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Frequently Reported Blood Biomarkers in Sarcopenia Clinical Trials: A Systematic Review and Meta-Analysis

Emma Calluy[1,2,3] | Yveline Malrechauffé[4] | Emma Boretti[4] | Sophie Van Heden[1] | Dolores Sanchez-Rodriguez[5,6] | Yoke Mun Chan[7,8] | Etienne Cavalier[2,3] | Aurélie Ladang[2] | Jean-Yves Reginster[9] | Jonathan Douxfils[4,10,11] | Charlotte Beaudart[1]

[1]Public Health Aging Research & Epidemiology (PHARE) Group, Research Unit in Clinical Pharmacology and Toxicology (URPC), NAmur Research Institute for LIfe Sciences (NARILIS), Department of Biomedical Sciences-Faculty of Medicine, University of Namur, Namur, Belgium | [2]Department of Clinical Chemistry, Center for Interdisciplinary Research on Medicines, Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium | [3]University of Liège, Liège, Belgium | [4]Research Unit in Clinical Pharmacology and Toxicology (URPC), NAmur Research Institute for LIfe Sciences (NARILIS), Department of Pharmacy, Faculty of Medicine, University of Namur, Namur, Belgium | [5]Geriatrics Department, Brugmann University Hospital, Université Libre de Bruxelles, Brussels, Belgium | [6]Rehabilitation Research Group, Hospital Del Mar Research Institute, Barcelona, Spain | [7]Department of Dietetics, Faculty of Medicine and Health Sciences, University Putra Malaysia, Serdang, Malaysia | [8]Malaysian Research Institute on Ageing, University Putra Malaysia, Serdang, Malaysia | [9]Protein Research Chair, Biochemistry Department, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia | [10]QUALIresearch, QUALIblood s.a., Namur, Belgium | [11]Department of Biological Hematology, Centre Hospitalier Universitaire Clermont-Ferrand, Hopital Estaing, Clermont-Ferrand, France

Correspondence: Emma Calluy (emma.calluy@unamur.be)

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ABSTRACT

This systematic review and meta-analysis aims to identify the most frequently reported blood-based biomarkers (BBMs) in randomised controlled trials (RCTs) addressing sarcopenia management, and to perform a preliminary evaluation of the effects of sarcopenia-specific interventions on BBMs concentrations. Medline, Embase and CENTRAL databases were searched to retrieve RCTs published until March 2024 (PROSPERO: CRD42024603238) on older participants with sarcopenia. Eligible studies applied a consensus definition of sarcopenia and reported BBM values before and after intervention. Meta-analyses were performed for BBMs reported in a minimum of 2 RCTs using a random effects model with a standardised mean difference (SMD) and a 95% confidence interval. Among 58 RCTs on sarcopenia management, only 21 (36.2%) assessed BBMs and none involved pharmacological interventions. Altogether, 47 distinct BBMs were identified. The most frequently reported were C-reactive protein, interleukin 6, tumour necrosis factor α, Insulin-like Growth Factor 1 (IGF-1). Muscle-specific BBM, follistatin, growth differentiation factor 8 and 15 were assessed in only 2 RCTs. Among non-muscle-specific BBMs, IGF-1 was significantly impacted by the studied interventions (SMD = 0.46, CI = [0.04; 0.88]). However, this change was not significant when analyses were restricted to RCTs reporting significant improvement in key sarcopenia measures. Despite substantial heterogeneity, few BBMs assessed in sarcopenia RCTs were muscle-specific and limited biomarkers responded to interventions. There is an urgent need to adopt recommendations regarding muscle-specific BBMs to be assessed in sarcopenia RCTs. Developing a standardised Core Outcome Set for sarcopenia intervention studies would enhance the standardisation of sarcopenia RCTs and ultimately improve disease management.

1 | Background

Sarcopenia is characterised by a progressive loss of muscle mass and strength, as defined by the European Working Group on Sarcopenia in Older People (EWGSOP2) (Cruz-Jentoft et al. 2019). Although sarcopenia was officially recognised as a disease by the International Classification of Diseases in 2016 (Cao and Morley 2016), a universal consensus on its definition is still lacking, with multiple diagnostic criteria currently in use (Ben Kirk et al. 2024). This lack of standardisation affects epidemiological estimates; as an example, the reported prevalence of sarcopenia among individuals over 65 years old ranges from 10% to 22%, depending on the study and diagnostic criteria used (Fanny Petermann-Rocha et al. 2022; Shafiee et al. 2017; Shuai Yuan 2023).

Beyond its important prevalence among older individuals, sarcopenia has major consequences at both the individual and societal levels. Sarcopenia significantly reduces quality of life (Beaudart et al. 2023), increases the risk of falls, fractures, hospitalisations, functional decline and mortality (Beaudart et al. 2017), while imposing a significant economic burden on healthcare systems (Beaudart et al. 2017; Bruyere et al. 2019). With the rapid ageing of the global population, the number of affected individuals is expected to rise dramatically in the next few years (Ethgen et al. 2017), making sarcopenia a major global public health issue.

Although recognised as a disease, the underlying pathophysiology of sarcopenia remains poorly understood. Sarcopenia is known to result from an imbalance between anabolic and catabolic factors regulating muscle metabolism. First, key anabolic regulators such as testosterone, growth hormone, and insulin-like growth factor-1 (IGF-1) promote muscle protein synthesis and regeneration (William J. Kraemer et al. 2020). Second, myostatin and activin A act as catabolites, inhibiting muscle growth and increasing muscle breakdown (Esther Latres et al. 2017). Yet, several unknowns remain, such as the aetiology of the disease, highlighting the need for further research in the field.

As a potential reversible disease (Shen et al. 2023), sarcopenia can be managed through targeted interventions. Nowadays, approaches for the management of sarcopenia mainly include exercise, nutrition, and pharmacological treatments, although no approved medicinal product is currently available (Reginster et al. 2021; Rolland et al. 2023). Indeed, clinical research faces significant challenges due to inconsistencies in outcome measures related to muscle mass, strength and physical function, making it difficult to compare findings across studies (Doza et al. 2024).

To improve the inter-study comparability in sarcopenia biomarkers measurement, an expert group gathered under the Auspices of the World Health Organisation Collaborating Centre for the Epidemiology of Musculoskeletal Conditions and Ageing in 2023. This group of experts from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the Centre Académique de Recherche et d'Expérimentation en Santé (CARES SPRL) published a consensus manuscript providing a list of biochemical markers of musculoskeletal health and ageing that should ideally be measured in Phase II and Phase III clinical trials evaluating new chemical entities for sarcopenia treatment (Ladang et al. 2023). Experts further categorised biomarkers into musculoskeletal biochemical markers, biomarkers of the neuromuscular junction and markers of muscle turnover (Ladang et al. 2023). Biomarkers specific to inflammation, adipokines and hormones were also reported as relevant for sarcopenia (Ladang et al. 2023).

Building on this background, our work aims to investigate to what extent current RCTs in sarcopenia may complement this guidance by performing a systematic review to identify all RCTs published in the field of sarcopenia and reporting, first, a list of blood-based biomarkers (BBMs) that are currently reported in those RCTs and, second, by performing a preliminary analysis of the effects of proposed interventions on muscle-specific BBMs and other BBMs recommended by experts in their consensus paper, using a meta-analytical model. Identifying reliable surrogate outcomes for sarcopenia will eventually ease its management while optimising resource allocation by focusing on the most relevant biomarkers for clinical and therapeutic applications (Curcio et al. 2016; Kwak et al. 2018; Marzetti et al. 2019).

2 | Methods

This systematic review and meta-analysis was carried out and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis requirements (PRISMA 2020) (Page et al. 2021) with a complete PRISMA checklist available in the appendix (Figure S1). A research protocol was established and published on PROSPERO (identification number: CRD42024603238). The review was designed according to the PICOs framework as follows: P (Population): Adults from 60 years old (mean sample age was above 60 years or results were reported separately for persons aged 60 years or over) with a diagnosis of sarcopenia defined by at least a measurement of two key parameters of sarcopenia (e.g., muscle mass + (muscle strength or physical function)), I (Intervention): Intervention aiming at the management of patients with sarcopenia with any kind of intervention (nutritional, exercise, pharmacological, combined/other interventions), C (Comparator): intervention using any kind of control (usual care, standard of care, any control intervention), O (Outcome): blood-based biomarker measurement, S (Study design): Randomised controlled trials.

2.1 | Literature Search

A search strategy combining Mesh terms and keywords was applied, in March 2024, on MEDLINE (via Ovid), Cochrane Central Register of Controlled Trials (via Ovid) and Embase to identify all peer-reviewed and published randomised controlled trials (RCTs) aiming at the management of sarcopenia. Among these RCTs, only those reporting BBMs, with both baseline and follow-up values available, were included in the present project for the systematic literature review. The complete search strategy used for each database is available in the appendix (Figure S2).

