American Journal of Medicine and Medical Sciences 2025, 15(10): 3713-3717
DOI: 10.5923/j.ajmms.20251510.93

Sarcopenia in the Context of Metabolically Associated Fatty Liver Disease: Clinical Manifestations and Interrelationships

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Abstract The aim of the study was to conduct a systematic analysis of scientific data to evaluate the clinical features of the combined course of sarcopenia and metabolically associated fatty liver disease (MAFLD). **Materials and Methods.** A search for scientific publications was carried out in international databases such as PubMed, Google Scholar, as well as in the Russian database Elibrary.ru. The review included studies published between 2017 and 2024. Special attention was given to works describing the clinical features of patients with sarcopenia and MAFLD, including data on epidemiology, pathogenetic mechanisms, and clinical outcomes. **Conclusions.** The coexistence of sarcopenia and MAFLD forms a specific clinical phenotype, driven by overlapping pathogenetic mechanisms. Loss of muscle mass and strength in sarcopenia frequently accompanies MAFLD and is associated with insulin resistance, chronic inflammation, and metabolic disturbances. The interaction between these conditions is reflected in impaired energy metabolism, activation of pro-inflammatory cytokines, and progressive tissue damage. The presence of sarcopenia in patients with MAFLD worsens the clinical course of the disease by accelerating liver fibrosis progression, reducing physical activity tolerance, and increasing mortality. These findings highlight the need for comprehensive diagnostics and individualized approaches to rehabilitation and treatment aimed at simultaneous correction of both pathological processes.

Keywords Sarcopenia, Metabolically associated fatty liver disease (MAFLD), Epidemiology, Pathogenetic mechanisms, Comorbidity, Insulin resistance, Chronic systemic inflammation

1. Introduction

In recent decades, there has been a significant increase in the number of patients suffering from sarcopenia and metabolic-associated fatty liver disease (MAFLD), driven by the global obesity epidemic, population aging, and the rising prevalence of metabolic disorders [1]. These conditions not only frequently coexist but also share common pathogenic mechanisms, including insulin resistance, chronic inflammation, and mitochondrial dysfunction, which makes their combined course particularly challenging for diagnosis and treatment.

Sarcopenia, characterized by a reduction in muscle mass and strength, has been recognized as an important factor influencing the prognosis of patients with MAFLD [2]. Studies indicate that the presence of sarcopenia in individuals with MAFLD is associated with a higher degree of liver fibrosis, impaired physical performance, and an increased risk of adverse clinical outcomes. Conversely, MAFLD, as a systemic metabolic disorder, negatively affects muscle tissue, contributing to its atrophy and functional decline.

The prevalence of MAFLD reaches 25.0–30.0% in the general population and continues to rise, especially among individuals with obesity and type 2 diabetes mellitus [3]. At the same time, sarcopenia affects up to 10.0% of people over the age of 60, with its frequency being significantly higher in patients with metabolic disorders. These data highlight the importance of studying the pathogenetic interrelationship between sarcopenia and MAFLD, as well as their clinical characteristics, in order to develop effective approaches to diagnosis and treatment [4].

Considering the multifactorial nature of pathogenesis, the diversity and nonspecificity of clinical manifestations, as well as the significant impact of these conditions on patients' quality of life and functional status, investigating their combined course remains a pressing issue in modern medicine.

Received: Sep. 28, 2025; Accepted: Oct. 23, 2025; Published: Oct. 31, 2025
Published online at http://journal.sapub.org/ajmms

Objective. The aim of the study was to investigate, based on the analysis of current scientific evidence and clinical aspects, the combined course of sarcopenia and metabolic-associated fatty liver disease (MAFLD), with a focus on their mutual influence and potential directions for optimizing diagnosis and treatment.

2. Materials and Methods

To conduct the study, a search for scientific publications addressing the clinical features of the coexistence of sarcopenia and MAFLD was performed. The search was carried out in electronic databases such as *PubMed.gov*, *Google Scholar.com*, and *Elibrary.ru*. Publications were selected based on predefined keywords, including "sarcopenia" and "metabolic-associated fatty liver disease." A total of 29 sources that met the inclusion criteria were analyzed from 620 identified publications. The review considered studies published within the last 10 years, with emphasis on those describing the relationship between these conditions and their impact on clinical outcomes.

