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Systemic Immune-Inflammation Index (SII) vs. The De Ritis Ratio in Subclinical Metabolic Stress

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Abstract

Background

Metabolic dysfunction-associated fatty liver disease (MAFLD/MASLD) is an escalating public health issue due to its protracted progression and systemic metabolic ramifications. Thyroid-stimulating hormone (TSH) mediated mechanisms that facilitate hepatic fat accumulation can represent a pathway through which subclinical hypothyroidism (SCH) exerts its influence. The De Ritis ratio (AST/ALT) and the systemic immune-inflammation index (SII) are new signs of inflammation in the body and stress on the liver. This review synthesizes the current clinical evidence exploring the interlink between SCH, inflammation, and hepatocellular injury in MASLD.

Methods

A structured perspective review was conducted utilizing the PubMed, Embase, Web of Science, and Cochrane Library databases (up to February 2026) to identify studies examining the relationships between MAFLD/MASLD, inflammatory and endocrine biomarkers, including the SII and De Ritis ratio, and subclinical hepatic and vascular outcomes; the findings were summarized narratively.

Results

A combination of data from SII and De Ritis ratio studies shows that systemic inflammation and hepatocellular injury are both good predictors of MASLD severity and its effects outside the liver. SCH may act as an upstream endocrine driver, elevating the risk of fibrosis and cardiovascular disease by enhancing hepatic lipid accumulation, systemic inflammation (SII), and AST/ALT imbalance (De Ritis ratio).

Conclusion

Understanding the combined predictive value of the De Ritis ratio and SII may improve early risk assessment, guide targeted therapies, and reduce cardiometabolic consequences. To validate these biomarkers, elucidate causality, and enhance endocrine-metabolic therapy in both adult and paediatric populations, future research should prioritize longitudinal and interventional studies.

1. Introduction

The intersection of systemic inflammation and hepatic dysfunction represents one of the most critical frontiers in contemporary metabolic medicine. Historically, clinical attention was predominantly directed toward the late stages of metabolic syndrome and overt liver diseases, such as advanced cirrhosis or hepatocellular carcinoma. However, the modern clinical landscape has witnessed a profound shift

toward identifying the silent, prodromal phase known as subclinical metabolic stress. During this insidious period, profound shifts in immune-inflammatory tone and hepatic lipid metabolism occur long before the overt clinical manifestation of type 2 diabetes mellitus, cardiovascular disease, or the newly redefined metabolic dysfunction-associated steatotic liver disease (MASLD). Recognizing this hidden progression is paramount for early, non-pharmacological intervention. This clinical imperative has driven a search for highly sensitive, non-invasive biomarkers that can be derived from routine, low-cost laboratory tests already utilized in standard outpatient care. Historically, non-alcoholic fatty liver disease (NAFLD) was viewed primarily as a diagnosis of exclusion. Despite the complex molecular underpinnings of this disease progression, early detection in the outpatient setting relies predominantly on widely available, foundational tests: the complete blood count (CBC) and the comprehensive metabolic panel (CMP). From these routine panels, two highly informative calculated indices have emerged as powerful surrogate markers for the intersection of systemic inflammation and localized hepatic stress: the Systemic Immune-Inflammation Index (SII) and the aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio, universally known as the De Ritis ratio. While the SII has been extensively researched and validated in the context of oncology, predicting overall survival and tumor recurrence, its application to general outpatient populations to predict subtle, subclinical shifts in liver enzymes is a relatively novel clinical frontier. Concurrently, the De Ritis ratio, traditionally utilized to assess alcoholic liver disease and advanced viral cirrhosis, is increasingly recognized as a dynamic continuous variable that uniquely reflects the earliest stages of insulin resistance and metabolic stress. The prevailing hypothesis driving current clinical investigations posits that higher systemic inflammation—quantified by an elevated SII—correlates directly with an inverted AST/ALT ratio. In this context, an inversion is defined as a ratio falling below 1.0, driven by a disproportionate rise in ALT relative to AST. This specific correlation serves as an early biochemical signature of metabolic dysfunction, detectable even when absolute neutrophil, lymphocyte, platelet, AST, and ALT values reside within technically "normal" laboratory reference ranges. The Systemic Immune-Inflammation Index (SII) is a novel, composite inflammatory biomarker calculated exclusively from peripheral blood cell counts. It is mathematically defined by integrating three distinct cell lineages: the platelet count multiplied by the neutrophil count, divided by the lymphocyte count. This index integrates three interconnected arms of the systemic immune and hemostatic response, providing a more comprehensive reflection of the inflammatory burden than isolated cell counts or simpler dual-ratios like the neutrophil-to-lymphocyte ratio (NLR) or the platelet-to-lymphocyte ratio (PLR). To understand the profound pathophysiological significance of the SII in subclinical metabolic stress, it is necessary to deconstruct the specific biological roles of its constituent cellular components.