In addition to the search strategy applied on bibliographic databases, a manual search was also performed. The bibliographies of included articles were assessed to retrieve further articles and the references of previous systematic literature reviews published on a similar topic were also investigated. Then, experts

in the field of biomarkers and sarcopenia were contacted to enrich the literature search with potential missing studies and grey literature. Research was limited to English language (Morrison et al. 2012). The identified articles were imported in Covidence Software (https://app.covidence.org/reviews/419021) for data management as recommended by the Cochrane collaboration (Higgins et al. 2024).

2.2 | Study Selection

The first screening of articles included in the study was based on the title and abstract with inclusion criteria as a screening decision tool. Two independent reviewers (C.B., D.S-R., Y.M.C.) performed the screening independently to exclude articles not matching the inclusion criteria. The second step for reference selection was the reading of the full text of each article selected by the first inclusion step. Disagreements during inclusion were resolved by consensus between the 2 reviewers or with the support of a third independent reviewer.

2.3 | Data Extraction

Data were independently extracted by three reviewers working in rotating pairs (E.B., E.C., Y.M.) and coded in a standardised Excel file. The following information were extracted: article information (e.g., first author, title and year of publication), population characteristics (e.g., description of the population and sarcopenia diagnosis), outcomes (e.g., biomarker measurement and results), comments, funding, conflict of interest and conclusion. Disagreements were resolved by consensus and when needed, with the help of an additional reviewer (Y.M., C.B.). When data were missing, authors of individual articles were contacted.

2.4 | Data Synthesis

Because of the heterogeneity observed in the types of BBMs, BBMs were classified in 4 subgroups to facilitate the organisation of information, that is, (1) Muscle-specific BBMs recommended by ESCEO guidelines, (2) Non-muscle-specific BBMs recommended by ESCEO guidelines, (3) additional muscle-specific BBMs identified in RCTs but not recommended by ESCEO guidelines and finally, (4) Non-muscle-specific BBMs not recommended by ESCEO guidelines according to the article of Ladang et al. 2023.

A meta-analysis was conducted for all BBMs that fell into the first three categories and were reported in at least two RCTs. Other biomarkers were summarised using a narrative synthesis. The initial analysis included the maximum number of RCTs, regardless of the intervention's effect on the primary endpoint. A second, more restrictive analysis was then performed, focusing only on studies that demonstrated a significant improvement in muscle mass and/or muscle strength. This second analysis aimed to identify potential changes in BBMs following interventions deemed effective in improving key parameters of sarcopenia.

Due to the expected heterogeneity in blood-based biomarkers measurements and in sarcopenia definitions across studies, a random effects model was chosen. The mean concentration and standard deviation (SD) of each biomarker were extracted for each study arm from the included RCTs. When data were missing or not expressed as mean and SD in the original paper, the authors were first contacted to obtain the missing or appropriately formatted values. If the latter data were not available, multiple methods were used to include all the selected articles in the review and to ensure exhaustivity within the collected data. When p-values or 95% confidence intervals were reported instead of SDs, the methods described in section 7.7.3 of the Cochrane Handbook for Systematic Review were used (Higgins et al. 2024). If a median and interquartile range were mentioned, the Mean Variance Estimation method published as 'Estimating the sample mean and standard deviation (SD) from the five-number summary and its application in meta-analysis' (https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) was used to back transform the value into mean and SDs. The difference in each biomarker concentration before and after the intervention was reported using a standardised mean difference (SMD) with a 95% confidence interval (CI) because different units, measurement methods and automats were used to measure biomarkers within the RCTs.

According to the theoretical principles of a meta-analysis, one individual cannot be found more than once in a meta-analysis. Therefore, in cases where RCTs included multiple intervention groups compared to a single control group, relevant intervention groups were pooled to avoid duplication of participants in the analysis. Additional information is available on Open Science Framework (OSF: https://osf.io/wtv5z/).

Heterogeneity within the results was assessed using the Cochran's Q statistic and the I^2 statistic. To further investigate heterogeneity, when a sufficient number of RCTs was available, subgroup analyses were performed based on the type of intervention (exercise, nutritional, pharmacological and combined/others intervention). Then, publication bias was assessed using a funnel plot and the Egger's regression asymmetry test in meta-analyses containing a minimum of 6 RCTs. When the funnel plot and the Egger's test demonstrated some significant heterogeneity, the Trim and Fill statistical analysis was performed.

Finally, to test the robustness of the model when one study is removed at a time, a leave-one-out sensitivity analysis was performed. All statistical analyses were performed on R Software (R-4.4.2) on RStudio with the appropriate package (meta) and significance was reached with a p-value ≤ 0.05.

2.5 | Risk of Bias Assessment

RCTs' risk of bias was assessed using the Cochrane RoB2.0 tool, a risk-of-bias tool for RCTs, by three independent reviewers working in rotating pairs (Y.M.C., S.V.H., E.C.) with consensus or the intervention of a third party in case of disagreement (Sterne et al. 2019).

The Cochrane RoB2.0 tool assesses the following 5 domains: randomisation process, deviation from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. A judgement per domain and an

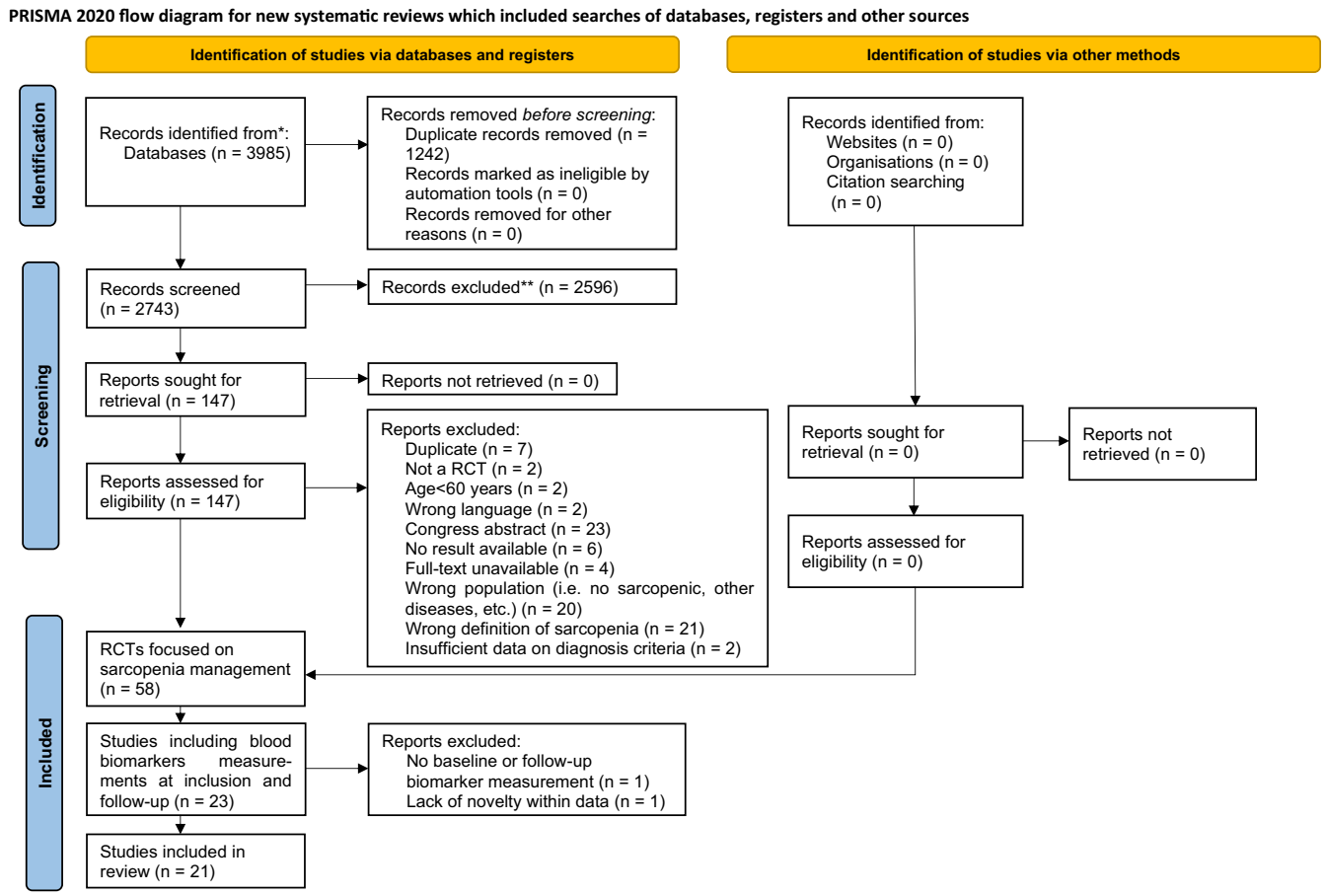

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA 2020 Flowchart.

overall judgement of risk of bias was provided for each included article and studies were rated as having low risk of bias, some concerns, or high risk of bias. When a study did not publish a protocol, domain 5 was automatically rated as 'some concerns'. Also, when a study was not double-blinded, domain 2 was automatically rated as 'some concerns' as well.

