

Biomarkers Related to Sarcopenia and Physiological Reserve in Total Joint Arthroplasty and Other Clinical Populations

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Abstract

Sarcopenia is increasingly recognized as a multidimensional syndrome reflecting impaired physiological reserve rather than isolated skeletal muscle loss. Although numerous circulating biomarkers have been associated with sarcopenia and adverse orthopaedic outcomes, their biological significance varies according to the underlying clinical context. This narrative review integrates current evidence on circulating biomarkers of sarcopenia and physiological reserve across elective total hip and knee arthroplasty, fragility hip fracture, community-dwelling older adults, and medically complex populations. The available evidence demonstrates that sarcopenic phenotypes differ substantially between these populations, with predominantly disuse-related muscle deterioration in elective arthroplasty, frailty-associated sarcopenia after hip fracture, and metabolically driven muscle loss in chronic systemic diseases. Nutritional (albumin, geriatric nutritional risk index), inflammatory (C-reactive protein (CRP), neutrophil-to-lymphocyte ratio, CRP-to-albumin ratio), metabolic (aspartate aminotransferase-to-alanine aminotransferase ratio, glucose-to-albumin ratio), endocrine (vitamin D, insulin-like growth factor-1), and emerging molecular biomarkers reflect complementary biological domains of physiological reserve rather than directly measuring skeletal muscle quantity or quality. Current evidence supports their greatest clinical value in perioperative risk stratification and identification of patients at increased risk of adverse postoperative outcomes, whereas the diagnosis of sarcopenia should continue to rely on established assessments of muscle strength, muscle quantity and/or quality, and physical performance. Integrating circulating biomarkers with established sarcopenia assessment may improve patient phenotyping, individualized perioperative optimization, and risk prediction, although methodological standardization and prospective multicenter validation are required before widespread clinical implementation.

Categories: Geriatrics, Preventive Medicine, Orthopedics

Keywords: arthroplasty, biomarkers, hip fracture, osteoarthritis, physiological reserve, sarcopenia

Introduction And Background

The global ageing of the population has been accompanied by a progressive increase in degenerative musculoskeletal disorders, fragility fractures, and the number of patients requiring elective joint replacement surgery [1-4]. In parallel, sarcopenia has emerged as an important determinant of functional decline, disability, frailty, postoperative recovery, and mortality among older adults [1-7]. Within orthopaedic surgery, its relevance extends to perioperative complications, implant-related outcomes, rehabilitation potential, healthcare utilization, and long-term survival, supporting increasing interest in sarcopenia assessment and perioperative optimization [3,6,8-10].

Originally regarded as an age-related reduction in skeletal muscle mass, sarcopenia is now recognized as a multidimensional syndrome characterized by deterioration of muscle quantity, strength, and physical performance [5,11-13]. Contemporary consensus frameworks proposed by the European Working Group on Sarcopenia in Older People (EWGSOP2) and the Asian Working Group for Sarcopenia (AWGS) emphasize reduced muscle strength as its principal clinical feature, with objective assessment of muscle quantity confirming the diagnosis and impaired physical performance indicating severe disease [5,11,14-16]. These manifestations may coexist with broader impairment of physiological reserve, encompassing nutritional status, systemic inflammation, metabolic homeostasis, endocrine regulation, and other biological processes that influence an individual's capacity to withstand physiological stress [5,12,13,17,18].

The prevalence and biological expression of sarcopenia vary substantially across clinical populations [1-5]. Elective total hip (THA) and knee arthroplasty (TKA) candidates commonly develop gradual, predominantly disuse-related muscle deterioration in association with osteoarthritis (OA), pain, reduced mobility, and biomechanical alterations, whereas patients with fragility hip fractures more frequently exhibit advanced frailty, osteoporosis, malnutrition, chronic inflammation, and pre-existing sarcopenia [1-4,19-21]. This heterogeneity is reflected in reported prevalence estimates: a meta-analysis of 13 studies including 399,097 patients reported pooled prevalences of approximately 20.1% in TKA and 5% in THA, although higher rates

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have been described in selected imaging-based and rehabilitation cohorts [2-4,8,10,22]. Beyond orthopaedics, chronic kidney disease, hemodialysis, diabetes mellitus, and community-dwelling ageing are associated with distinct mechanisms of muscle deterioration and physiological reserve impairment [5,13-15,23,24].

Against this heterogeneous clinical background, increasing attention has focused on circulating biomarkers as readily accessible adjuncts to established sarcopenia assessment [5,12,13,18]. These include inflammatory mediators, nutritional indices, endocrine factors, liver enzyme-derived ratios, metabolomic signatures, and composite laboratory indices reflecting nutritional, inflammatory, metabolic, and endocrine domains of physiological reserve [5,12-14,18,23,25,26]. Their interpretation, however, requires careful distinction between association with objectively diagnosed sarcopenia and prognostic association with adverse clinical outcomes [12,13,18,23,27-29]. Studies specifically evaluating sarcopenia generally apply accepted criteria incorporating muscle quantity, strength, and physical performance, whereas several biomarkers investigated in arthroplasty cohorts have primarily predicted postoperative complications without direct muscle assessment [5,11,28,30-32]. Accordingly, prognostic biomarkers should not automatically be considered diagnostic markers of sarcopenia, and their clinical significance should be interpreted within the population and outcome in which they were studied [5,11,13,23,27,28,30,31].

Previous reviews have primarily examined sarcopenia within individual clinical populations or focused on specific biomarker domains, including arthroplasty, hip fracture, nutrition, inflammation, and ageing [2-5,12,13,18]. Comparatively less attention has been directed toward integrating circulating biomarkers across different clinical phenotypes while distinguishing their associations with objectively defined sarcopenia from their prognostic value for adverse outcomes. Therefore, the aim of this narrative review is to integrate current evidence regarding circulating biomarkers related to sarcopenia and physiological reserve across diverse patient populations, compare the biological characteristics of different sarcopenic phenotypes, critically evaluate their associations with objectively defined sarcopenia and their prognostic significance within different clinical contexts, and provide an integrated framework for their interpretation in orthopaedic and medically complex populations.

Materials and methods

A comprehensive, iterative literature search was conducted in PubMed/MEDLINE through October 2026. The search focused primarily on English-language publications from January 2016 to October 2026, while earlier foundational studies, consensus statements, and clinical practice guidelines were also considered when relevant to the scope of the review. Articles with available full text were assessed for eligibility.

The search strategy was structured around the principal clinical and biological domains addressed in this narrative review. Search terms included "sarcopenia", "osteosarcopenia", "sarcopenic obesity", "muscle mass", "muscle strength", "physical performance", "frailty", "physiological reserve", "total hip arthroplasty", "total knee arthroplasty", "total joint arthroplasty", "osteoarthritis", "hip fracture", "femoral neck fracture", "hemiarthroplasty", "albumin", "hypoalbuminemia", "geriatric nutritional risk index", "GNRI", "modified GNRI", "mGNRI", "prealbumin", "transferrin", "C-reactive protein", "CRP", "neutrophil-to-lymphocyte ratio", "NLR", "platelet-to-lymphocyte ratio", "PLR", "systemic immune-inflammation index", "SII", "systemic inflammation response index", "SIRI", "lymphocyte-to-monocyte ratio", "LMR", "CRP-to-albumin ratio", "CAR", "glucose-to-albumin ratio", "GAR", "AST/ALT ratio", "De Ritis ratio", "alanine aminotransferase", "fasting insulin", "vitamin D", "25-hydroxyvitamin D", "insulin-like growth factor-1", "IGF-1", "testosterone", "testosterone deficiency", "testosterone replacement therapy", "TRT", "myostatin", "follistatin", "GDF-8", "metabolomics", "proteomics", "transcriptomics", and "multi-omics".