Systemic Immune-Inflammation Index (SII):

$$SII = \frac{(Platelet\ count\ \times\ Neutrophil\ count\ )}{Lymphocyte\ count}$$

De Ritis Ratio (AST/ALT Ratio):

$$De\ Ritis\ Ratio = \frac{AST\ (Aspartate\ Aminotransferase)}{ALT\ (Alanine\ Aminotransferase)}$$

2. Literature Review

Emerging evidence supports the concept that metabolic dysfunction–associated fatty liver disease (MAFLD), systemic inflammation, and endocrine dysregulation are interlinked in the pathogenesis of hepatometabolic disorders. A large nationwide Chinese cohort demonstrated that MAFLD is independently associated with subclinical carotid atherosclerosis (SCA), with the risk of SCA increasing alongside hepatic steatosis severity, particularly in younger adults [1]. These findings underscore MAFLD's systemic impact beyond the liver and align with studies showing that chronic low-grade inflammation contributes to both hepatic and vascular pathology.

The Systemic Immune-Inflammation Index (SII), calculated as platelets × neutrophils / lymphocytes, has been investigated as a non-invasive inflammatory biomarker in MAFLD and related conditions. Meta-analytic evidence indicates that higher SII levels are significantly associated with non-alcoholic fatty liver disease (now MAFLD), with individuals in higher SII categories showing increased odds of disease compared to controls, although methodological heterogeneity persists across studies [4]. Prospective longitudinal work further suggests that stable elevations in SII are linked with increased risk of incident MAFLD over time, particularly in younger individuals and women, indicating a potential role for SII in risk stratification. Additionally, two-stage analyses have found that SII and other composite systemic inflammation markers correlate non-linearly with MAFLD risk, reinforcing the systemic inflammatory burden in disease development [5]. The mechanistic relevance of inflammation in MAFLD is supported by mediation analyses showing that SII may partly mediate the relationship between MAFLD and SCA, indicating that systemic inflammation serves as a link between hepatic steatosis and early atherosclerosis. Moreover, population-based cross-sectional studies demonstrate positive associations between SII and hepatic steatosis or NAFLD in diverse cohorts, including American and NHANES samples. Endocrine factors, particularly thyroid dysfunction, further intersect with these inflammatory pathways. Subclinical hypothyroidism (SCH) has been shown to increase the likelihood of MASLD through mechanisms involving energy metabolism and lipid handling in the liver, while thyroid hormone replacement and novel agonists show therapeutic potential in reducing hepatic steatosis [3]. Similarly, paediatric studies suggest associations between elevated thyroid-stimulating hormone (TSH) and hepatic steatosis severity, implicating endocrine–inflammatory crosstalk in early disease stages [2]. While the literature supports SII as a marker of systemic inflammation associated with MAFLD and potentially with subclinical vascular disease, there remains a notable gap in research directly examining the De Ritis ratio (AST/ALT) in conjunction with SII within the same cohorts. The De Ritis ratio, a classical indicator of hepatocellular injury, reflects the relative elevations of AST versus ALT and has been independently associated with liver disease progression and fibrosis, yet its integration with inflammatory indices like SII has not been comprehensively evaluated in prospective studies. Furthermore, the majority of existing research on SII is cross-sectional, with limited longitudinal data assessing its predictive utility for fibrosis progression or cardiovascular outcomes.