3 | Results

3.1 | Literature Search and Studies Characteristics

A total of 3985 references were identified from the electronic databases. After removing duplicates, 2743 references were assessed for eligibility based on titles/abstracts and 147 were further assessed based on full texts. Fifty-eight RCTs aiming at the management of sarcopenia were identified. Studies excluded during the full-text screening stage are available in OSF alongside their reason of exclusion. From these 58 studies, only 21 RCTs (36.2%) measured at least one BBM (Flowchart of study selection available in Figure 1). The characteristics of the 21 RCTs finally included in the present systematic review are reported in Table 1.

The 21 RCTs measuring at least one BBM, published between November 2016 and March 2024, gathered a total of 1902 participants with sarcopenia, 936 individuals in the control groups and 966 individuals in the intervention groups. The median of sample included in the selected RCTs equals 53 individuals (interquartile range [IQR] = 34, 90) and the median of the length of intervention is 12 weeks (IQR = 8, 13). Regarding definitions of sarcopenia, the majority of the studies used the AWGS definition (7 RCTs, 33.3%), the EWGSOP criteria (4 RCTs, 19.0%) or the criteria of the EWGSOP2 (2 RCTs, 9.5%).

Regarding types of intervention, 6 RCTs (28.6%) used a nutritional intervention, 6 (28.6%) used an exercise intervention and 9 (42.9%) used a combination of both or another type of intervention. None were pharmacological interventions.

A median of 2 primary endpoints was reported per RCT (range 1–9 primary endpoints per study). BBMs were assessed as one of the primary endpoints in 14 RCTs and as a secondary endpoint in the rest of the RCTs. Only 1 RCT reported specifically measuring BBMs for safety (Yang et al. 2023) and 1 RCT reported measuring some BBMs as exploratory measurements (Rondanelli et al. 2020).

Ten out of 21 RCTs (47.7%) included in this systematic review could not demonstrate any significant change in all the primary endpoints following the proposed interventions.

Regarding risk of bias (RoB) assessment, 12 RCTs were scored as 'low risk' of bias studies, 6 of the RCTs were categorised with 'some concerns regarding the risk of bias' and 3 RCTs as high risk of bias. Details of assessment are available in Figure S3.

TABLE 1 | Characteristics of RCTs included in the systematic review.

References	Study description	Population and sample size included in the analysis	Population characteristics: mean age (SD)	Randomised sample size (*n*)		Sample size analysed (*n*)		Analysis strategy	Reasons of participants' drop out	Criteria for assessing sarcopenia	Primary outcome	Biomarkers
				IG	CG	IG	CG					
Exercise intervention												
Chen et al. (2018)	RCT 12 weeks Intervention: Kettlebell training (KT) Control: Daily lifestyle without exercise (CON)	Older women with sarcopenia (65–75 years) 33 participants Women 33 (100%) Intervention group $n = 17$ Control Group $n = 16$	IG 72.89 (7.02) CG 71.44 (5.22)	17	16	17	16	ITT	N/A	AWGS	Body composition (weight, SMM, BFM, ASM, VFA, sarcopenia index)	CRP IL-6 TNF-α
de Sa Souza et al. (2022)	RCT 12 weeks Intervention: resistance exercise training (RET) Control: control placebo	Patients with sarcopenia (≥ 65 years) 28 participants Women: 18 (64.29%) Intervention group $n = 14$ Control Group $n = 14$	IG: 77.42 (6.25) CG: 74.6 (7.13)	14	14	14	14	ITT	N/A	EWGSOP2	Polysomnography Pitsburgh sleep quality index Actigraphy Biochemical assessments SPPB Body composition HG strength	Cortisol GH IGF-1 IL-1 RA IL-10 IL-6 Testosterone TNF-α
Moghadam et al. (2020)	RCT 8 weeks Intervention • *R* + E • E + *R* Control: No exercise	Older men with sarcopenia (60–70 years) 30 participants Intervention • *R* + E $n = 10$ • E + *R* $n = 10$ Control $n = 10$	E + *R* 64.1 (3.3) *R* + E 63.8 (3.6) CG 65.0 (3.9)	10 10	10	10 10	10	ITT	N/A	HG strength values of < 26–30 kg, walking speed of < 0.8 m/s over 4 m, and a SMI of less than two standard deviations below the average young adult population		Myf5 Myog Pax3 Pax7

(Continues)

TABLE 1 | (Continued)

References	Study description	Population and sample size included in the analysis	Population characteristics: mean age (SD)	Randomised sample size (*n*)		Sample size analysed (*n*)		Analysis strategy	Reasons of participants' drop out	Criteria for assessing sarcopenia	Primary outcome	Biomarkers
				IG	CG	IG	CG					
Rezaei et al. (2024)	RCT 8 weeks Intervention: TRX Suspension Training group Control: routine lifestyle	Older men with sarcopenia (≥ 65 years) 23 participants Intervention group *n* = 12 Control Group *n* = 11	IG: 72.5 (4.17)[1] CG: 76.5 (3.53)[1]	12	11	10	9	PP	Excluded due to corona virus pandemic or personal issues	AWGS (2019) and EWGSOP2	CAF levels Follistatin levels GDF-15 levels Myostatin levels	CAF Follistatin GDF-8 GDF-15
Seo et al. (2021)	RCT 16 weeks Intervention: resistance training Control: no exercise	Women with sarcopenia (≥ 65 years) 27 participants Women: 27 (100%) Intervention group *n* = 12 Control Group *n* = 10	IG: 70.3 (5.38)[1] CG: 72.9 (4.75)[1]	14	13	12	10	PP	Personal reasons or refused post- tests	IWGS & EWGSOP	Muscle quality (MVIC, RMVIC) Muscle growth factors	Activin A GDF-8 GDF-15 Follistatin
Yuenyongchaiwat et al. (2023)	RCT 12 weeks Intervention: walking and resistance exercises Controls: daily life tasks	Men and women (≥ 60 years) 90 participants Women: 62 (69%) Intervention group *n* = 30 Control Groups • No sarcopenia *n* = 30 • Sarcopenia *n* = 30	IG: 69.23 (6.71) CG • No sarcopenia: 68.30 (5.40) • Sarcopenia: 71.93 (5.19)	30	30 30	28	23 29	PP	7 participants without sarcopenia: refused/busy 3 participants with sarcopenia: knee pain (2 in the IG and 1 in the CG)	AWGS	Depressive symptoms Inflammatory markers	IL-6 TNF-α

(Continues)

TABLE 1 | (Continued)

References	Study description	Population and sample size included in the analysis	Population characteristics: mean age (SD)	Randomised sample size (*n*)		Sample size analysed (*n*)		Analysis strategy	Reasons of participants' drop out	Criteria for assessing sarcopenia	Primary outcome	Biomarkers
				IG	CG	IG	CG					
Nutritional intervention												
Bo et al. (2019)	RCT 6 months Intervention: whey protein, vitamin D and vitamin E nutritional supplementation Control: isocaloric control product	Older adults with sarcopenia (60–85 years) 60 participants Women: 33 (55%) Intervention group $n = 30$ Control Group $n = 30$	IG: 73.23 (6.52) CG: 74.83 (6.43)	30	30	30	30	ITT	N/A	(1) RSMI $< 5.7\,kg/m^2$ for women and $< 7.0\,kg/m^2$ for men using BIA (2) handgrip strength $< 18\,kg$ for women and $< 26\,kg$ for men, or 6-m usual walk speed $< 0.8\,m/s$	Limb skeletal muscle mass (AMM) 6 m pace Chair sit-stand test Stand-up and walk timing	25-(OH)-vitamin D Albumin CRP HDL cholesterol IGF-1 IL-2 IL-6 LDL cholesterol Triglycerides TNF-α Total cholesterol Total protein Vitamin E
Cramer et al. (2016)	RCT 24 weeks Intervention: Medical food with AN777 Control: oral nutritional formula	Malnourished men and women with sarcopenia (≥ 65 years) 330 participants Women: 205 (62%) Intervention group $n = 165$ Control Group $n = 165$	IG: 77 (71.81) CG: 77 (71.81)	165	165	131	146	PP	Early exit IG: 34 including 2 deaths due to infection CG: 19	Low grip strength (< 20 kg women; < 30 kg men) and/or low gait speed (< 0.8 m/s) in conjunction with low skeletal mass index	Knee extensor strength (Isokinetic PT)	25-(OH)-vitamin D