3. Results

According to the results of a meta-analysis by C. Deng et al. (2024), which summarized data from 88,000 individuals, the prevalence of sarcopenia was significantly higher among patients with MAFLD compared to the control group. The odds ratio (OR) reached 1.74 (95% confidence interval [CI]: 1.39–2.17), confirming a strong association between these pathologies [5]. Regional analysis revealed ethnic differences: in patients with MAFLD from Asian countries, the risk of sarcopenia was the highest (OR = 1.97; 95% CI: 1.54–2.51), while in American (OR = 1.31; 95% CI: 0.71–2.40) and European (OR = 0.99; 95% CI: 0.21–4.69) populations, no statistically significant association was found. Importantly, sarcopenia in patients with MAFLD was associated with an increased risk of significant liver fibrosis (OR = 1.97; 95% CI: 1.44–2.70), highlighting the importance of assessing muscle status for predicting the course of liver disease [5].

A meta-analysis by A. Malik et al. (2024) also demonstrated that sarcopenia significantly increases the likelihood of developing MAFLD (OR = 1.25; 95% CI: 1.08–1.44; P = 0.003). At the same time, the skeletal muscle mass index (SMMI) showed no significant differences between the groups (OR = 1.02; 95% CI: 0.91–1.15; P = 0.7). The presence of sarcopenia in patients with MAFLD was associated with an increased risk of liver fibrosis (OR = 1.49; 95% CI: 1.03–2.14; P = 0.03) [6].

In the meta-analysis by C. Cai et al. (2020), which included 25 studies, sarcopenia was found to increase the likelihood of developing MAFLD by 25.0% (OR = 1.25; 95% CI: 1.08–1.44; P = 0.003) and raised the risk of liver fibrosis by 49% (OR = 1.49; 95% CI: 1.03–2.14; P = 0.03) [7]. A study by R. Yu et al. (2018) revealed a significant association between sarcopenia and steatohepatitis (OR = 2.35; 95% CI: 1.45–3.81), as well as advanced liver fibrosis (OR = 2.41; 95% CI: 1.94–2.98) [8].

Thus, data from numerous meta-analyses confirm a strong epidemiological association between MAFLD and sarcopenia. Patients with MAFLD are at increased risk of developing sarcopenia, particularly in Asian populations, while sarcopenia, in turn, significantly raises the likelihood of developing MAFLD and its complications, such as advanced fibrosis and steatohepatitis.

The clinical course of sarcopenia in patients with MAFLD is characterized by mutual aggravation. Sarcopenia accelerates the progression of MAFLD and worsens its outcomes. Loss of muscle mass is accompanied by reduced physical activity, which exacerbates metabolic disturbances, insulin resistance (IR), and visceral fat accumulation [9]. Insulin resistance, acting as a common pathogenic link, impairs glucose utilization by muscles, enhances oxidative stress, and sustains systemic inflammation, thereby worsening glycemic control and increasing the risk of cardiovascular diseases. The presence of sarcopenia in patients with type 2 diabetes mellitus is associated with a higher risk of both all-cause and cardiovascular mortality [10].

The cytokine and adipokine profile characteristic of sarcopenia contributes to enhanced hepatic inflammation, thereby aggravating hepatocyte injury and fibrosis progression. At the same time, chronic inflammation in MAFLD initiates catabolic processes in skeletal muscle, promoting the development of sarcopenia and creating a vicious cycle.

Analysis from the ATTICA study demonstrated that a reduction in skeletal muscle mass is associated with an increased risk of MAFLD and a significantly elevated cardiovascular risk in sarcopenia, independent of waist circumference [11]. These findings are supported by a study involving 11,000 patients, in which the coexistence of sarcopenia and MAFLD was associated with higher all-cause mortality, as well as increased cancer- and diabetes-related mortality [12].

