more likely to be referred, then speciality cohorts will over-represent fibrosis and complications and may overestimate progression rates if incident disease is not adequately captured.^[17,20,21] The direction of bias depends on where events are recorded and whether outcomes can be linked across care settings.^[22] Conversely, mortality and complication estimates can be underestimated if large segments of the population experience outcomes outside the facilities generating the datasets, or if deaths are not linked to clinical registries.^[3,8] These competing biases can coexist within the same country, producing paradoxical

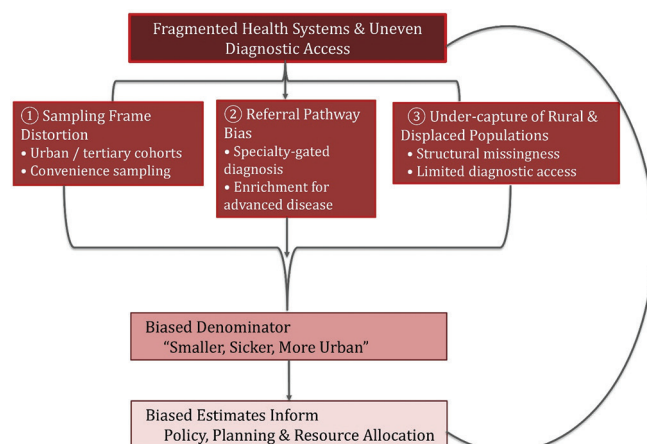


Figure 2: Bias and the hidden burden of MASLD in the MENA region

findings such as “high prevalence” alongside “low recorded advanced disease,” which may reflect surveillance failure rather than biology.^[10,22] These apparently contradictory directions of bias occur because each estimate is generated from a different denominator. Tertiary and specialty cohorts may inflate the apparent prevalence of advanced fibrosis because they preferentially include referred, symptomatic, insured, or metabolically complex patients. At the same time, population-level estimates of complications and mortality may be underestimated when events occur outside linked hospital systems, when deaths are not assigned to liver disease, or when displaced and rural populations remain outside registries. Thus, the same surveillance ecosystem can overestimate disease severity among those who enter specialty care while underestimating the total burden of advanced disease and death at the population level [Figure 2].

Third, undercapture of rural and displaced populations is not a marginal issue in the MENA region, but a defining methodological challenge. These groups are systematically absent from many household surveys, registries, and administrative datasets, which makes missingness structural rather than incidental. Conflict and displacement reshape denominators by moving populations across borders and within countries, altering exposure profiles, and disrupting continuity of chronic disease care. At the same time, ethical, legal, and data-protection constraints can limit the systematic collection and linkage of health data for displaced populations, further complicating surveillance and follow-up. Evidence from refugee-focused noncommunicable disease (NCD) reviews in the MENA region describes fragmented access and inconsistent health information systems, conditions that plausibly delay MASLD recognition and weaken longitudinal outcome capture.^[23] For MASLD, these barriers likely translate into delayed diagnosis, sparse fibrosis assessment, and incomplete complication capture. Yet, displacement status is rarely incorporated into surveillance as an analytic dimension.^[23] Mobile health platforms, community health worker models, and humanitarian NCD clinics may offer partial solutions for displaced and mobile populations, particularly when formal registries are unavailable. However, these approaches require careful governance, data protection safeguards, and mechanisms for continuity across borders and care providers. Rural communities face different but equally consequential barriers, including reduced access to imaging, laboratory testing, and specialist referral pathways that are embedded in guideline-dependent care models.^[8,24]

The “hidden denominator” problem becomes most visible when we compare recorded diagnoses with expected

prevalence. Real-world primary care data from Europe show that recorded MASLD prevalence can be far lower than expected from population studies, illustrating how underdiagnosis and under-recording can dominate administrative estimates.^[22] In the MENA region, where primary care coding may be less mature and imaging may be less systematically available, the gap between recorded and true prevalence is likely to be at least as large, with a magnitude that will vary by country and data system.^[8,15] Primary care functions as the front line of epidemiologic surveillance, not only of clinical care, and deficiencies in primary care coding propagate bias throughout all downstream MASLD estimates. Evidence from a primary care-focused report in the United States similarly emphasizes that underdiagnoses in routine care are a major problem, reinforcing that the denominator failure is a global phenomenon that may be amplified in resource-constrained contexts.^[25]