(Continues)

TABLE 1 | (Continued)

References	Study description	Population and sample size included in the analysis	Population characteristics: mean age (SD)	Randomised sample size (*n*)		Sample size analysed (*n*)		Analysis strategy	Reasons of participants' drop out	Criteria for assessing sarcopenia	Primary outcome	Biomarkers
				IG	CG	IG	CG					
Hill et al. (2019)	RCT 13 weeks Intervention: whey protein, leucine, carbohydrates, fat, vitamin D, calcium and a mixture of vitamins, minerals and fibres Control: Isocaloric control product	Non-malnourished older participants (> 65 years) with mobility limitations and reduced muscle mass 380 participants Women: 249 (69.2%) Intervention group *n* = 184 Control Group *n* = 196	IG: 77.3 (6.7) CG: 78.1 (7.0)	184	196	184	196	ITT	302 participants completed all three study visits (79% completion rate) Adverse events (*n* = 45) Serious adverse event (*n* = 2) Withdrawal of informed consent (*n* = 15) Lost to follow up (*n* = 2) Protocol deviation (*n* = 1) Another reason (*n* = 13)	SPPB score 4–9 and low-skeletal Muscle Mass Index ≤ 37% in men and ≤ 28% in women	Bone health measurements (BMD)	25-(OH)-vitamin D Calcium CTx IGF-1 Osteocalcin P1NP PTH
Liberman et al. (2019)	RCT 13 weeks Intervention: 20 g of whey protein, 3 g of leucine and 800 IU vitamin D nutritional supplement Control: isocaloric control product	Adults with sarcopenia and mobility limitations and a body mass index of 20-30 kg/m^2 (≥ 65 years) 380 participants Women: 237 (65%) Intervention group *n* = 184 Control Group *n* = 196	IG: Male: 77.87 (6.60) IG: Female: 77.17 (6.66) CG: Male: 78.02 (7.45) CG: Female 78.00 (6.70)[2]	184	196	137	151	PP	IG 40 lost to follow-up 23 adverse events 1 serious adverse event 10 withdrew consent 1 could not be located 5 other reasons CG 37 lost to follow-up 22 adverse events 1 serious adverse event 5 withdrew consent 1 could not be located 9 other reasons	SPPB score 4–9 and low-skeletal Muscle Mass Index	Chronic low-grade inflammation	25-(OH)-vitamin D CRP IL-1 RA IL-6 IL-8 Pre-albumin sTNFR-1

(Continues)

TABLE 1 | (Continued)

References	Study description	Population and sample size included in the analysis	Population characteristics: mean age (SD)	Randomised sample size (*n*)		Sample size analysed (*n*)		Analysis strategy	Reasons of participants' drop out	Criteria for assessing sarcopenia	Primary outcome	Biomarkers
				IG	CG	IG	CG					
Nasimi et al. (2021)	RCT 12 weeks Intervention: fortified yogurt with HMB, vitamins D and C Control: plain yogurt	Older adults with sarcopenia (≥ 65 years) 66 participants Women 49.5 (75%) Intervention group $n = 33$ Control Group $n = 33$	IG: 71.178 (3.4873) CG: 70.2457 (7.362)	33	33	33	31	PP	CG: refusal to continue	AWGS	Lean mass and ALM	25-(OH)-vitamin D CRP IGF-1 Insulin Malondialdehyde
Yoshimura et al. (2019)	RCT 8 weeks Intervention: leucine-enriched amino acid supplement Control: no specific supplement	Post-stoke older patients with sarcopenia (≥ 65 years) 44 participants Women: 30 (68.2%) Intervention group $n = 21$ Control Group $n = 23$	IG: 80.8 (7.1) CG: 78.9 (6.3)	24	25	21	23	PP	Lost to follow-up Reasons IG • Early discharge ($n = 1$) • Consent withdrawn ($n = 2$) CG • Early discharge ($n = 1$) • Consent withdrawn ($n = 1$)	AWGS	Physical function score determined by FIM	Albumin
Combined intervention												
Chiang et al. (2021)	RCT 12 weeks Interventions: Exercise+ • Milk supplement • Soymilk supplement Control: Exercise only	Older subjects with sarcopenia in a nursing home (> 75 years) Women: 6 (17.1%) 35 participants Intervention groups • Milk $n = 12$ • Soymilk $n = 11$ Control Group $n = 12$	IG Milk: 85.25 (5.38) Soymilk 85 (5.62) CG 84.67 (7.5)	12 12	12	12 11	12	PP	Bellyache after drinking soymilk ($n = 1$)	AWGS	ASM index Height CC HG GS	25-(OH)-Vitamin D ALT Creatinine Fasting blood glucose HbA1c CRP IGF-1 Insulin Prealbumin

(Continues)

TABLE 1 | (Continued)

References	Study description	Population and sample size included in the analysis	Population characteristics: mean age (SD)	Randomised sample size (*n*)		Sample size analysed (*n*)		Analysis strategy	Reasons of participants' drop out	Criteria for assessing sarcopenia	Primary outcome	Biomarkers
				IG	CG	IG	CG					
da Cruz Alves et al. (2022)	RCT 14 weeks Intervention: exercise and fish oil Control: exercise and placebo	Older women with sarcopenia (≥ 65 years) 34 participants Women 34 (100%) Intervention group $n = 17$ Control Group $n = 15$	IG: 70.6 (3.94) CG: 71.4 (6.21)	17	17	17	15	PP	Aggravation of existing health conditions ($n = 2$)	EWGSOP	Muscular strength of the lower limbs measured by maximum torque	IL-1β IL-6 IL-8 IL-10 TNF-α
Monti et al. (2023)	RCT 2 years Intervention: MultiComponent Intervention (MCI) Control: Healthy Ageing Lifestyle Education (HALE)	Older patients with sarcopenia (≥ 70 years) 45 participants Women: 34 (75.56%) Intervention group $n = 24$ Control Group $n = 21$	IG: 78.0 (6.1) CG: 79.6 (5.8)	24	21	24	21	ITT	N/A	EWSGSOP	Preservation of the neuromuscular system	CAF NfL
Rondanelli et al. (2018)	RCT 4 weeks Interventions: exercise+ • M • eAA • eAAM Control: P	Older patients with sarcopenia 200 participants Women: 117 (73.6%)[3] M $n = 50$ eAA $n = 50$ eAAM $n = 50$ P $n = 50$	M 81.64 (7.04) eAA 80.55 (6.76) eAAM 81.42 (8.02) P 81.86 (6.83)	M $n = 50$ eAA $n = 50$ eAAM $n = 50$	50	M $n = 42$ eAA $n = 40$ eAAM $n = 33$	44	PP	NA	SMI < 7.23 kg/m^2 in men and < 5.45 kg/m^2 in women and loss of strength, evaluated by dynamometer and defined as < 30 kg for men and < 20 kg for women, using the average value of the two HG measurements of the dominant hand	Change in total fat mass and total free fat mass (DXA) Change in HG	Albumin CRP

(Continues)

TABLE 1 | (Continued)

References	Study description	Population and sample size included in the analysis	Population characteristics: mean age (SD)	Randomised sample size (*n*)		Sample size analysed (*n*)		Analysis strategy	Reasons of participants' drop out	Criteria for assessing sarcopenia	Primary outcome	Biomarkers
				IG	CG	IG	CG					
Rondanelli et al. (2020)	RCT 8 weeks Intervention: exercise + whey protein-based nutritional formula enriched with leucine and vitamin D Control: P	Older patients with sarcopenia who are candidates for inpatient rehabilitation without severe cognitive impairment (≥ 65 years) 140 participants Women: 88 (63%) Intervention group *n* = 70 Control Group *n* = 70	IG: 81 (7) CG: 82 (5)	70	70	64	63	Modified ITT	Discontinuation of the assigned nutritional intervention (product dislike) IG: 6 participants CG: 7 participants	EWGSOP	Gait speed	25-(OH)-vitamin D Albumin ALAT ASAT Calcium Creatinine CRP Total cholesterol
Rondanelli et al. (2022)	RCT 8 weeks Intervention: exercise + oral dose of omega-3 fatty acid, leucine, and probiotic LPPS23 (OLEP) Control: isocaloric formula	Patients with sarcopenia (≥ 55 years) 60 participants OLEP *n* = 30 Control Group *n* = 30	OLEP 78.84 (5.80) 80.50 (3.74)	30	30	22	28	ITT	Lost to follow-up OLEP: 8 CG: 2	EWGSOP2	ALM	ALAT ASAT GGT Fasting blood glucose CRP
Takeuchi et al. (2019)	RCT 8 weeks Intervention: Exercise and amino acids and vitamin D supplementation Control: Isocaloric control	Post-acute older adults with sarcopenia and mobility limitations (≥ 65 years) 68 participants Intervention group *n* = 35 Control Group *n* = 33	IG: 78.8 (5.1)[4] CG: 80.9 (6.3)[5]	35	33	35	33	ITT	Lost to follow-up Reasons IG • Early discharge *n* = 1 • Consent withdrawn *n* = 2 CG • Early discharge *n* = 1 Consent withdrawn *n* = 1	AWGS	The change in physical function measured by FIM	Albumin