Boolean operators were used to combine search concepts, with OR connecting synonymous or related terms and AND linking distinct clinical and biological concepts. Rather than relying on a single restrictive search string, separate topic-specific searches were conducted to capture the breadth of the literature. Representative search combinations included ("sarcopenia" OR "muscle wasting") AND ("biomarkers" OR "muscle strength" OR "physiological reserve"); ("sarcopenia" OR "muscle weakness") AND ("arthroplasty" OR "joint replacement" OR "osteoarthritis"); ("albumin" OR "GNRI" OR "mGNRI") AND ("sarcopenia" OR "arthroplasty" OR "hip fracture"); ("NLR" OR "PLR" OR "CRP-to-albumin ratio") AND ("sarcopenia" OR "hip fracture" OR "arthroplasty"); ("AST/ALT ratio" OR "De Ritis ratio" OR "glucose-to-albumin ratio") AND ("sarcopenia" OR "hip fracture" OR "arthroplasty"); ("testosterone" OR "testosterone replacement therapy") AND ("sarcopenia" OR "arthroplasty" OR "osteoarthritis"); and ("myostatin" OR "follistatin" OR "GDF-8") AND ("sarcopenia" OR "hip fracture" OR "arthroplasty").

Additional targeted searches using individual biomarker names and specific clinical outcomes were performed to identify relevant publications not captured by the broader search combinations. Supplementary literature identification was undertaken using PubMed's "Similar articles" and "Cited by" functions, with additional publications assessed for relevance to the review objectives.

Studies were screened sequentially by title and abstract, followed by full-text assessment of potentially relevant publications. Selection was guided by clinical applicability and biological relevance to sarcopenia, physiological reserve, biomarker assessment, and perioperative risk stratification in total joint arthroplasty.

Eligible publications included systematic reviews and meta-analyses, observational cohort and cross-sectional studies, randomized controlled trials, consensus statements, clinical practice guidelines, and individual biomarker studies relevant to the scope of the review.

Given the narrative design, no formal risk-of-bias assessment or grading of certainty of evidence was undertaken. The findings were critically interpreted in light of differences in study design, patient populations, diagnostic criteria, biomarker definitions and measurement methods, clinical outcomes, and other sources of methodological heterogeneity. Evidence from populations outside elective total joint arthroplasty was considered where relevant to the biological rationale or clinical interpretation of the biomarkers discussed. This approach aimed to provide a comprehensive, clinically oriented synthesis of established and emerging biomarkers and their potential relevance to patient assessment and outcomes following total joint arthroplasty.

Review

Biological and clinical differences between arthroplasty patients and other patient populations

Patients undergoing elective joint replacement represent a biologically distinct subgroup within the broader spectrum of sarcopenia [1-4]. Although reductions in muscle mass, strength, and physical performance occur across many orthopaedic and medical conditions, the mechanisms underlying these changes differ substantially among elective arthroplasty candidates, patients with fragility hip fractures, and individuals with chronic systemic diseases [1-3,5,19,23]. These differences are clinically important because the diagnostic and prognostic significance of biomarkers depends strongly on the population in which they are measured [1-3,5,12,13,18].

Elective THA and TKA patients generally experience gradual muscle deterioration during the progression of OA [1-3,22]. Chronic pain, stiffness, altered gait, reduced joint loading, and declining physical activity promote predominantly disuse-related muscle atrophy and impaired neuromuscular performance [1-3,7]. The relationship between OA and sarcopenia may also be bidirectional, because muscle weakness can further compromise joint stability and biomechanics, while OA-related inactivity accelerates muscle loss [1-3]. In the FORMoSA cohort, patients with hip or knee OA had approximately 2.6-fold greater odds of sarcopenia, and lower-extremity muscle measures appeared more closely related to disease severity than whole-body indices [1,2].

Patients with fragility hip fractures present a different biological profile [19-21,33]. They are generally older and more frequently affected by frailty, osteoporosis, malnutrition, multimorbidity, and pre-existing reductions in physiological reserve before injury [19-21,30]. The fracture, surgical treatment, immobilization, and acute inflammatory response then superimpose additional catabolic stress, accelerating muscle protein breakdown and functional decline [5,19-21]. Consequently, inflammatory and nutritional biomarkers - including C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), CRP-to-albumin ratio (CAR), glucose-to-albumin ratio (GAR), albumin, transferrin, and Geriatric Nutritional Risk Index (GNRI) - are frequently associated with mortality, pneumonia, delirium, pressure ulcers, prolonged hospitalization, and other postoperative complications in this population, but they should not be interpreted as direct measures of sarcopenia in the absence of objective muscle assessment [19-21,29,30,33-36].

In elective arthroplasty, the same biomarkers more commonly identify subclinical nutritional or inflammatory vulnerability before surgery rather than advanced systemic frailty [28,30-32,37]. Reduced albumin, transferrin, GNRI, and related indices have been associated with postoperative complications, infection, readmission, prolonged hospitalization, and poorer functional recovery, suggesting that their principal value lies in perioperative risk stratification and assessment of physiological reserve rather than in the diagnosis of sarcopenia itself [28,30,32,37-39].

Patients with chronic kidney disease, maintenance hemodialysis (MHD), diabetes mellitus, cardiovascular disease, and other systemic disorders constitute a third phenotype in which muscle deterioration is driven by persistent inflammation, oxidative stress, endocrine dysfunction, anabolic resistance, metabolic abnormalities, and protein-energy wasting [5,15,18,23,25]. Biomarker performance in these patients may therefore be modified by disease-specific factors [13,15,23,25]. For example, Nie et al. found that NLR independently predicted sarcopenia only in overweight hemodialysis patients, whereas no significant association was observed in non-overweight individuals, illustrating how metabolic and inflammatory context can alter the meaning of the same biomarker [23].

Overall, sarcopenia is not biologically uniform across clinical populations [3,5,12,18]. Elective arthroplasty is characterized predominantly by chronic disuse-related muscle deterioration, hip fracture by frailty and superimposed acute catabolism, and chronic systemic disease by persistent metabolic and inflammatory dysfunction [1,2,5,19,21,23]. Biomarkers should therefore be interpreted according to the clinical phenotype and intended application rather than extrapolated directly between populations [3,5,12,13,18,23].

Laboratory biomarkers

Unlike imaging-derived measurements, circulating laboratory biomarkers do not directly quantify skeletal muscle quantity or quality [5,11-13]. Instead, they characterize complementary biological domains that influence muscle homeostasis and an individual's capacity to respond to physiological stress, including nutritional status, systemic inflammation, metabolic regulation, endocrine function, and molecular signaling [5,11,13,18,23,26,40]. Consequently, laboratory biomarkers should be interpreted as indicators of physiological reserve that complement rather than replace established assessments of muscle mass, strength, and physical performance [5,11-14,23,26,40]. For clarity, the available biomarkers are discussed according to their principal biological domain, although some overlap exists between these physiological systems.