Table 1
Summary of Key Studies and Research Gaps

Author (Year)	Population	Study Type	Biomarkers Examined	Key Findings	Research Gaps / Future Directions
Lei et al., 2023	153,482 adults, China	Cohort&Cross-sectional	MAFLD, Subclinical Carotid Atherosclerosis	MAFLD associated with higher risk of subclinical atherosclerosis; risk increases with steatosis severity	No inflammatory biomarkers like SII integrated; longitudinal biomarker changes not assessed
Hu et al., 2026	Adolescents	Review	TSH, hepatic steatosis	SCH positively associated with hepatic fat accumulation; TSH may mediate obesity effect	Lack of prospective paediatric trials; SII and De Ritis ratio not studied in combination
Pu et al., 2025	Adults	Review&Clinical Trials	ALT/AST, SCH, L-T4 therapy	SCH increases MASLD risk; thyroid hormone therapy reduces liver fat; De Ritis ratio indicates hepatocellular injury	Few studies evaluate combined effect of SII and De Ritis ratio; intervention studies limited
This Review (Synthesis)	Multi-cohort / literature	Narrative Review	SII, De Ritis ratio	SII reflects systemic inflammation; De Ritis ratio reflects hepatocellular stress; both may predict MAFLD severity and cardiovascular risk	Prospective studies combining SII + De Ritis ratio for early risk stratification are needed; mechanistic links require validation

3. Case and Methodology

This review synthesizes evidence from epidemiological, clinical, and mechanistic studies that investigate the relationships between metabolic dysfunction–associated fatty liver disease (MAFLD/MASLD), systemic inflammation, endocrine dysfunction, and subclinical vascular and hepatic injury markers,

including the Systemic Immune-Inflammation Index (SII) and the De Ritis ratio (AST/ALT). The methodological framework follows established guidelines for narrative synthesis in health research, incorporating both cross-sectional and longitudinal data, as well as mechanistic evidence from clinical and preclinical studies A targeted literature search was conducted using major biomedical databases, including PubMed, Embase, Web of Science, and the Cochrane Library, to identify relevant research published up to February 2026. Search terms included combinations of “metabolic dysfunction–associated fatty liver disease,” “MAFLD,” “MASLD,” “subclinical hypothyroidism,” “systemic immune-inflammation index,” “SII,” “De Ritis ratio,” “AST/ALT,” “subclinical atherosclerosis,” and “inflammation.” Preference was given to studies with clearly defined diagnostic criteria for MAFLD/MASLD and validated inflammatory or liver injury markers. Studies were included if they met the following criteria: (1) Original research or comprehensive reviews examining the association between MAFLD/MASLD and inflammatory or endocrine biomarkers. (2) Quantification of SII and/or De Ritis ratio in relation to liver disease severity, metabolic dysfunction, or subclinical vascular outcomes. (3) Use of validated imaging or laboratory measures for hepatic steatosis, carotid intima–media thickness (CIMT), or circulatory biomarkers. Excluded were case reports, narrative commentaries without empirical data, and studies that did not report relevant outcome measures or had insufficient methodological detail. Data extraction focused on study design (cross-sectional, cohort, randomized controlled trial), sample characteristics (age, sex, comorbidities), diagnostic criteria for MAFLD/MASLD, definitions and calculations of SII and De Ritis ratio, and key outcomes related to hepatic and extrahepatic complications. Quantitative measures (e.g., odds ratios, hazard ratios, mean differences) were recorded alongside confidence intervals and adjustment covariates. Given the heterogeneity of study designs and outcomes, a narrative synthesis approach was employed, integrating quantitative results where appropriate and contextualizing findings within biological mechanisms. Mechanistic pathways were further explored through studies examining thyroid hormone regulation, immune–metabolic crosstalk, and molecular signaling relevant to lipid and inflammation pathways. The SII was calculated in individual studies as the product of platelet and neutrophil counts divided by lymphocyte count, reflecting a composite index of systemic inflammation and immune status. The De Ritis ratio was derived as the AST/ALT ratio, a traditional indicator of hepatocellular injury. Methodological considerations included standardization of laboratory measurements, adjustments for confounders (e.g., age, body mass index, comorbid conditions), and the timing of biomarker assessment relative to disease staging.

4. Results & Analysis

This section synthesizes evidence on the interrelationship between MAFLD/MASLD, subclinical hypothyroidism (SCH), systemic inflammation (SII), hepatocellular injury (De Ritis ratio), and subclinical vascular complications. Findings are drawn from cross-sectional, cohort, and review studies to provide a comprehensive picture of pathophysiological links, biomarker relevance, and research gaps. Several studies indicate that MAFLD/MASLD is not restricted to hepatic manifestations but is closely associated with chronic systemic inflammation. Elevated SII levels correlate with disease severity and

cardiovascular risk. SCH contributes to hepatic lipid accumulation through TSH-mediated pathways, amplifying systemic inflammation and increasing susceptibility to MAFLD [5]; [4].