(Continues)

TABLE 1 | (Continued)

References	Study description	Population and sample size included in the analysis	Population characteristics: mean age (SD)	Randomised sample size (*n*)		Sample size analysed (*n*)		Analysis strategy	Reasons of participants' drop out	Criteria for assessing sarcopenia	Primary outcome	Biomarkers
				IG	CG	IG	CG					
Yang et al. (2023)	RCT 12 weeks Intervention: exercise + HMB group Control: placebo group	Patients with sarcopenia (≥ 60 years) 34 participants Women: 22 (64.71%) Intervention group $n = 18$ Control group $n = 16$	72.89 (7.02) 71.44 (5.22)	18	16	18	16	ITT	IG: change of residence $n = 1$ CG: change of residence $n = 1$, travel $n = 1$, refusal of venous blood collection repeatedly $n = 1$	AWGS (2019)	HG strength	Fasting blood glucose HDL cholesterol IL-18 LDL cholesterol Total cholesterol Triglycerides TWEAK
Other intervention												
Soares Mendes Damasceno et al. (2019)	Randomised study Intervention: acupuncture (sarcopenia) Controls • No acupuncture (sarcopenia) • No acupuncture (no sarcopenia)	Older people (≥ 60 years) 53 participants	IG: 72 (7.9) CG • 65.5 (3.3) • 67.4 (7.7)	N/A	N/A	11	4 12	PP	Sample loss	EWGSOP	Improvement of muscle strength and function (bioimpedance, dynamometry and test up and go)	IL-6 IL-10 TNF-α

Abbreviations: 25-(OH)-vitamin D, 25-(OH)-vitamin D; AHN, apnea hypopnea index (n/h); ALAT, alanine aminotransferase; ALM, appendicular lean mass; ASAT, aspartate aminotransferase; ASM, appendicular skeletal muscle mass; AWGS, Asian Working Group for Sarcopenia; BFM, body fat mass; BMD, bone mineral density; CAF, C-terminal agrin fragment; CC, calf circumferences; CG, control group; CRP, C-reactive protein; CTx, C-terminal telopeptide; DXA, dual-energy X-ray absorptiometry; E + *R*, endurance training followed by resistance training; eAA, essential amino acids; eAAM, essential amino acids plus melatonin; EWGSOP, European Working Group on Sarcopenia in Older People; FIM, functional independence measure; GDF-15, growth differentiation factor 15; GDF-8, growth differentiation factor 8 (myostatin); GGT, gamma-glutamyl transferase; GH, growth hormone; GS, gait speed; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; HG, hand grip; HMB, beta-hydroxy-beta-methylbutyrate; IG, intervention group; IGF-1, insulin-like growth factor 1; IL, interleukin; IL-1 RA, interleukin-1 receptor antagonist; ISI, Insomnia Severity Index; ITT, intention to treat; IWGS, International Working Group on Sarcopenia; LB power, lower body power; LDL, low-density lipoprotein; LPPS23, *Lactobacillus paracasei* PS23; M, melatonin; MVIC, maximum voluntary isomeric contraction; Myf5, myogenic factor 5; Myog, myogenin; N/A, not applicable; N1, sleep staging 1; NfL, neurofilament light chain; NMJ, neuromuscular junction; P, isocaloric placebo; P1NP, procollagen type 1 N-terminal propeptide; Pax3, paired box 3; Pax7, paired box 7; PBF, percent body fat; PP, per protocol; PT, peak torque; PTH, parathyroid hormone; *R* + E, resistance training followed by endurance training; RCT, randomised controlled trial; RMVIC, relative maximum voluntary isomeric contraction; RSMI, relative skeletal mass index; SD, standard deviation; SMI, skeletal muscle index; SMM, skeletal muscle mass; SPPB, short physical performance battery; sTNFR, soluble tumour necrosis factor receptor; TNF-α, tumour necrosis factor α; TWEAK, TNF-related weak inducer of apoptosis; UB power, upper body power; VFA, visceral fat area; VO2max, maximum rate of oxygen consumption.

3.2 | Frequency of Biomarkers Reporting

A total of 47 different BBMs were measured across the 21 RCTs with a median of 4 BBMs per study (Table 2). The most frequently reported BBMs were c-reactive protein (CRP) (8/21 RCTs, 38.1%), interleukin-6 (IL-6) (7/21 RCTs, 33.3%), tumour necrosis factor α (TNF-α) (6/21 RCTs, 28.6%), 25-(OH)-vitamin D (6/21 RCTs, 28.6%), insulin growth factor-1 (IGF-1) (5/21 RCTs, 23.8%), albumin (5/21 RCTs, 23.8%), fasting blood glucose (4/21 RCTs, 19.0%) and finally, alanine aminotransferase (ALAT), total cholesterol, creatinine and IL-10 (3/21 RCTs each, 14.3%). Aminotransferases (ASAT), serum calcium, follistatin, growth differentiation factor-15 (GDF-15), GDF-8, high density lipoproteins (HDL), low density lipoproteins (LDL), IL-1 receptor antagonist (IL-1RA), IL-8, insulin, triglycerides and C-terminal agrin fragment (CAF) were all assessed in 2 RCTs (9.5%). Within the different RCTs, the biomarkers were measured with different methods and automats leading to biomarker levels expressed in different units and with different degrees of sensitivity, specificity and accuracy.

Only two out of the 21 RCTs (9.5%) (Rezaei et al. 2024; Seo et al. 2021) measured one of the muscle-specific biomarkers recommended by the ESCEO guidelines (Ladang et al. 2023), that is, GDF-15, GDF-8 and follistatin. None of the other recommended muscle-specific biomarkers were measured in any of the included RCTs (Table 3).

3.3 | Impact of Intervention on BBMs Concentration

The impact of each RCT interventions on BBMs concentration is presented in Table 2.

3.3.1 | Muscle-Specific BBMs Recommended by ESCEO Guidelines (Follistatin, GDF-8, GDF-15)

From the list of muscle-specific BBMs recommended by ESCEO guidelines, only follistatin, GDF-8 and GDF-15 were currently measured in RCTs aiming at the management of sarcopenia, each of them being reported by 2 RCTs using exercises as intervention.

Using a meta-analysis model, none of these three BBMs were impacted by the interventions (Figure 2a–c).

3.3.2 | Non-Muscle-Specific BBMs Recommended by ESCEO Guidelines (CRP, IL-6, TNF-α, IGF-1)

Among the non-muscle-specific BBMs recommended by ESCEO guidelines Ladang et al. 2023, CRP was measured in 8 RCTs, IL-6 in 7 RCTs, TNF-α in 6 RCTs and IGF-1 in 5 RCTs. No significant effect of intervention was found on IL-6, CRP and TNFα (Figure 3a–c).

A moderate significant effect of RCTs interventions was observed on IGF-1 concentration, with a SMD of 0.46 (95% CI = 0.04; 0.88, $p = 0.0326$) (Figure 3d). The model was associated with significant heterogeneity ($I^2 = 70.3\%$, Q test p-value = 0.0092). The leave-one out analysis of IGF-1 showed that the omission of the study of de Sa Souza et al. (2022) (de Sa Souza et al. 2022) increased the general SMD (SMD = 0.56 vs. SMD = 0.46) (Figure S4). Subgroup analyses did not reveal any difference regarding the type of interventions used on IGF-1 concentration (Figure S5). No publication bias was associated with the model (Figure S6).

3.3.3 | Muscle-Specific BBMs Not Recommended by ESCEO Guidelines (CAF)

Besides the list of muscle-specific BBMs recommended within ESCEO guidelines (Ladang et al. 2023), one other muscle-specific BBM was identified in the panel of RCTs, namely CAF ($n = 2$). This BBM was not impacted by the interventions proposed (Figure 4).

3.3.4 | Non-muscle-specific BBMs not recommended by ESCEO guidelines (ALAT, albumin, ASAT, calcium, cholesterol, creatinine, fasting blood glucose, HDL, IL-1RA, IL-8, IL-10, insulin, LDL, triglycerides, 25-(OH)-Vitamin D)

25-(OH)-Vitamin D concentration was measured in 6 RCTs; 3 of them were nutritional interventions (Cramer et al. 2016; Hill et al. 2019; Nasimi et al. 2021) and the 3 others had combined interventions (Bo et al. 2019; Chiang et al. 2021; Rondanelli et al. 2020). A general augmentation of 25-(OH)-Vitamin D was observed in the RCTs, but due to the supplementation of participants in vitamin D during RCTs, this BBM was not studied in a meta-analytical model. The same phenomenon was observed for calcium, reported in 2 RCTs.