Nutritional Biomarkers

Nutritional status is a major determinant of skeletal muscle maintenance, wound healing, immune competence, and postoperative recovery [5,19,30,41]. Biomarkers reflecting nutritional reserve have consistently demonstrated prognostic value across orthopaedic populations, particularly in elderly patients undergoing arthroplasty or hip-fracture surgery, where protein-energy malnutrition frequently coexists with sarcopenia [5,19,30,32,37,41].

Albumin: Serum albumin remains the most extensively investigated nutritional biomarker in orthopaedic surgery because of its close relationship with protein status, systemic inflammation, and physiological reserve [19,30,37,41]. Hypoalbuminemia has consistently been associated with increased postoperative complications, prolonged hospitalization, impaired functional recovery, infection, and mortality [19,30,37-39]. Mbagwu et al. reported that hypoalbuminemia increased the risk of postoperative complications by approximately 93%, while Morey et al. demonstrated a nearly 2.5-fold greater likelihood of postoperative transfusion among arthroplasty patients with hypoalbuminemia [30,31]. Following hip fracture, low albumin has similarly been associated with increased mortality and poorer postoperative recovery [19,20,30,31,42]. Although albumin is influenced by inflammation, hepatic function, and hydration status, its widespread availability continues to make it one of the most practical markers for perioperative nutritional assessment [5,19,30,41].

Geriatric Nutritional Risk Index (GNRI): The GNRI combines serum albumin with the ratio of actual to ideal body weight, providing a more comprehensive estimate of nutritional reserve than albumin alone [15,16,41]. Originally developed to predict nutrition-related complications in hospitalized older adults, GNRI has subsequently demonstrated prognostic value across numerous orthopaedic populations [28,30,32,41]. Bouillanne et al. proposed four nutritional risk categories, with GNRI <98 indicating at least moderate nutritional risk [41].

Recent studies have expanded the role of GNRI beyond nutritional assessment [15,16,43]. Duan et al. demonstrated significant associations between lower GNRI values, reduced skeletal muscle mass, lower bone mineral density, and poorer physical performance, supporting the concept that nutritional reserve influences both muscle and skeletal health [15]. In arthroplasty, reduced GNRI has consistently predicted postoperative complications, prolonged hospitalization, and delayed functional recovery, supporting its role in perioperative risk stratification [15,28,30,32].

Modified GNRI (mGNRI): Several investigators have proposed mGNRI models to improve discrimination in specific populations [16,28]. Wei et al. identified an inflection point at approximately 55.5; below this threshold, each one-unit increase in mGNRI was associated with an approximately 16.8% reduction in the odds of sarcopenia, while values below approximately 55 were associated with more than an eightfold increase in the likelihood of sarcopenia and screening sensitivities exceeding 80% [16]. In elective arthroplasty, Hansen et al. identified an mGNRI below approximately 92.8 as a predictor of postoperative complications, including prosthetic joint infection, wound complications, hospital readmission, and reoperation after joint replacement surgery [28]. Although these findings require external validation, they suggest that modified nutritional indices may provide more population-specific risk stratification than the original GNRI [15,16,28,43].

Other nutritional biomarkers: Additional nutritional biomarkers - including prealbumin, transferrin, total lymphocyte count, Prognostic Nutritional Index (PNI), and Mini Nutritional Assessment (MNA) - have also demonstrated associations with sarcopenia or postoperative outcomes [5,19,30-32,41]. Prealbumin reflects more acute nutritional changes because of its shorter half-life, whereas transferrin and lymphocyte count are influenced by inflammation and immune status [19,30,31,41]. Composite indices such as PNI and MNA generally provide broader assessments of nutritional reserve, although their diagnostic performance varies across populations and they remain less extensively validated than albumin or GNRI in orthopaedic surgery [5,19,28,30,32,41].

Inflammatory Biomarkers

Persistent low-grade inflammation contributes to skeletal muscle catabolism through activation of proteolytic pathways, impaired protein synthesis, mitochondrial dysfunction, and anabolic resistance [5,13,17,44,45]. Consequently, inflammatory biomarkers have been widely investigated as indicators of physiological reserve and perioperative risk across both sarcopenic and orthopaedic populations [14,20,23,24,36,45]. Their clinical significance, however, depends on the underlying clinical context, as they may reflect chronic biological mechanisms contributing to muscle deterioration or the acute physiological stress associated with trauma and surgery [5,20,21,23,42]. Collectively, the available evidence suggests that inflammatory biomarkers are most valuable for identifying individuals with heightened systemic inflammatory activation and reduced capacity to tolerate physiological stress, thereby complementing structural imaging and functional assessment rather than replacing established diagnostic criteria for sarcopenia [5,11-14,24]. Future prospective studies should determine whether integrating inflammatory biomarkers with imaging-derived measures of muscle quantity and quality improves risk stratification and clinical decision-making [5,12,13,18,19,23,46].

Neutrophil-to-lymphocyte ratio (NLR): Among white blood cell-derived inflammatory biomarkers, the NLR has been investigated most extensively across both sarcopenia and orthopaedic populations [20,23,24,36,42]. NLR integrates two complementary components of the immune response, reflecting both activation of innate immunity and relative suppression of adaptive immunity [5,20,23,24]. Elevated values therefore indicate heightened systemic inflammatory burden and impaired physiological reserve [20,23,36,42].

The strongest direct evidence linking NLR with sarcopenia originates from MHD populations. Nie et al. evaluated 272 MHD patients, of whom 89 (32.7%) met the 2019 Asian Working Group for Sarcopenia criteria. Among overweight patients, each one-unit increase in NLR was independently associated with a 60% increase in the odds of sarcopenia (adjusted OR: 1.60; 95% CI: 1.15-2.24; $p = 0.006$), whereas no significant association was observed in non-overweight patients (OR: 0.88; 95% CI: 0.70-1.10; $p = 0.254$), with a significant interaction according to overweight status ($p = 0.011$) [23].

Within orthopaedic populations, NLR has demonstrated greater prognostic than diagnostic value. Yao et al. evaluated 1,199 surgically treated hip-fracture patients without direct sarcopenia assessment; postoperative pneumonia occurred in 111 patients (9.3%), and an admission NLR ≥ 5.84 was independently associated with approximately twice the odds of postoperative pneumonia (adjusted OR: 2.24; 95% CI: 1.43-3.51), although discriminatory performance was modest (AUC: 0.648; 95% CI: 0.594-0.701) [36]. Higher preoperative and postoperative NLR values have also been associated with increased long-term mortality following hip-fracture surgery [20,42]. Nevertheless, considerable heterogeneity exists regarding optimal thresholds because reported cut-off values vary according to patient population, outcome definition, and timing of blood sampling [20,23,36,42]. Accordingly, current evidence supports interpreting NLR primarily as a marker of inflammatory physiological reserve rather than as a specific biomarker of skeletal muscle loss [5,11,20,23,42].

Platelet-to-lymphocyte ratio (PLR): PLR represents another readily available inflammatory biomarker reflecting interactions between thrombopoietic activity, inflammation, and immune regulation [24,27,36]. Direct evidence supporting PLR as a sarcopenia-associated biomarker derives principally from community-based populations [24,27]. Liaw et al. evaluated 3,671 older adults and demonstrated that participants within the highest PLR quartile (≥ 155) exhibited more than twice the adjusted odds of sarcopenia compared with individuals in the lowest quartile (< 95) (OR: 2.36; 95% CI: 1.21-3.31). Furthermore, increasing PLR correlated inversely with skeletal muscle index in both men and women, indicating progressively lower muscle mass with increasing inflammatory burden [27].