Administrative datasets can also misclassify MASLD because diagnosis codes do not perfectly map to clinical definitions, and their accuracy depends on local coding practices.^[26] Validation studies show that ICD-based approaches have variable sensitivity and specificity, and, as a result, coded data are not a neutral mirror of clinical reality.^[27] Innovative approaches, including natural language processing applied to radiology and clinical text, can reveal large reservoirs of uncoded steatosis and thereby expose the scale of denominator undercapture in routine datasets.^[28] These methods are best used as complements to probability sampling and sentinel surveillance because they can quantify hidden disease within existing systems and improve ascertainment without waiting for new national surveys.^[28,29]

The question that arises, thus, is: What should change in practice, policy, and research if we take denominator bias seriously? A recently published roadmap by Steatotic Liver Disease Study group in the Middle East and North Africa (SLMENA) explicitly reframed the regional agenda away from prevalence point estimates alone and toward upstream determinants of measurement quality, implementation capacity, and data readiness.^[9] In this two Delphi round survey study, MENA experts ranked a 52-item research and action agenda spanning six domains as priorities, including burden, care models, disease management, education and awareness, patient and community perspectives, and leadership and policy. The highest-ranked research priorities included developing regional MASLD registries and validating noninvasive diagnostic tools, which directly target the hidden denominator by improving ascertainment beyond tertiary

care settings.^[9] This agenda is therefore not merely descriptive, but methodological, because it identifies denominator governance as a prerequisite for credible regional estimates and trial readiness. In other words, the SLMENA agenda points to a simple conclusion: Fixing biased estimates requires changing the systems that generate them and not merely reanalyzing existing datasets. The next step is therefore to translate these priorities into concrete actions at the level of care pathways, referral architecture, and surveillance design.^[9,30] Implementation should be tiered according to health system maturity rather than presented as a uniform regional prescription. In high-income Gulf Cooperation Council settings with advanced health information systems, the priority should be linkage between primary care, laboratory, imaging, hospital, and mortality datasets, supported by registry-based quality indicators. In middle-income countries with partial digital infrastructure, such as Egypt, Jordan, Tunisia, and Morocco, the immediate priority may be sentinel surveillance, standardized coding, staged fibrosis risk assessment in primary care, and periodic probability-based surveys. In fragile or conflict-affected settings, including Libya, Syria, Yemen, and parts of Iraq and Palestine, the first step may be more basic: preserving minimum chronic disease datasets, using mobile or community-based follow-up where feasible, and integrating MASLD-relevant variables into humanitarian NCD services. Financing and governance of this agenda will also require regional and international partnerships. In lower-resource and fragile settings, external technical and financial support may be needed to strengthen health information systems, harmonize surveillance standards, and integrate MASLD indicators within broader NCD monitoring frameworks. Regional collaborations, academic networks, and cross-country implementation partnerships could also support registry development, workforce capacity building, data linkage, and implementation research beyond the limits of individual national budgets.

For a start, clinicians and guideline writers should be explicit that risk stratification pathways can inadvertently widen epidemiologic blind spots if implemented only in speciality-rich settings and not integrated into primary care and community services.^[18,21,31] This is not an argument against guideline-based care. Still, there is a call for implementation designs that include rural primary care, shared care models, and referral systems that do not require patients to self-navigate to tertiary centers.^[8,18,21] Next, policymakers should treat MASLD surveillance as health system infrastructure; invest in linkable data across primary care, hospitals, laboratories, and mortality registries; and define a minimum national dataset for MASLD reporting,

including at least coded diagnosis, diagnostic modality, BMI or waist circumference, diabetes status, key metabolic comorbidities, liver enzymes, platelet count, fibrosis risk score, liver stiffness or imaging results where available, care setting, referral source, and linkage to liver-related outcomes and mortality.^[9,32] A practical starting point is to map country-specific data sources and their catchments because denominator bias is often sustained by fragmented knowledge of existing data and what they represent.^[32]