Albumin was quantified in 5 RCTs, 2 with nutritional interventions (Bo et al. 2019; Yoshimura et al. 2019) and 3 others with combined interventions (Rondanelli et al. 2020; Rondanelli et al. 2018; Takeuchi et al. 2019), with contradictory results within RCTs. Similarly, fasting blood glucose was measured in 4 combined interventions RCTs with contradictory results concerning fasting blood glucose concentrations.

Cholesterol, creatinine and ALAT concentrations were assessed in 3 RCTs. For cholesterol, 2 RCTs involved combined interventions (Rondanelli et al. 2020; Yang et al. 2023) and 1 involved a nutritional intervention (Bo et al. 2019) while all the 3 RCTs in which ALAT and creatinine were measured were combined intervention studies (Chiang et al. 2021; Rondanelli et al. 2020, 2022). Cholesterol and ALAT concentrations generally increased following the interventions whereas results were inconsistent across the RCTs for creatinine.

HDL, LDL, and triglycerides were assessed in 2 RCTs; one was a nutritional intervention (Bo et al. 2019) and the other was a combined intervention (Yang et al. 2023). LDL concentration was generally increased after the interventions, while the results were contradictory within the RCTs for HDL and triglycerides concentrations.

IL-1Ra, IL-8, IL-10, insulin, ASAT were evaluated in 2 RCTs. Results within RCTs were contradictory for ASAT, IL-10, and

TABLE 2 | Table of biomarkers studied in the included articles and the impact of the RCTs interventions on the concentrations of biomarkers.

Biomarkers	Frequency of blood-based biomarker reporting	References	Biomarker evolution per clinical trial arm	
			CG	IG
Muscle-specific BBM recommended by ESCEO				
Follistatin	2 (9.5%)	Seo et al. 2021;	↔	↑
		Rezaei et al. 2024	↔	↑
GDF-8 (myostatin)	2 (9.5%)	Seo et al. 2021;	↔	↔
		Rezaei et al. 2024	↔	↓
GDF-15	2 (9.5%)	Seo et al. 2021;	↔	↔
		Rezaei et al. 2024	↑	↑
Non-muscle-specific BBM recommended by ESCEO				
Cortisol	1 (4.8%)	de Sa Souza et al. 2022	↔	↔
CRP	8 (38.1%)	Chen et al. 2018; Rondanelli	↑	↓
		et al. 2018; Bo et al. 2019;	↔	↔
		Liberman et al. 2019;	↔	↔
		Rondanelli et al. 2020;	↑	↔
		Chiang et al. 2021;	↔	↓
		Nasimi et al. 2021;	↔	Milk: ↔; Soy milk: ↔
		Rondanelli et al. 2022	↑	↔
			↔	↓
IGF-1	5 (23.8%)	Bo et al. 2019; Hill	↔	↑
		et al. 2019; Chiang	↔	↑
		et al. 2021; Nasimi	↔	Milk: ↔; Soy milk: ↔
		et al. 2021; de Sa	↔	↑
		Souza et al. 2022	↔	↔
IL-6	7 (33.3%)	Chen et al. 2018; Bo	↔	↔
		et al. 2019; Liberman	↔	↔
		et al. 2019; Soares Mendes	↔	↔
		Damasceno et al. 2019;	G2: ↔; G3: ↔	G1: ↔
		da Cruz Alves et al. 2022;	↔	↔
		de Sa Souza et al. 2022;	↔	↔
		Yuenyongchaiwat et al. 2023	No SP: ↔; Cont: ↔	↔
Testosterone	1 (4.8%)	de Sa Souza et al. 2022	↔	↔
TNF-α	6 (28.6%)	Chen et al. 2018; Bo	↔	↔
		et al. 2019; Soares Mendes	↔	↔
		Damasceno et al. 2019 ;	G2: ↔; G3: ↔	G1: ↔
		da Cruz Alves et al. 2022;	↔	↔
		de Sa Souza et al. 2022;	↔	↔
		Yuenyongchaiwat et al. 2023	No SP: ↔; Cont: ↔	↓
Muscle-specific BBM not recommended by ESCEO				
Activin A	1 (4.8%)	Seo et al. 2021	↔	↔
CAF	2 (9.5%)	Monti et al. 2023;	↑	↔
		Rezaei et al. 2024	↔	↑
Myf5	1 (4.8%)	Moghadam et al. 2020	↔	*R* + E ↑; E + *R*↑
Myog	1 (4.8%)	Moghadam et al. 2020	↔	*R* + E ↑; E + *R*↑
Pax3	1 (4.8%)	Moghadam et al. 2020	↔	*R* + E ↑; E + *R*↑
Pax7	1 (4.8%)	Moghadam et al. 2020	↔	*R* + E ↑; E + *R*↑

(Continues)

TABLE 2 | (Continued)

Biomarkers	Frequency of blood-based biomarker reporting	References	Biomarker evolution per clinical trial arm	
			CG	IG
Non-muscle-specific BBM not recommended by ESCEO				
25-(OH)-vitamin D	6 (28.6%)	Cramer et al. 2016; Bo et al. 2019; Hill et al. 2019; Rondanelli et al. 2020; Chiang et al. 2021; Nasimi et al. 2021	↑ ↓ ↔ ↔ ↔ ↔	↑ ↑ ↑ ↑ Milk: ↔; Soy milk: ↔ ↑
ALAT	3 (14.3%)	Rondanelli et al. 2020; Chiang et al. 2021; Rondanelli et al. 2022	N/R ↔ ↔	N/R Milk: ↔; Soy milk: ↔ ↑
Albumin	5 (23.8%)	Rondanelli et al. 2018; Bo et al. 2019; Takeuchi et al. 2019; Yoshimura et al. 2019; Rondanelli et al. 2020	↔ ↓ ↔ ↔ ↓	M: ↓; eAAM: ↓ ↓ ↔ ↔ ↑
ASAT	2 (9.5%)	Rondanelli et al. 2020; Rondanelli et al. 2022	N/R ↔	N/R ↔
Calcium	2 (9.5%)	Hill et al. 2019; Rondanelli et al. 2020	↔ N/R	↑ N/R
Creatinine	3 (14.3%)	Rondanelli et al. 2020; Chiang et al. 2021; Rondanelli et al. 2022	↔ ↔ ↔	↑ Milk: ↔; Soy milk: ↔ ↔
CTx	1 (4.8%)	Hill et al. 2019	↔	↓
Fasting blood glucose	3 (14.3%)	Rondanelli et al. 2022; Chiang et al. 2021; Yang et al. 2023	↔ ↔ ↔	↔ Milk: ↔; Soy milk: ↔ ↔
GGT	1 (4.8%)	Rondanelli et al. 2022	↔	↔
GH	1 (4.8%)	de Sa Souza et al. 2022	↔	↔
HbA1c	1 (4.8%)	Chiang et al. 2021	↔	Milk: ↔; Soy milk: ↔
HDL	2 (9.5%)	Bo et al. 2019; Yang et al. 2023	↔ ↔	↔ ↔
IL-10	3 (14.3%)	Soares Mendes Damasceno et al. 2019; da Cruz Alves et al. 2022; de Sa Souza et al. 2022	G2: ↓; G3: ↔ ↔ ↔	G1: ↔ ↔ ↑
IL-1β	1 (4.8%)	da Cruz Alves et al. 2022	↔	↔
IL-1 RA	2 (9.5%)	Liberman et al.2019; de Sa Souza et al. 2022	↔ ↔	↔ ↑
IL-2	1 (4.8%)	Bo et al. 2019	↑	↔
IL-8	2 (9.5%)	Liberman et al. 2019; da Cruz Alves et al. 2022	↔ ↔	↔ ↔
IL-18	1 (4.8%)	Yang et al. 2023	↔	↓
Insulin	2 (9.5%)	Chiang et al. 2021; Nasimi et al. 2021	↔ ↔	Milk: ↔; Soy milk: ↔ ↔

(Continues)

TABLE 2 | (Continued)