A study including 852 patients with diabetes mellitus showed that the combination of sarcopenia and MAFLD was linked to a higher risk of carotid atherosclerosis progression over 6–8 years (OR = 2.2). Furthermore, the level of albuminuria—a marker of renal dysfunction and cardiovascular risk—was found to be significantly higher in patients with both conditions [13].

Fibrosis progression in the context of sarcopenia is actively studied. A recent study involving 2,400 patients revealed that in sarcopenic NAFLD, the prevalence of liver fibrosis was substantially higher compared to isolated NAFLD: the prevalence of advanced fibrosis was 18.3% versus 3.2%, with a similar trend observed for severe fibrosis stages [14].

The coexistence of sarcopenia and MAFLD also worsens surgical outcomes and long-term survival in patients with hepatocellular carcinoma (HCC). Sarcopenia has been identified as an independent risk factor for both recurrence-free and overall survival in patients with sarcopenic MAFLD

and HCC [15]. In addition, sarcopenia in MAFLD is associated with higher rates of depression, increased fatigue, and reduced quality of life [16].

Taken together, these findings underscore the need for a comprehensive approach to assessing patients with concomitant MAFLD and sarcopenia, one that considers not only hepatic and metabolic parameters but also muscular, functional, and psycho-emotional aspects.

According to the findings of Z. Feng et al. (2024), patients with MAFLD who do not have sarcopenia demonstrate more favorable clinical characteristics compared to those with sarcopenia. Fibrosis burden and the risk of atherosclerotic cardiovascular disease (ASCVD) significantly increased in a stepwise manner from the non-MAFLD group, to non-sarcopenic patients with MAFLD, and finally to sarcopenic patients with MAFLD (p for trend <0.001). Compared with subjects without MAFLD, non-sarcopenic patients with MAFLD had a 1.8-fold (based on FIB-4) and 2.2-fold (based on NFS) increased risk of significant liver fibrosis, whereas sarcopenic patients with MAFLD had a 3.7-fold and 5.6-fold higher risk, respectively. Similarly, the risk of ASCVD was 2.1 times higher in non-sarcopenic MAFLD patients and 7.9 times higher in sarcopenic MAFLD patients compared with the non-MAFLD group.

This trend persisted even after comprehensive statistical adjustment for confounding factors. The use of a representative population-based dataset (n > 8,000) ensured statistical robustness and enabled the analysis of fibrosis burden and ASCVD risk in patients with MAFLD according to sarcopenia status. The large cohort size also allowed for validation of the main findings through sensitivity analysis. The prevalence of MAFLD (37.3%) was consistent with data from other studies [17,18], supporting the representativeness of the sample.

This study was the first to demonstrate that sarcopenia status assessment may be valuable for identifying high-risk subgroups among patients with MAFLD who face unfavorable long-term outcomes due to greater fibrosis burden and ASCVD risk. Current evidence indicates that disease severity and prognosis may vary even within the same MAFLD category [19], which supports the rationale for risk stratification based on sarcopenia status. Moreover, the risk of developing sarcopenia increased in parallel with the number of metabolic criteria for MAFLD, highlighting the association between metabolic burden and the risk of muscle dysfunction.

The association between sarcopenia and fatty liver disease has been actively studied in recent years in the context of shared pathophysiological mechanisms, including insulin resistance, chronic inflammation, altered secretion of myokines, vitamin D deficiency, and physical inactivity [20,21]. Epidemiological studies demonstrate a positive relationship between sarcopenia and the severity of NAFLD [7,22,23,24]. A recent meta-analysis of 19 studies showed that, among patients with sarcopenia, the risks of nonalcoholic steatohepatitis (OR = 2.42) and significant liver fibrosis (OR = 1.56) were higher compared with patients without sarcopenia in NAFLD cohorts [24]. These findings are consistent with current results. The risk of significant fibrosis and ASCVD increased significantly from non-sarcopenic to sarcopenic patients with NAFLD ($p \leq 0.001$). Thus, sarcopenia may serve as a marker for identifying subgroups with different degrees of fibrosis among patients with MAFLD, confirming the clinical value of assessing muscle mass [7,22,23].