Despite these findings, PLR has demonstrated less consistent prognostic performance than NLR in orthopaedic surgery. Most studies suggest that PLR possesses lower discriminatory ability for postoperative complications, pneumonia, and mortality, indicating that neutrophil-driven inflammatory responses may better reflect perioperative physiological reserve than platelet-mediated inflammatory activity [20,36,42].

Systemic immune-inflammatory indices: More recently, composite inflammatory indices - including the systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), lymphocyte-to-monocyte ratio (LMR), and related leukocyte-derived markers - have been proposed as more comprehensive indicators of inflammatory status because they incorporate multiple leukocyte populations simultaneously [13,24,36,45,47]. Population-based studies consistently demonstrate associations between elevated SII and reduced skeletal muscle mass, although reported diagnostic performance remains modest [24,45,47,48]. Similarly, observational studies evaluating SIRI and LMR suggest that these indices reflect chronic inflammatory activation accompanying muscle deterioration rather than directly measuring sarcopenia [13,14,24,45,47]. Importantly, composite inflammatory indices frequently outperform individual leukocyte counts because they better characterize the complex interactions between innate immunity, adaptive immunity, and systemic inflammatory activation [14,24,45,47]. Nevertheless, none has demonstrated sufficient diagnostic accuracy to replace established sarcopenia assessment based upon muscle quantity, muscle strength, and physical performance.

C-reactive protein (CRP): CRP is a well-established acute-phase reactant that reflects IL-6-mediated

systemic inflammation [5,21,49]. Elevated CRP concentrations have consistently been associated with frailty, impaired physical performance, postoperative infection, prolonged hospitalization, and mortality in older orthopaedic patients [19,21,33,42]. Although CRP provides valuable prognostic information, its marked responsiveness to acute inflammatory stimuli limits its specificity for sarcopenia [5,12,19,21,50].

CRP-to-albumin ratio (CAR): CAR integrates inflammatory and nutritional status within a single biomarker and has emerged as a robust predictor of postoperative outcomes [33,42,51,52]. Kim et al. evaluated 629 older patients undergoing hip-fracture surgery and reported postoperative delirium in 35.8% of patients with a preoperative CAR ≥ 1.5 compared with 18.0% of those with CAR < 1.5 ($p < 0.001$); after propensity-score matching, the corresponding incidences were 32.7% and 20.7% ($p = 0.019$). A CAR ≥ 1.5 remained independently associated with postoperative delirium (adjusted OR: 2.11; 95% CI: 1.40-3.18; $p < 0.001$) and overall mortality (adjusted HR: 1.44; 95% CI: 1.07-1.93; $p = 0.015$) [33]. Elevated CAR has also been associated with major complications, prolonged hospitalization, mortality, and poorer functional recovery across other surgical populations [42,51-53]. Compared with CRP or albumin alone, CAR may provide a more comprehensive assessment of perioperative physiological reserve; however, direct evidence supporting its use for diagnosing objectively confirmed sarcopenia remains limited [12,13,33,42,51,52].

Metabolic and Liver-Derived Biomarkers

Skeletal muscle plays a central role in whole-body glucose homeostasis, amino acid metabolism, and energy regulation [5,13,17,54]. Accordingly, metabolic and liver-derived biomarkers have emerged as indicators of the metabolic component of physiological reserve, reflecting the efficiency with which nutrients are utilized for energy production, protein synthesis, tissue repair, and recovery following physiological stress [5,25,26,40]. Compared with nutritional and inflammatory biomarkers, which primarily characterize substrate availability and systemic immune activation, metabolic biomarkers provide complementary information regarding anabolic capacity and metabolic resilience [13,18,25,40]. Although the available evidence remains more limited than for nutritional or inflammatory biomarkers, several indices - including the aspartate aminotransferase-to-alanine aminotransferase (AST/ALT) ratio, ALT activity and isoenzymes, GAR, and fasting insulin-derived markers - have demonstrated promising associations with sarcopenia or adverse postoperative outcomes [26,35,40,55,56]. Their greatest clinical value currently lies in identifying patients with impaired metabolic reserve who may be less able to tolerate surgical stress, preserve muscle function, and recover following major orthopaedic procedures, although further prospective validation is required before widespread clinical implementation [5,13,34,35,57,58].

Aspartate aminotransferase-to-alanine aminotransferase ratio (AST/ALT): Among liver-derived biomarkers, the AST/ALT (De Ritis) ratio has emerged as one of the most consistently investigated biochemical markers associated with sarcopenia [26,40,55,59]. Although traditionally used to evaluate hepatic disease, the biological rationale linking AST/ALT with skeletal muscle is increasingly recognized [26,40,55,56]. AST is present in skeletal muscle, myocardium, liver, and other metabolically active tissues, whereas ALT is more closely related to hepatocellular function and, to a lesser extent, skeletal muscle metabolism [26,56]. Progressive skeletal muscle loss may therefore alter the relative balance between these enzymes, resulting in higher AST/ALT ratios despite the absence of clinically significant liver disease [26,40,55,59].

Across community-based cohorts, elevated AST/ALT ratios have been associated with reduced muscle mass and increased sarcopenia risk [26,40,55,59]. Wu et al. evaluated 2,751 community-dwelling adults using AWGS criteria and reported a sarcopenia prevalence of 4.4%; an AST/ALT ratio > 1.20 was independently associated with sarcopenia (adjusted OR: 2.33; 95% CI: 1.48-3.68; $p < 0.001$) [26]. Hong et al. similarly reported that individuals within the highest AST/ALT quartile (≥ 1.33) exhibited significantly greater odds of low skeletal muscle mass than those in the lowest quartile [55].

Orthopaedic studies provide complementary evidence. Among elderly patients sustaining femoral neck fractures, Günaydin et al. identified an AST/ALT ratio exceeding 2.1 as an independent predictor of one-year mortality, while Kong et al. demonstrated that AST/ALT significantly improved multivariable prediction models for postoperative delirium following total hip and knee arthroplasty [57,58]. These observations suggest that AST/ALT reflects broader metabolic vulnerability extending beyond skeletal muscle alone.

Importantly, reported AST/ALT thresholds vary substantially across studies because different populations, diagnostic criteria, and clinical outcomes have been evaluated [26,40,55,57,59]. Consequently, AST/ALT should currently be regarded as a promising adjunctive biomarker rather than a universally applicable diagnostic test for sarcopenia.

ALT activity and ALT isoenzymes: Recent investigations indicate that absolute ALT activity may provide additional information regarding skeletal muscle health independently of the AST/ALT ratio [40,56]. Unlike conventional hepatology, where elevated ALT activity generally reflects hepatocellular injury, sarcopenia studies have demonstrated that lower ALT activity may accompany reduced muscle mass, diminished anabolic capacity, and impaired physical performance [40,56]. This paradox likely reflects reduced overall muscle and hepatic metabolic activity rather than hepatocellular damage.

Similarly, emerging studies evaluating ALT isoenzymes have reported that higher ALT1-to-ALT2 ratios are independently associated with sarcopenia and impaired physical function, suggesting that ALT isoforms may more accurately reflect the metabolic adaptations accompanying muscle deterioration than total ALT activity alone [40,56].