Biomarkers	Frequency of blood-based biomarker reporting	References	Biomarker evolution per clinical trial arm	
			CG	IG
LDL	2 (9.5%)	Bo et al. 2019; Yang et al. 2023	↔ ↔	↔ ↔
Malondialdehyde	1 (4.8%)	Nasimi et al. 2021	↓	↓
NfL	1 (4.8%)	Monti et al. 2023	↔	↔
Osteocalcin	1 (4.8%)	Hill et al. 2019	↔	↔
P1NP	1 (4.8%)	Hill et al. 2019	↔	↔
Prealbumin	1 (4.8%)	Chiang et al. 2021	↓	Milk: ↓; Soy milk: ↑
PTH	1 (4.8%)	Hill et al. 2019	↔	↔
sTNFR	1 (4.8%)	Liberman et al. 2019	↔	↔
Total cholesterol	3 (14.3%)	Bo et al. 2019; Rondanelli et al. 2020; Yang et al. 2023	↔ ↔ ↔	↑ ↔ ↔
Total protein	1 (4.8%)	Bo et al. 2019	↔	↔
Triglycerides	2 (9.5%)	Bo et al. 2019; Yang et al. 2023	↔ ↔	↓ ↔
TWEAK	1 (4.8%)	Yang et al. 2023	↔	↓
Vitamin E	1 (4.8%)	Bo et al. 2019	↑	↑

Note: ↑ Statistically significant increase in the study arm; ↓ statistically significant decrease in the study arm; ↔ non-statistically significant effect within study arm.
Abbreviations: 25-(OH)-vitamin D, 25-hydroxy vitamin D; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CAF, cancer-associated fibroblast; Cont, control; CRP, C-reactive protein; CTx, C-terminal telopeptide; E + *R*, endurance training followed by resistance training; G1, group 1; G2, group 2; G3, group 3; GDF-15, growth differentiation factor 15; GDF-8, growth differentiation factor 8 (myostatin); GGT, gamma-glutamyl transferase; GH, growth hormone; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; IL, interleukin; IL-1 RA, interleukin-1 receptor antagonist; LD, low-density lipoprotein; Myf5, myogenic factor 5; Myog, myogenin; N/R, not reported; NfL, neurofilament light chain; No SP, no sarcopenia; P1NP, procollagen type 1 N-terminal propeptide; Pax, paired box; PTH, parathyroid hormone; *R* + E, resistance training followed by endurance training; sTNFR, soluble tumour necrosis factor receptor; TNF-α, tumour necrosis factor α; TWEAK, TNF-related weak inducer of apoptosis.

IL-1Ra, while insulin concentration was generally increased and IL-8 concentration was decreased after the interventions.

3.4 | Evolution of BBMs in RCTs That Demonstrated a Significant Improvement of Key Measures of Sarcopenia

Among the 21 RCTs included in this meta-analysis, 14 reported significant improvements in muscle mass and/or muscle strength following intervention. Looking specifically at this panel of studies, CRP and 25-(OH)-vitamin D were significantly impacted in 3 of these RCTs. Albumin and follistatin concentrations were impacted in two of the latter RCTs and GDF-8, GDF-15, CAF, TNF-Related Weak Inducer of Apoptosis (TWEAK), myogenic factor (Myf) 5, myogenin (Myog), paired box (Pax) 3, Pax 7, IL-1RA, creatinine, IL-2, LDL cholesterol, vitamin E and IGF-1 in one of them. The detailed assessment of BBMs evolution in studies that demonstrated a significant improvement in key measures of sarcopenia is available in Table 3.

A meta-analysis including only the RCTs demonstrating a significant improvement in muscle mass and/or muscle strength was performed for BBMs recommended by ESCEO (Ladang et al. 2023); (Figures S7 and S8). Meta-analysis models were performed for IL-6, CRP, TNF-α and IGF-1, and all failed demonstrating any significant effect of interventions specific to sarcopenia.

4 | Discussion

Our systematic review identified 58 studies aiming at the management of sarcopenia. The proposed interventions in these RCTs were mainly exercise-based interventions and nutrition-based interventions. Among these 58 studies, only 21 RCTs reported a measurement of BBM with no studies evaluating new chemical entities for sarcopenia treatment. Among the 21 RCTs, 47 distinct BBMs were measured at both baseline and follow-up, with a median of four biomarkers assessed per study. The important number of different BBMs identified in this review confirms the heterogeneity among sarcopenia outcomes highlighted by the paper of Van Heden et al. 2025 in which 253 different outcomes were identified for the diagnosis of sarcopenia. This systematic review reinforces the need for a harmonised Core Outcome Set for sarcopenia.

TABLE 3 | Selection of RCTs that showed an improvement on one of the two main outcomes of sarcopenia (muscle mass, muscle strength) according to the EWGSOP2 and the GLIS, and analysis of their impact on BBM concentrations.

Study reference	Key criteria of sarcopenia in RCTs' interventions (p-value)		Biomarker evolution (intervention group)	Biomarker evolution (control group)	Inter-group biomarker evolution
Bo et al. (2019)	Muscle strength Muscle mass	Handgrip strength (kg), $p=0.009$ Relative skeletal muscle index, $p=0.040$ Fat mass (kg), $p=0.428$ Appendicular muscle mass (kg), $p=0.050$	25-(OH)-vitamin D, $p=0.031$ Albumin, $p=0.001$ HDL cholesterol, $p=0.129$ IL-2, $p=0.655$ LDL cholesterol, $p=0.269$ Triglycerides, $p=0.021$ Total cholesterol, $p=0.027$ Total protein, $p=0.747$ Vitamin E, $p<0.001$ CRP, $p=0.555$ IL-6, $p=0.076$ IGF-1, $p=0.010$ TNF-α, $p=0.562$	25-(OH)-vitamin D, $p<0.001$ Albumin, $p=0.006$ HDL cholesterol, $p=0.469$ IL-2, $p=0.016$ LDL cholesterol, $p=0.077$ Triglycerides, $p=0.847$ Total cholesterol, $p=0.978$ Total protein, $p=0.563$ Vitamin E, $p=0.005$ CRP, $p=0.402$ IL-6, $p=0.698$ IGF-1, $p=0.733$ TNF-α, $p=0.175$	**25-(OH)-vitamin D,** ↑, $p<0.001$ Albumin, NS HDL cholesterol, NS **IL-2**, ↓, $p=0.038$ **LDL cholesterol,** ↑, $p=0.019$ Triglycerides, NS Total cholesterol, NS Total protein, NS **Vitamin E,** ↑, $p=0.001$ CRP, NS IL-6, NS **IGF-1,** ↑, $p=0.023$ TNF-α, NS
Chen et al. (2018)	Muscle strength Muscle mass	Left handgrip, $p<0.0001$ Right handgrip, $p<0.0001$ Back strength, $p<0.0001$ Skeletal muscle mass, $p=0.001$ Body fat mass, N/A Visceral fat area, $p=0.011$ Appendicular skeletal muscle mass, $p=0.000$ Sarcopenia index (ASM/m^2), $p=0.000$	CRP, ↓, $p<0.05$ IL-6, NS TNF-α, NS	CRP, ↑, $p<0.05$ IL-6, NS TNF-α, NS	**CRP**, ↓, $p<0.0001$ IL-6, NS TNF-α, NS

(Continues)

TABLE 3 | (Continued)

Study reference	Key criteria of sarcopenia in RCTs' interventions (p-value)		Biomarker evolution (intervention group)	Biomarker evolution (control group)	Inter-group biomarker evolution
Cramer et al. (2016)	Muscle strength Muscle mass	Grip strength, $p<0$ 0.05 Leg strength, $p<0$ 0.05 Muscle quality, $p<0$ 0.05 Tested leg muscle mass, NS	25-(OH)-vitamin D, $p<0.0001$	25-(OH)-vitamin D, $p<0.05$	**25-(OH)-vitamin D**, ↑, $p=0.03$
Da Cruz Alves et al. (2022)	Muscle strength Muscle mass	Handgrip Strength, $p=0.843$ Peak Torque, $p=0.003$ Lower Limb Muscle Power, $p=0.635$ Skeletal Muscle Mass Index, $p<0.001$ Quadriceps Cross-Sectional Area, $p=0.23$ Muscle Quality, $p=0.004$	IL-6, $p=0.11$ TNF-α, $p=0.58$ IL-1β, $p=0.94$ IL-8, $p=0.77$ IL-10, $p=0.94$	IL-6, $p=0.36$ TNF-α, $p=0.85$ IL-1β, $p=0.45$ IL-8, $p=0.29$ IL-10, $p=0.21$	IL-6, NS TNF-α, NS IL-1β, NS IL-8, NS IL-10, NS
de Sa Souza et al. (2022)	Muscle strength Muscle mass	Handgrip strength values, $p<0.05$ Peak torque, $p<0.001$ Appendicular muscle index, N/A	GH, NS IL-1 RA, $p<0.05$ IL-10, $p<0.05$ Testosterone, NS Cortisol, NS IGF-1, NS IL-6, NS TNF-α, NS	GH, NS IL-1 RA, NS IL-10, NS Testosterone, NS Cortisol, NS IGF-1, NS IL-6, NS TNF-α, NS	GH, NS **IL-1 RA**, ↑, $p<0.05$ IL-10, NS Testosterone, NS Cortisol, NS IGF-1, NS IL-6, NS TNF-α, NS