Additionally, researchers in MENA should prioritize denominator-honest designs, including probability-based household sampling embedded in existing NCD surveys, oversampling of rural and displaced groups, and transparent weighting strategies that reflect population structure and missingness.^[33] However, embedding liver-specific assessment into general NCD surveys will not be equally feasible across the region. Imaging-based strategies and elastography require equipment, trained operators, and quality assurance systems that may be unavailable in lower-resource settings. A pragmatic staged approach may therefore begin with harmonized metabolic risk variables, liver enzymes, platelet count, and simple fibrosis scores, followed by targeted elastography or imaging in sentinel sites where capacity exists. In the absence of explicit, population-based denominators, increasingly refined MASLD estimates may convey false certainty rather than epidemiologic clarity. The economic consequences of denominator bias are not theoretical because regional cost narratives and service planning frequently rely on modeled burden trajectories when local longitudinal data are sparse.^[34] In a regional discussion of MASLD management, the authors highlight both economic and clinical implications and illustrate MENA trends in prevalence, mortality, and disability-adjusted life years using Global Burden of Disease-derived data, emphasizing how estimates are propagated into planning assumptions.^[34] If the denominator is biased, the resulting burden and cost projections will be prejudiced, potentially misdirecting investment toward prevention, diagnostic capacity, or specialist services. Health economic models used for MASLD planning in the region should therefore include sensitivity analyses around denominator assumptions, including underdiagnosis in primary care, rural under-ascertainment, displaced population exclusion, and tertiary referral enrichment. Testing these assumptions would make cost projections more transparent and reduce the risk of misdirected investment.

Finally, the nomenclature transition should be leveraged as an opportunity to modernize coding and surveillance rather than as a purely semantic change.^[11,12] The nomenclature

transition will only improve epidemiology if it is implemented consistently across clinical documentation, research datasets, and patient-facing communication in the languages clinicians actually use.^[35] In the Arab region, the absence of harmonized Arabic medical terminology can lead to misclassification, undermining case identification and comparability across settings. A recent mixed-methods consensus established Arabic terminology for steatotic liver disease, providing a pragmatic bridge between global definitions and local documentation practices.^[35] For denominator validity, this kind of linguistic standardization is not cosmetic because it directly affects how diagnoses are recorded, how patients are labeled, and how data are extracted into registries and administrative datasets.^[35]

Global consensus efforts have emphasized the need for more precise clearer definitions and care pathways for MASLD and steatohepatitis. Still, the operational benefits will be realized only if terminology is translated into billing, coding, and registry architecture that clinicians actually use.^[11,19] The tailored MASLD model of care has been proposed as an operational response to fragmented pathways, emphasizing that screening and risk stratification must reach large numbers of at-risk individuals and that multidisciplinary implementation should be guided by national strategies.^[18] The proposed model highlights screening, risk stratification, and the establishment of a clinical care pathway for management and explicitly discusses the implications of nomenclature change for care delivery.^[18] These care pathway designs matter methodologically because they can shift diagnosis and staging upstream, reducing reliance on tertiary referral funnels that distort both prevalence denominators and outcome capture.^[18,21] Without this infrastructure, the MENA region will continue to generate precise-looking numbers that are systematically biased, and decisions about resource allocation, screening intensity, and service configuration will be made on unstable ground.

MENA does not lack MASLD studies; it lacks clarity about the denominator.^[3,8,36] When sampling frames are convenience-based, when referral pathways determine who is “seen,” and when rural and displaced populations are poorly captured, prevalence and outcome estimates will remain biased regardless of analytic sophistication.^[37] The solution is not to abandon modeling or clinical cohorts but to connect them to explicit population denominators through probability sampling, improved primary care ascertainment, and linkable health information systems.^[22,33,37] The field should treat underdiagnosis and under-recording as measurable phenomena using validation studies, coding audits, and text-based ascertainment where appropriate.

If MENA aligns nomenclature, guidelines, surveillance infrastructure, and tiered implementation strategies, the region can move from persuasive but unstable estimates to decision-grade epidemiology capable of guiding prevention, resource allocation, trial readiness, and equitable care.

Ethical Considerations

Ethical approval from institutional ethics board was not required for this article as it a perspective article, where no new human subject data was collected or utilized.

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Conflicts of interest

Several authors are members of, or hold leadership roles within, the Steatotic Liver Diseases Study Foundation in Middle East and North Africa (SLMENA). The manuscript discusses priorities and actions that are aligned with previously published SLMENA work and cites some publications authored or co-authored by members of the present author group. These affiliations and self-citations reflect the authors’ regional academic and policy work in MASLD and do not represent a financial conflict of interest. No other conflicts of interest are declared.”

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