In addition to fibrosis, ASCVD risk was used in this study to validate stratification by sarcopenia, as ASCVD is a leading cause of morbidity and mortality in MAFLD [25,26,27]. Regarding MAFLD, two large national studies from the United Kingdom and South Korea also reported an increased ASCVD risk in this patient category [13,28]. Moreover, in patients with MAFLD without metabolic dysfunction (not meeting MAFLD criteria), the risk of ASCVD was lower than in those with MAFLD, which highlights the advantage of MAFLD criteria in identifying patients with metabolically complicated fatty liver disease and high cardiovascular risk [28].

Several limitations should be noted. First, for the diagnosis of hepatic steatosis and fibrosis, non-invasive surrogate markers were used. Furthermore, due to the absence of serum albumin data in the Korean National Health and Nutrition Examination Survey (KNHANES), the highest quartile rather than the standard threshold of 0.676 was applied for determining significant fibrosis using the MAFLD fibrosis score (NFS) [14], which requires further validation with imaging or histology. However, the non-invasive markers applied for steatosis [33] and fibrosis [29] have acceptable diagnostic accuracy and are widely validated, justifying their use in large-scale cohort studies. Their independent association with long-term outcomes in MAFLD [30] further supports the validity of this approach.

The cross-sectional design of the study does not allow for establishing causal relationships between sarcopenia and the risks of fibrosis/ASCVD. Prospective studies are required to determine whether correction of sarcopenia can influence long-term outcomes in patients with MAFLD. The study included only individuals of East Asian origin, which limits the generalizability of its findings to other ethnic groups. To assess ASCVD risk, the pooled cohort equation was applied, which does not evaluate the risk of actual cardiovascular events. However, this equation has been validated in multiethnic U.S. cohorts [34,35], and the predicted risk was clearly associated with ASCVD events in the Korean population [36].

Finally, a substantial number of subjects (n = 19,710) were excluded due to incomplete clinical data, which may have introduced selection bias. Although differences were observed between included and excluded patients in terms of age, obesity, comorbidity, and laboratory indicators (all $P \leq 0.05$), the key variables—skeletal muscle mass and sarcopenia index (SI)—were not statistically significant.

In conclusion, the study demonstrated that the degree of liver fibrosis and ASCVD risk vary significantly depending on sarcopenia status in patients with MAFLD, supporting the

need for muscle mass assessment as part of long-term risk stratification in this population.

4. Conclusions

The conducted systematic analysis of current scientific data convincingly demonstrates the existence of a close bidirectional pathogenetic relationship between sarcopenia and metabolic-associated fatty liver disease (MAFLD). The shared key mechanisms of development—primarily insulin resistance, chronic low-grade inflammation, and oxidative stress—create a vicious cycle in which each condition potentiates the progression of the other.

The clinical significance of the combined course of these diseases is reflected in a substantially less favorable prognosis. As confirmed by meta-analyses, the presence of sarcopenia in patients with MAFLD is associated with a significantly increased risk of liver fibrosis progression, development of steatohepatitis, as well as higher overall, cardiovascular, and cancer-related mortality. The coexistence of sarcopenia and MAFLD leads to a marked deterioration in patients' functional status, reduced quality of life, and increased risk of depression.

The findings of this review emphasize that the assessment of muscle status is an essential component of comprehensive management in patients with MAFLD. Risk stratification based on the presence and severity of sarcopenia appears to be a highly informative and clinically relevant tool for identifying patient subgroups at the highest risk of adverse hepatic and cardiovascular outcomes.

A promising direction for future research is the development of integrated therapeutic strategies simultaneously aimed at correcting metabolic disorders, slowing the progression of liver disease, and increasing muscle mass and function. The implementation of standardized protocols for sarcopenia screening and diagnosis in hepatology practice may help optimize the management of MAFLD patients and improve their long-term prognosis.

Financial and other conflicts of interest: The authors declare no financial or other conflicts of interest during the conduct and publication of this study.

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