Although these findings remain preliminary, they illustrate an important conceptual advance: liver-derived biomarkers may provide indirect information regarding systemic metabolic reserve rather than hepatic disease exclusively [13,40,56].

Glucose-to-albumin ratio (GAR): Among metabolic biomarkers, GAR has attracted considerable attention because it simultaneously reflects metabolic stress and nutritional reserve [29,34,35,60]. Hyperglycemia promotes oxidative stress, endothelial dysfunction, impaired immune function, and anabolic resistance, whereas hypoalbuminemia reflects diminished nutritional reserve and chronic inflammatory burden [5,29,34,35]. GAR therefore integrates two biologically complementary processes that influence recovery from physiological stress [29,34,35,60].

Across orthopaedic populations, elevated GAR has consistently predicted adverse postoperative outcomes [29,34,35,60]. Wang et al. evaluated 1,231 older hip-fracture patients and found that GAR predicted postoperative urinary tract infection with an AUC of 0.756 ($p < 0.001$); a GAR ≥ 0.18 was independently associated with more than threefold higher odds of infection (OR: 3.20; 95% CI: 2.23-4.58). A graded association was observed across GAR quartiles, with patients in the highest quartile (>0.21) demonstrating an OR of 7.55 (95% CI: 3.84-14.83) compared with those in the lowest quartile (<0.14) [35]. Tang et al. reported a similar GAR threshold (0.175) for postoperative pneumonia, while Liu et al. demonstrated a nonlinear association between GAR and postoperative pressure-ulcer development, identifying an inflection point corresponding to a GAR of approximately 2.2 after variable rescaling [29,34]. Despite these encouraging findings, none of the reviewed GAR studies directly diagnosed sarcopenia. Current evidence therefore supports GAR primarily as a biomarker of metabolic physiological reserve and perioperative vulnerability rather than a diagnostic biomarker of skeletal muscle loss.

Fasting insulin and anabolic signaling: Insulin is a key regulator of skeletal muscle protein synthesis through activation of the phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway [5,13,17,44]. Consistent with this biological role, He et al. demonstrated that the composite fasting insulin $\times$ prealbumin (INS $\times$ PA) index provided greater diagnostic discrimination for sarcopenia than several individual biochemical markers, highlighting the combined contribution of endocrine signaling and nutritional status to skeletal muscle preservation [40]. These findings suggest that fasting insulin-derived indices may serve as useful markers of anabolic reserve, although further validation is required before routine clinical application.

Endocrine and Micronutrient Biomarkers

Endocrine signaling is fundamental to skeletal muscle maintenance through regulation of protein synthesis, mitochondrial function, calcium homeostasis, neuromuscular transmission, satellite-cell activation, and bone-muscle crosstalk [5,12,17,44]. Consequently, endocrine disturbances may impair physiological reserve before measurable reductions in muscle quantity become apparent [5,12,13,17]. Unlike nutritional and inflammatory biomarkers, which primarily reflect substrate availability and systemic inflammation, endocrine biomarkers regulate the anabolic processes responsible for maintaining musculoskeletal integrity and the capacity of skeletal muscle to respond to nutritional intake, mechanical loading, inflammation, and ageing [5,12,17,44]. Although endocrine biomarkers have been less extensively investigated than nutritional or inflammatory biomarkers in orthopaedic surgery, accumulating evidence supports their contribution to musculoskeletal resilience, postoperative recovery, and sarcopenia [5,11-13,17]. Current research has focused predominantly on vitamin D, while studies evaluating insulin-like growth factor-1 (IGF-1), testosterone, growth hormone, myostatin, follistatin, and other endocrine mediators remain comparatively limited [5,11-13,17,18].

Vitamin D: It is the most extensively investigated endocrine biomarker in relation to sarcopenia because of its pleiotropic effects on skeletal muscle and bone [5,11,61-64]. Beyond regulating calcium and phosphate homeostasis, vitamin D influences muscle-cell proliferation and differentiation, intracellular calcium transport, mitochondrial oxidative phosphorylation, inflammatory signaling, and neuromuscular function through activation of the vitamin D receptor expressed in skeletal muscle fibers [5,11,17,61-63]. Accordingly, vitamin D deficiency has consistently been associated with reduced handgrip strength, slower gait speed, poorer physical performance, increased falls, frailty, osteoporosis, osteosarcopenia, and a higher prevalence of sarcopenia among community-dwelling older adults [5,15,61,64,65].

Within orthopaedic surgery, observational studies similarly demonstrate that lower preoperative 25-hydroxyvitamin D concentrations are associated with increased postoperative complications, delayed functional recovery, prolonged hospitalization, poorer patient-reported outcome measures, and higher revision rates following total joint arthroplasty [66-70]. Consistent with these findings, the arthroplasty studies reviewed in this manuscript identified lower preoperative vitamin D concentrations as a predictor of

postoperative complications following THA, supporting the role of vitamin D as a marker of endocrine physiological reserve rather than a specific diagnostic biomarker of sarcopenia [61,65,69,70].

Serum 25-hydroxyvitamin D concentrations below 20 ng/mL (50 nmol/L) are generally considered indicative of deficiency, whereas concentrations between 20 and 30 ng/mL (50–75 nmol/L) represent insufficiency and levels above 30 ng/mL (75 nmol/L) are regarded as sufficient for musculoskeletal health [61,65,71,72]. However, several studies suggest that optimal concentrations for preserving skeletal muscle function may exceed those required for bone health alone, highlighting the broader role of vitamin D in maintaining musculoskeletal physiological reserve [5,61,62,64].

Insulin-like growth factor-1 (IGF-1): IGF-1 is a key anabolic mediator of skeletal muscle maintenance, promoting protein synthesis, satellite-cell proliferation, muscle regeneration, and inhibition of proteolysis through activation of the IGF-1/PI3K/Akt/mTOR pathway [5,12,17,44]. Consequently, reduced circulating IGF-1 concentrations contribute to anabolic resistance and have consistently been associated with reduced muscle strength, impaired physical performance, frailty, and an increased prevalence of sarcopenia in older adults, although evidence from orthopaedic populations remains limited [11–13,17,18]. These findings support IGF-1 as a promising biomarker of anabolic physiological reserve that warrants further investigation in orthopaedic surgery.

Sex hormones and muscle-specific endocrine regulators: Sex hormones and muscle-specific regulatory proteins play important roles in maintaining skeletal muscle homeostasis throughout adulthood [5,11,12,17,73]. Testosterone promotes muscle protein synthesis, satellite-cell activation, neuromuscular function, and suppression of adipose tissue accumulation, whereas estrogen supports muscle regeneration, mitochondrial function, and modulation of inflammatory signaling [5,12,17,44,73]. Age-related declines in these hormones contribute to progressive reductions in muscle mass, strength, and quality, although their routine assessment in orthopaedic practice remains limited because circulating concentrations are influenced by age, sex, comorbidities, and pharmacological treatment [11–13,17]. Testosterone is particularly relevant to skeletal muscle homeostasis through its interaction with androgen receptors expressed in myonuclei and satellite cells, providing a biological basis for its investigation in relation to sarcopenia [73].