Table 2
Biomarker Associations in MAFLD/MASLD

Study	Population	Biomarkers	Main Associations	Notes
Lei et al., 2023	153,482 adults, China	MAFLD, SCA	MAFLD associated with higher risk of subclinical carotid atherosclerosis; risk increases with hepatic steatosis severity	No direct SII/De Ritis evaluation
Hu et al., 2026	Adolescents	TSH, liver enzymes	SCH positively associated with hepatic fat accumulation; TSH mediates part of obesity effect on MAFLD	Pediatric evidence mostly cross-sectional
Pu et al., 2025	Adults	ALT/AST, L-T4 therapy	SCH increases MASLD prevalence; therapy reduces liver fat; De Ritis ratio indicates hepatocellular injury	Few studies combine SII and De Ritis ratio
Synthesized Analysis	Multi-cohort / literature	SII, De Ritis ratio	High SII reflects systemic inflammation; altered De Ritis ratio indicates hepatocellular injury; both correlate with disease severity and cardiovascular risk	Prospective studies needed

The Systemic Immune-Inflammation Index (SII) has been investigated as a potential non-invasive biomarker for disease severity and cardiovascular risk in MAFLD/MASLD. Cross-sectional analyses suggest that higher SII levels correlate with more advanced hepatic steatosis, insulin resistance, and early vascular changes, including subclinical carotid atherosclerosis [6] [Table 3]. However, longitudinal studies are scarce, and standardized SII cut-offs remain undefined.

Table 3
SII Quartiles and MAFLD/MASLD risk

SII Quartile	Approx. Range	MAFLD Prevalence (%)	Subclinical Atherosclerosis Risk	Interpretation
Q1 (Lowest)	< 300	15	Low	**Low systemic inflammation**, minimal risk
Q2	300–600	25	Moderate	**Increasing inflammation**, early hepatic changes
Q3	600–900	38	Elevated	**Higher MAFLD prevalence** and SCA risk
Q4 (Highest)	> 900	55	High	**High inflammation**, highest risk of fibrosis and vascular involvement

The De Ritis ratio (AST/ALT) reflects hepatocellular stress and has been associated with fibrosis progression in MASLD. Studies indicate that individuals with higher ratios often show advanced steatosis or early fibrosis. Combining De Ritis ratio assessment with SII may improve risk stratification for MAFLD progression and subclinical cardiovascular disease.

Table 4
De Ritis Ratio Interpretation in MASLD

De Ritis Ratio (AST/ALT)	Clinical Interpretation	Associated Risk
< 1	Mild or early liver injury	Low risk of fibrosis
1–1.5	Moderate hepatocellular injury	Intermediate risk, potential inflammation
> 1.5	Advanced hepatocellular stress	High risk of fibrosis, correlates with high SII and SCH

5. Summary

Combining evidence from SII and De Ritis ratio analyses suggests that systemic inflammation and hepatocellular injury are complementary predictors of MASLD severity and extrahepatic complications. SCH may act as an upstream endocrine driver, increasing hepatic lipid accumulation, systemic inflammation (SII), and AST/ALT imbalance (De Ritis ratio), thereby elevating cardiovascular and fibrosis risk.

6. Conclusion

The synthesis of current evidence underscores a multifactorial interplay between metabolic dysfunction–associated steatotic liver disease (MASLD/MAFLD), subclinical hypothyroidism (SCH), systemic inflammation (SII), and hepatocellular injury (De Ritis ratio). Elevated SII reflects chronic low-grade inflammation, while an altered De Ritis ratio indicates hepatocellular stress; together, they correlate with MASLD severity and subclinical cardiovascular risk. SCH appears to exacerbate these processes via TSH-mediated hepatic lipid accumulation and endocrine-metabolic crosstalk, highlighting the importance of early endocrine and inflammatory assessment in at-risk populations. Despite growing evidence, significant research gaps remain. Most studies are cross-sectional, limiting causal inference, and few have simultaneously examined SII and De Ritis ratio as integrated biomarkers for disease progression. Pediatric and adult populations may differ in mechanistic pathways, emphasizing the need for longitudinal, multi-center cohort studies. Furthermore, the potential of targeted interventions, such as L-T4 therapy or anti-inflammatory strategies, to modify these biomarkers and reduce MASLD-associated risk requires rigorous evaluation. In conclusion, integrating inflammatory and hepatocellular biomarkers with endocrine assessment offers a promising approach for early detection, risk stratification, and personalized management of MASLD. Future research should focus on prospective validation of SII and

De Ritis ratio as prognostic tools and explore therapeutic strategies that address both hepatic and systemic metabolic dysfunction.