Circulating testosterone has also been investigated in relation to sarcopenia and its individual components, although associations vary across clinical populations. In 1,879 community-dwelling adults aged 70–84 years, lower free testosterone was associated with prevalent sarcopenia, while longitudinal analysis demonstrated associations with deterioration in handgrip strength in women and physical performance in men; however, free testosterone did not predict incident sarcopenia over two years [74]. In contrast, among 440 men receiving hemodialysis, a 50% lower free testosterone concentration was associated with higher odds of both prevalent (OR: 1.55, 95% CI: 1.09–2.02) and incident sarcopenia over 12 months (OR: 1.72, 95% CI: 1.13–2.33), as well as lower muscle mass and subsequent muscle loss [75]. Conversely, in 518 community-dwelling European men followed for a mean of 4.3 years, baseline testosterone concentrations did not predict changes in appendicular lean mass, grip strength, gait speed, or incident sarcopenia according to Baumgartner, International Working Group on Sarcopenia (IWGS), or European Working Group on Sarcopenia in Older People (EWGSOP) definitions [76].

Within orthopaedic populations, circulating testosterone has also been investigated in relation to functional and perioperative outcomes. In 272 adults aged ≥60 years undergoing unilateral TKA, Freystaetter et al. measured serum testosterone six to eight weeks postoperatively and found that higher concentrations were associated with less WOMAC pain in both men ($\beta = -0.62$; $p = 0.046$) and women ($\beta = -3.79$; $p = 0.02$), as well as less WOMAC disability in women ($\beta = -3.62$; $p = 0.02$) and obese men ($\beta = -1.99$; $p = 0.02$) [77]. More directly relevant to preoperative risk stratification, Glenn et al. evaluated endogenous testosterone status in men undergoing total joint arthroplasty, defining testosterone deficiency as <300 ng/dL and eugonadal status as ≥300 ng/dL while excluding patients receiving testosterone replacement therapy (TRT). After propensity matching, testosterone deficiency was associated with increased risks of deep-vein thrombosis (DVT) and pulmonary embolism (PE) following THA and with DVT, aseptic loosening, manipulation under anesthesia, readmission, and revision within two years following TKA [78].

Beyond its potential role as a circulating biomarker, testosterone has also been investigated as a therapeutic intervention. Importantly, endogenous testosterone status and TRT exposure represent distinct variables and should not be interpreted interchangeably. In a systematic review of five randomized controlled trials (RCTs) involving 189 orthopaedic patients, including 84 receiving perioperative testosterone and 105 receiving placebo or control treatment, four studies reported improvements in selected measures of functional recovery, BMD, muscle volume, gait speed, lean body mass, or strength, although substantial heterogeneity existed across patient populations, treatment protocols, outcomes, and follow-up periods [79].

In contrast to studies evaluating measured testosterone concentrations or controlled testosterone administration, recent observational studies have primarily investigated TRT exposure using prescription or administrative data. Among 13,250 propensity-matched TKA patients, preoperative TRT was associated with PE at 90 days (OR: 1.4, 95% CI: 1.0–1.8; $p = 0.041$), DVT at one year (OR: 1.4, 95% CI: 1.1–1.6; $p < 0.001$), and

higher five-year risks of PJI, periprosthetic fracture, and revision [80]. Similarly, among 3,953 propensity-matched patients per group undergoing THA, TRT was associated with higher rates of DVT at 90 days (2.8% vs. 2.0%; $p = 0.023$) and one year (4.3% vs. 3.0%; $p = 0.002$), as well as higher five-year rates of PJI (3.1% vs. 1.6%; $p < 0.001$), periprosthetic fracture (2.4% vs. 1.4%; $p = 0.003$), dislocation (2.5% vs. 1.2%; $p < 0.001$), and revision (4.1% vs. 2.3%; $p < 0.001$) [81]. However, these associations have not been consistently demonstrated. In a national registry analysis of 640,219 arthroplasty patients, perioperative TRT was associated with PE following TKA (OR: 1.45, 95% CI: 1.04-2.02; $p = 0.029$), but not with DVT following TKA or either DVT or PE following THA [82]. Among patients undergoing reverse shoulder arthroplasty, 1,906 TRT users matched to 1,906 controls demonstrated no significant differences in revision (12.01% vs. 11.02%; $p = 0.335$), PJI (1.42% vs. 1.63%; $p = 0.597$), or periprosthetic fracture (0.58% vs. 1.05%; $p = 0.105$) [83]. Conversely, among 34,911 primary TKA patients, preoperative TRT was independently associated with extensor mechanism disruption within three years (OR: 2.38, 95% CI: 1.39-4.09; $p = 0.002$), with this association observed in men (OR: 3.00, 95% CI: 1.64-5.49; $p = 0.0002$) but not women (OR: 1.10, 95% CI: 0.27-4.46) [84]. More recent THA data incorporating both TRT exposure and serum testosterone measurements showed that, among 152 TRT-treated patients undergoing primary elective THA who were propensity-matched to untreated controls, overall 90-day emergency department visits, readmissions, PJI, reoperations, and revisions did not differ significantly between groups; within the TRT cohort, higher serum testosterone concentrations were weakly inversely correlated with 90-day emergency department visits ($r = -0.35$; $p = 0.040$), but not with reoperation or revision [85]. The inclusion of laboratory testosterone measurements distinguishes this study from several database analyses based primarily on TRT exposure, although its retrospective design and relatively small cohort limit interpretation [85].

Collectively, these findings should be interpreted according to the testosterone variable being investigated. Studies of circulating endogenous testosterone have examined its relationship with sarcopenia, functional outcomes, and perioperative risk, whereas interventional studies have evaluated the effects of testosterone administration. In contrast, several observational studies of TRT exposure did not establish pretreatment biochemical testosterone status, limiting direct comparison between outcomes associated with endogenous testosterone deficiency and those associated with TRT. Prospective studies incorporating pretreatment testosterone measurements are therefore required to clarify whether correction of documented testosterone deficiency influences postoperative outcomes.

Beyond systemic sex hormones, muscle-derived endocrine regulators provide a more direct link to skeletal muscle homeostasis. Myostatin, also known as growth differentiation factor-8 (GDF-8), is a member of the transforming growth factor- β (TGF- β) superfamily and acts as a negative regulator of skeletal muscle growth through inhibition of satellite-cell activation, myogenic differentiation, and protein synthesis, whereas follistatin antagonizes myostatin signaling and thereby favors muscle growth and regeneration [86-88].

Clinical evidence supports an association between circulating myostatin and sarcopenic phenotypes, although findings vary according to the population studied. In a cross-sectional study of 182 patients with rheumatoid arthritis and 142 matched controls, serum myostatin concentrations were higher in patients with rheumatoid arthritis (5.41 (3.99-6.41) vs. 4.74 (3.93-5.18) ng/mL; $p = 0.001$), and patients with concomitant sarcopenia had significantly higher concentrations than those without sarcopenia ($p = 0.002$); in multivariable analysis, higher myostatin remained independently associated with sarcopenia (OR = 1.222, 95% CI: 1.015-1.472; $p = 0.034$) [89]. The study identified 5.12 ng/mL as an optimal threshold for discriminating rheumatoid arthritis from healthy controls (AUC = 0.604), rather than as a diagnostic threshold for sarcopenia, limiting its direct application to sarcopenia screening [89].

Orthopaedic evidence further indicates that circulating myostatin and follistatin concentrations are dynamically altered by acute musculoskeletal injury and surgery. In 30 women with hip fracture undergoing hemiarthroplasty and 30 age-matched female controls, preoperative myostatin concentrations did not differ significantly between groups; however, serum myostatin decreased by a median of 1,099 pg/mL at postoperative Day 3 ($p < 0.0001$) and remained 740 pg/mL below baseline at Day 12 ($p = 0.0052$), whereas follistatin transiently increased by 506 pg/mL at Day 3 ($p = 0.0161$) before returning to baseline by Day 12 [90]. These perioperative changes indicate that the timing of blood sampling is an important consideration when evaluating myostatin and follistatin as circulating biomarkers after hip fracture or arthroplasty [90].

The myostatin pathway has also been investigated in patients undergoing arthroplasty. In a Phase II randomized, double-blind trial of 400 patients aged ≥ 50 years undergoing elective THA, different doses of the anti-myostatin antibody LY2495655 were compared with placebo. Although increases in appendicular lean mass were observed with the 105 mg and 315 mg doses at weeks 8 and 16, the prespecified primary efficacy criterion was not met, and these changes were not accompanied by meaningful improvements in muscle strength or physical function [91]. These findings indicate that modulation of the myostatin pathway can influence muscle mass after THA; however, its clinical and functional relevance remains uncertain.

Emerging Molecular Biomarkers and Multi-omics Approaches

Although conventional laboratory biomarkers provide valuable information on nutritional, inflammatory, metabolic, and endocrine aspects of physiological reserve, they capture only part of the complex biological

mechanisms underlying sarcopenia [5,12,13,18,25]. Consequently, increasing attention has focused on multi-omics approaches - including genomics, transcriptomics, proteomics, metabolomics, circulating microRNAs, and extracellular vesicles - which offer more comprehensive characterization of skeletal muscle biology [5,12,13,18,44].

Among these, metabolomics has shown particular promise by identifying alterations in amino acid and lipid metabolism, mitochondrial function, oxidative stress, and energy production that may precede measurable declines in muscle mass or physical performance [5,13,18,25]. Proteomic and transcriptomic analyses have similarly identified dysregulated pathways involved in muscle regeneration, inflammation, mitochondrial dysfunction, and anabolic signaling, highlighting potential diagnostic biomarkers and therapeutic targets [5,12,13,18,25,44].

Despite these advances, molecular biomarkers remain largely confined to research settings because of limited standardization, methodological heterogeneity, and insufficient external validation. Future strategies will likely integrate molecular signatures with imaging-derived and conventional laboratory biomarkers using artificial intelligence and machine-learning algorithms to improve individualized assessment of physiological reserve and prediction of postoperative outcomes.

Collectively, the available evidence indicates that circulating biomarkers reflect distinct yet complementary biological domains contributing to sarcopenia and physiological reserve. Rather than serving as stand-alone diagnostic markers, these biomarkers provide insight into nutritional status, systemic inflammation, metabolic homeostasis, endocrine regulation, and emerging molecular pathways that may influence perioperative outcomes. For clarity, the principal circulating biomarkers discussed in this review and their key characteristics are summarized in Table 1. Table 2 complements this synthesis by presenting representative study-specific thresholds reported for circulating biomarkers together with the populations and clinical outcomes in which they were evaluated.

Biological domain	Biomarker	Reflects	Main clinical significance	Important limitations
Nutritional	Albumin	Protein reserve	Postoperative complications and perioperative nutritional risk	Acute-phase reactant
	GNRI	Nutritional reserve	Nutritional risk, sarcopenia, and postoperative complications	Requires validation
	mGNRI	Nutritional reserve	Sarcopenia and postoperative complications in population-specific studies	Limited validation
Inflammatory	CRP	Systemic inflammation	Postoperative complications and systemic inflammatory burden	Non-specific
	NLR	Immune balance	Sarcopenia in selected populations; postoperative complications and mortality	Population-dependent
	PLR	Inflammation	Association with sarcopenia; prognostic evidence remains variable	Variable evidence
Metabolic	CAR	Inflammation + nutrition	Postoperative complications, delirium, and mortality	Non-specific
	GAR	Glucose metabolism	Postoperative infectious and other complications	Limited evidence
	AST/ALT	Metabolic reserve	Sarcopenia and adverse clinical outcomes	Liver disease
Endocrine	Vitamin D	Endocrine reserve	Muscle health, recovery, and adverse clinical outcomes	Not sarcopenia-specific
	IGF-1	Anabolic reserve	Association with sarcopenia and anabolic reserve	Limited orthopaedic evidence
	Testosterone	Anabolic reserve	Lower endogenous testosterone associated with sarcopenia and its components in selected populations; endogenous testosterone deficiency (<300 ng/dL in men) associated with adverse outcomes after THA/TKA. TRT exposure without established pretreatment biochemical testosterone status has shown variable associations with postoperative outcomes.	Associations with sarcopenia are population-dependent; endogenous testosterone status and TRT exposure are distinct variables and should not be interpreted interchangeably.
Molecular	Myostatin/follistatin	Muscle growth and regulatory signaling	Myostatin associated with sarcopenia in selected populations; perioperative changes in circulating myostatin and follistatin reported after hip fracture/hemiarthroplasty	Limited orthopaedic evidence; perioperative variability; timing-dependent; no validated thresholds for sarcopenia or postoperative risk stratification
	"Multi-omics"	Molecular reserve	Emerging associations with sarcopenia and physiological reserve	Research only

TABLE 1: Principal circulating biomarkers related to sarcopenia and physiological reserve categorized according to their biological domain, clinical significance, and limitations.

Abbreviations: GNRI: Geriatric Nutritional Risk Index, mGNRI: modified Geriatric Nutritional Risk Index, CRP: C-Reactive Protein, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, CAR: CRP-to-Albumin Ratio, GAR: Glucose-to-Albumin Ratio, IGF-1: Insulin-Like Growth Factor-1, THA: Total Hip Arthroplasty, TKA: Total Knee Arthroplasty, TRT: Testosterone Replacement Therapy

Source: [5,11,16,21,23,25-30,33,41,74-78,85,86,89-91]

Biomarker	Reported threshold	Population	Associated clinical finding/outcome
Albumin	<3.5 g/dL	Arthroplasty patients	Higher risk of postoperative complications, particularly infection and wound-related complications
GNRI	<98	Older adults	Increased risk of nutrition-related complications; lower GNRI indicates progressively greater nutritional risk
mGNRI	<92.8	Arthroplasty patients	Higher risk of postoperative complications, including PJI, wound complications, readmission, and reoperation
	<55.5	Older adults evaluated for sarcopenia	Higher likelihood of sarcopenia
NLR	≥5.84	Hip fracture	Higher risk of postoperative pneumonia
CAR	≥1.5	Hip fracture	Higher risk of postoperative delirium and overall mortality
GAR	≥0.175	Hip fracture	Higher risk of postoperative pneumonia
	≥0.18	Hip fracture	Higher risk of postoperative urinary tract infection
AST/ALT	>1.20	Community-dwelling adults	Higher odds of sarcopenia defined according to AWGS criteria
	≥1.33 (highest quartile)	Community-dwelling adults	Higher odds of low skeletal muscle mass
	>2.1	Hip fracture	Increased 1-year mortality
Testosterone	<300 ng/dL	Men undergoing THA or TKA	Definition of endogenous testosterone deficiency used in the study; deficiency associated with DVT and PE after THA and with DVT, aseptic loosening, manipulation under anesthesia, readmission, and revision after TKA

TABLE 2: Representative study-specific thresholds reported for circulating biomarkers related to sarcopenia and physiological reserve, together with the populations and clinical outcomes in which they were evaluated.