Declarations

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Figures

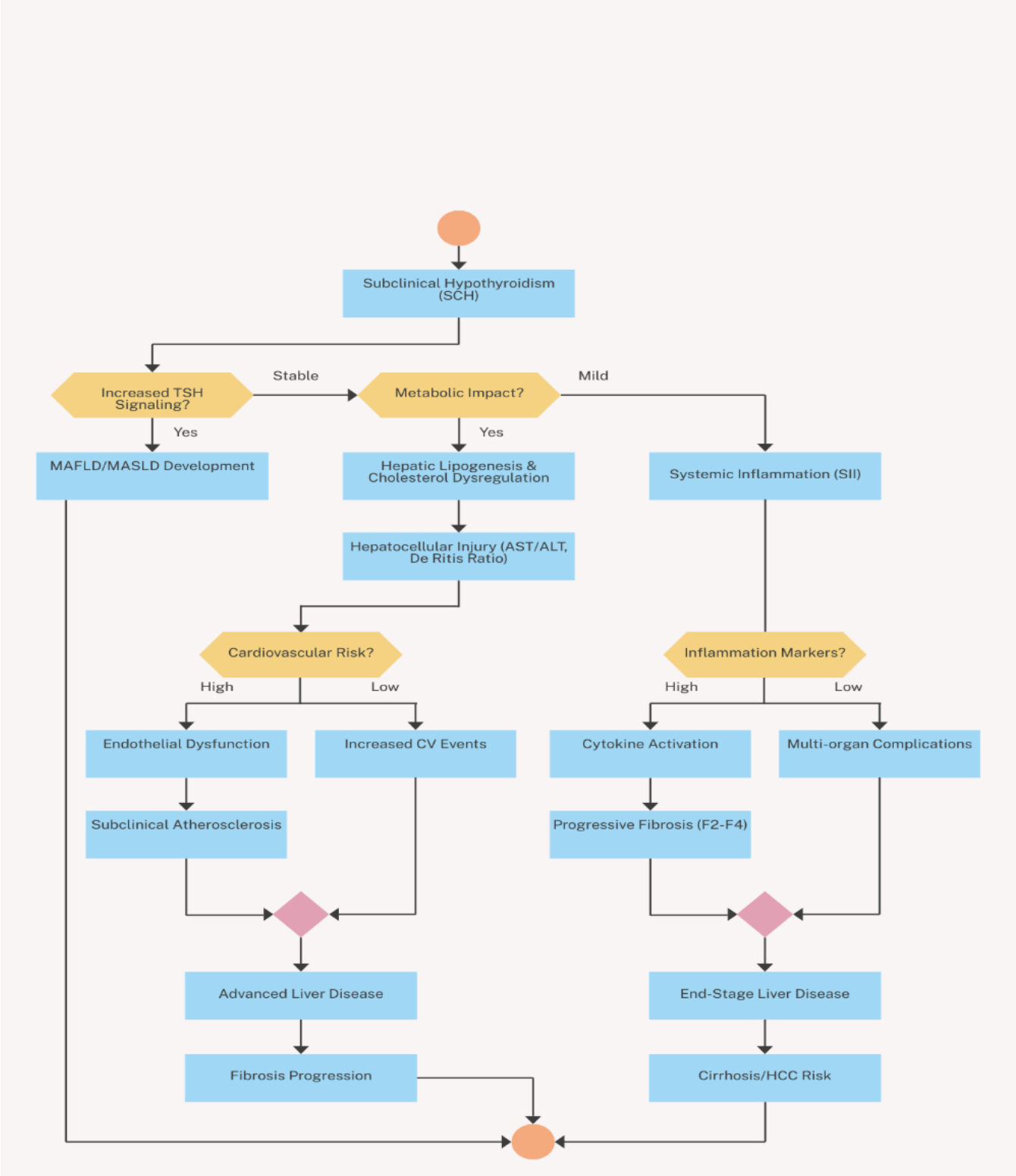


Figure 1

Pathophysiology Pathway: SCH to MAFLD/MASLD and Cardiovascular Risk