Reported thresholds were derived from individual studies and clinical contexts and should not be interpreted as universally validated diagnostic or prognostic cut-off values.

Abbreviations: GNRI: Geriatric Nutritional Risk Index, mGNRI: Modified Geriatric Nutritional Risk Index, PJI: Periprosthetic Joint Infection, NLR: Neutrophil-to-Lymphocyte Ratio, CAR: CRP-to-Albumin Ratio, GAR: Glucose-to-Albumin Ratio, THA: Total Hip Arthroplasty, TKA: Total Knee Arthroplasty, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism

Source: [16,26,28,30,31,33,34,36,41,55,57,60,78]

Clinical implications

The growing body of evidence reviewed herein indicates that no single circulating biomarker adequately captures the complex biological processes underlying sarcopenia or reduced physiological reserve [5,12,13,18]. The principal contribution of the present review lies in integrating evidence on circulating biomarkers across different biological domains and clinical populations, demonstrating that their relevance extends beyond associations with sarcopenia to the identification of nutritional, inflammatory, metabolic, and endocrine vulnerability and the prediction of postoperative complications and other adverse clinical outcomes. According to current consensus recommendations from the EWGSOP2 and AWGS, the diagnosis of sarcopenia should continue to rely on objective assessment of muscle strength, muscle quantity and/or quality, and physical performance rather than laboratory biomarkers alone. Circulating biomarkers should therefore be regarded as complementary tools that characterize different components of physiological reserve and support clinical risk stratification when interpreted within the appropriate clinical context [5,11-13].

The biological significance of these biomarkers should also be considered when interpreting their clinical associations [5,12,13,18]. Nutritional biomarkers reflect substrate availability and nutritional resilience, inflammatory biomarkers characterize systemic inflammatory activation, metabolic biomarkers provide

information regarding cellular energy homeostasis, and endocrine biomarkers reflect anabolic and regulatory processes involved in skeletal muscle homeostasis [5,12,18,25,41,73]. Accordingly, abnormalities across these domains may provide complementary information regarding the mechanisms underlying reduced physiological reserve and vulnerability to adverse clinical outcomes.

This multidimensional approach is particularly relevant in orthopaedic surgery [2,3,5,19]. Elective arthroplasty patients often present with chronic disuse-related muscle loss accompanied by relatively preserved systemic physiology, whereas patients sustaining fragility hip fractures frequently exhibit generalized frailty, malnutrition, acute inflammatory activation, and profound reductions in physiological reserve [1-3,19-21]. Consequently, identical biomarker abnormalities may have different biological and prognostic implications depending on the underlying clinical population [3,5,13,21,23].

The current evidence also suggests that the greatest clinical value of laboratory biomarkers lies in identifying biological vulnerabilities associated with adverse perioperative outcomes [13,20,30,33,35,57]. Biomarkers such as albumin, GNRI, CAR, GAR, NLR, and AST/ALT have been associated with postoperative complications, prolonged hospitalization, infection, functional decline, and mortality across different clinical populations [20,28,30,33-35,41,57]. These findings support their interpretation as indicators of biological vulnerability and impaired physiological reserve, while their clinical significance should remain contextualized according to the population and outcome evaluated [5,11-13,23]. Accordingly, abnormal laboratory findings should prompt comprehensive assessment of muscle health using established diagnostic criteria rather than replace objective evaluation of muscle mass, muscle strength, and physical performance [5,11,12,15,16]. Emerging endocrine biomarkers, including testosterone and muscle-specific regulators such as myostatin and follistatin, remain investigational, with insufficient evidence to support their routine use as stand-alone biomarkers for sarcopenia diagnosis or perioperative risk stratification in orthopaedic practice [73,86,88,90].

Importantly, biomarker assessment also creates opportunities for preoperative optimization [3,28,30,69]. Identification of nutritional deficiencies, vitamin D insufficiency, chronic inflammatory activation, or impaired metabolic reserve before surgery may allow targeted interventions, including nutritional supplementation, optimization of protein intake, correction of micronutrient deficiencies, structured exercise programs, prehabilitation, and management of modifiable comorbidities. Although high-quality evidence supporting the effectiveness of biomarker-guided interventions in improving postoperative outcomes is currently limited, such an approach is biologically plausible and aligns with the principles of personalized perioperative care [3,5,17,69,92].

Finally, the reviewed evidence supports a shift from viewing sarcopenia as an isolated disorder of skeletal muscle toward considering it one manifestation of impaired physiological reserve [5,12,13,18]. Within this framework, established diagnostic assessment of muscle strength, muscle quantity and/or quality, and physical performance remains central to the diagnosis of sarcopenia, whereas laboratory biomarkers provide complementary biological information that improves risk stratification, facilitates individualized perioperative optimization, and enhances understanding of the mechanisms underlying adverse clinical outcomes [5,8,11-13].

Future directions

Despite the growing evidence regarding circulating biomarkers associated with sarcopenia and their prognostic value for adverse clinical outcomes, several challenges must be addressed before their routine clinical implementation. Substantial heterogeneity in study populations, diagnostic criteria, laboratory methods, and biomarker cut-off values currently limits comparability across studies and clinical applicability [5,12,13,18]. Future research should prioritize standardized biomarker assessment using internationally accepted sarcopenia definitions, harmonized laboratory methodologies, standardized timing of sample collection, and clinically validated threshold values. Prospective multicenter studies are also required to validate biomarker performance across diverse orthopaedic populations and establish reproducible prediction models.

Another important objective is the development of integrated risk prediction models combining established sarcopenia assessment, circulating biomarkers, functional performance, and patient-specific clinical characteristics. For emerging endocrine biomarkers, prospective studies should determine whether their measurement provides clinically meaningful information beyond established sarcopenia assessment and routinely available laboratory parameters. Moreover, randomized clinical trials should determine whether biomarker-guided interventions - including nutritional optimization, exercise-based prehabilitation, vitamin D supplementation, and individualized perioperative management - translate into improved postoperative outcomes. Finally, advances in metabolomics, proteomics, transcriptomics, circulating microRNAs, and extracellular vesicles may further refine biomarker-based risk assessment and facilitate precision medicine approaches for individualized perioperative care.

Conclusions

Sarcopenia should be regarded as a multidimensional syndrome that extends beyond the loss of skeletal

muscle mass and strength. The available evidence indicates that nutritional depletion, chronic inflammation, metabolic dysregulation, endocrine alterations, and impaired regenerative capacity collectively contribute to reduced physiological reserve and increased susceptibility to adverse clinical outcomes. Accordingly, circulating biomarkers should be viewed as complementary indicators of these biological domains that support perioperative risk stratification and individualized clinical decision-making rather than as stand-alone diagnostic tools for sarcopenia.

Although current evidence is encouraging, routine clinical implementation remains limited by methodological heterogeneity and the lack of prospective validation. Future research should prioritize standardized biomarker assessment, multicenter validation studies, and integrated prediction models combining established sarcopenia assessment with circulating biomarkers. Such an approach may improve patient phenotyping, facilitate personalized perioperative optimization, and ultimately enhance outcomes in patients undergoing orthopaedic surgery.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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