(Continues)

TABLE 3 | (Continued)

Study reference	Key criteria of sarcopenia in RCTs' interventions (p-value)		Biomarker evolution (intervention group)	Biomarker evolution (control group)	Inter-group biomarker evolution
Moghadam et al. (2020)	Muscle strength Muscle mass	Upper body power, $p<0.05$ Lower body power, $p<0.05$ Skeletal muscle mass, $p<0.05$ Percent body fat, p 0.05	Myf5, $p<0.05$ Myog, $p<0.05$ Pax3, $p<0.05$ Pax7, $p<0.05$	Myf5, NS Myog, NS Pax3, NS Pax7, NS	**Myf5**, ↑, p (E + *R* vs. Cont.) < 0.05 **Myog**, ↑, $p<0.05$ **Pax3**, ↑, $p<0.05$ **Pax7**, ↑, $p<0.05$
Rezaei et al. (2024)	Muscle strength Muscle mass	Handgrip strength test, $p=0.035$ Chair stand test, $p=0.016$ Appendicular skeletal muscle (m/h^2), $p=0.527$ Calf circumference, $p=0.192$ Body fat percentage, $p=0.089$ Skeletal muscle mass/height^2 (Kg/m^2), $p=0.527$	GDF-8, $p<0.001$ Follistatin, $p<0.001$ GDF-15, $p=0.001$ CAF, $p=0.001$	GDF-8, $p=0.983$ Follistatin, $p=0.689$ GDF-15, $p=0.035$ CAF, $p=0.540$	**GDF-8**, ↓, $p=0.002$ **Follistatin**, ↑, $p=0.001$ **GDF-15**, ↑, $p=0.049$ **CAF**, ↑, $p=0.031$

(Continues)

TABLE 3 | (Continued)

Study reference	Key criteria of sarcopenia in RCTs' interventions (p-value)		Biomarker evolution (intervention group)	Biomarker evolution (control group)	Inter-group biomarker evolution
Rondanelli et al. (2018)	Muscle strength Muscle mass	Handgrip strength (P, $p=1.0$; M, $p=0.92$; eAA, $p=0.82$; eAAM, $p=0.94$) Fat free mass (P, $p=0.58$; M, $p=0.11$; eAA, $p<0.01$; eAAM, $p<0.05$) Gynoid fat mass (P, $p=0.99$; M, $p<0.05$; eAA, $p=0.11$; eAAM, $p=0.66$) Android fat mass (P, $p=0.3$; M, $p=0.16$; eAA, $p<0.01$; eAAM, $p=0.97$) Skeletal muscle index, N/A	Albumin (M, $p<0.001$; eAA, $p=0.29$; eAAM, $p<0.05$) CRP (M, $p=0.33$; eAA, $p=0.22$; eAAM, $p=0.35$)	Albumin, $p=0.19$ CRP, $p=0.6$	**Albumin**, ↓, $p<0.05$ CRP, NS
Rondanelli et al. (2020)	Muscle strength Muscle mass	Handgrip strength, $p<0.001$ Chair stand test, $p<0.001$ Appendicular muscle mass, $p=0.011$ Skeletal muscle mass index, $p=0.023$	25-(OH)-vitamin D, ↑, $p<0.05$ Albumin, ↑, $p<0.05$ ALAT, $p<0.05$ ASAT, $p<0.05$ Calcium, $p<0.05$ Creatinine, $p<0.05$ Total cholesterol, NS CRP, $p<0.05$	25-(OH)-vitamin D, NS Albumin, ↓, $p<0.05$ ALAT, NS ASAT, NS Calcium, NS Creatinine, NS Total cholesterol, NS CRP, NS	**25-(OH)-vitamin D**, ↑, $p<0.001$ **Albumin**, $p<0.001$ ALAT, N/A ASAT, N/A Calcium, N/A **Creatinine**, ↑, $p=0.031$ Total cholesterol, NS **CRP**, ↓, $p<0.001$

(Continues)

TABLE 3 | (Continued)

Study reference	Key criteria of sarcopenia in RCTs' interventions (*p*-value)		Biomarker evolution (intervention group)	Biomarker evolution (control group)	Inter-group biomarker evolution
Rondanelli et al. (2022)	Muscle strength Muscle mass	Handgrip (kg), $p < 0.001$ ALM (g), $p = 0.245$ ALM/h^2, $p < 0.05$ SMI, $p = 0.208$ Waist Circumference (cm), $p < 0.001$ Fat mass (g), $p < 0.001$ Visceral adipose tissue (g), $p < 0.001$	ALAT, $p < 0.001$ ASAT, NS GGT, NS FBG, NS CRP, $p < 0.001$	ALAT, NS ASAT, NS GGT, NS FBG, NS CRP, NS	ALAT, NS ASAT, NS GGT, NS FBG, NS **CRP**, ↓, $p < 0.001$
Seo et al. (2021)	Muscle strength Muscle mass	Grip strength, $p < 0.001$ Waist circumference, NS Hip circumference, NS Waist-hip ratio, $p = 0.014$ Fat-free mass, NS Body fat percentage, NS Fat mass, NS Appendicular skeletal muscle mass, NS Mid-Thigh muscle quality, $p < 0.05$	Activin A, NS GDF-15, NS GDF-8, NS Follistatin, $p < 0.05$	Activin A, NS GDF-15, NS GDF-8, NS Follistatin, NS	Activin A, NS GDF-15, NS GDF-8, NS **Follistatin**, ↑, $p < 0.05$
Takeuchi et al. (2019)	Muscle strength Muscle mass	Handgrip strength, $p = 0.041$ Arm circumference, $p = 0.06$ Calf circumference, $p = 0.033$	Albumin, N/A	Albumin, N/A	**Albumin**, ↑, $p = 0.013$

(Continues)

TABLE 3 | (Continued)

Study reference	Key criteria of sarcopenia in RCTs' interventions (p-value)		Biomarker evolution (intervention group)	Biomarker evolution (control group)	Inter-group biomarker evolution
Yang et al. (2023)	Muscle strength Muscle mass	Handgrip strength test, $p < 0.001$ Five-time chair stand test, $p = 0.001$ Skeletal muscle mass (kg), $p = 0.935$ Skeletal muscle mass index (kg/m^2), $p = 0.814$ Fat-free mass (kg), $p = 0.619$ Soft lean mass (kg), $p = 0.515$ FFM right arm (kg), $p = 0.561$ Muscle quality, $p = 0.001$	FBG, N/A HDL cholesterol, N/A IL-18, N/A LDL cholesterol, N/A Total cholesterol, N/A Triglycerides, N/A TWEAK, N/A	FBG, N/A HDL cholesterol, N/A IL-18, N/A LDL cholesterol, N/A Total cholesterol, N/A Triglycerides, N/A TWEAK, N/A	FBG, NS HDL cholesterol, NS IL-18, NS LDL cholesterol, NS Total cholesterol, NS Triglycerides, NS **TWEAK**, ↓, $p = 0.041$
Yoshimura et al. (2019)	Muscle strength Muscle mass	Handgrip strength, $p = 0.002$ Skeletal muscle index, $p = 0.041$ Calf circumference, N/A	Albumin, N/A	Albumin, N/A	Albumin, NS

Note: ↓, concentration significantly decreased; ↑, concentration significantly increased. BBM-related with significant values are written in bold in the table.

Abbreviations: 25-(OH)-vitamin D, 25-hydroxy vitamin D; ALAT, alanine aminotransferase; ALM, appendicular lean mass; ASAT, aspartate aminotransferase; ASM, appendicular skeletal muscle mass; CAF, cancer-associated fibroblast; Cont, control; CRP, C-reactive protein; CTx, C-terminal telopeptide; E+*R*, endurance training followed by resistance training; eAA, essential amino acid; eAAM, essential amino acid and melatonin; FBG, fasting blood glucose; FFM, fat-free mass index; GDF-15, growth differentiation factor 15; GDF-8, growth differentiation factor 8 (myostatin); GGT, gamma-glutamyl transferase; GH, growth hormone; h, height; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; IL, interleukin; IL-1 RA, interleukin-1 receptor antagonist; interv., intervention; LD, low-density lipoprotein; M, melatonin; Myf5, myogenic factor 5; Myog, myogenin; N/A, not available; NfL, neurofilament light chain; NS, not significant; P, placebo; P1NP, procollagen type 1 N-terminal propeptide; Pax, paired box; PTH, parathyroid hormone; SMI, skeletal muscle index; SPPB, short physical performance battery; sTNFR, soluble tumour necrosis factor receptor; TNF-α, tumour necrosis factor α; TUG test, time up and go test; TWEAK, TNF-related weak inducer of apoptosis.

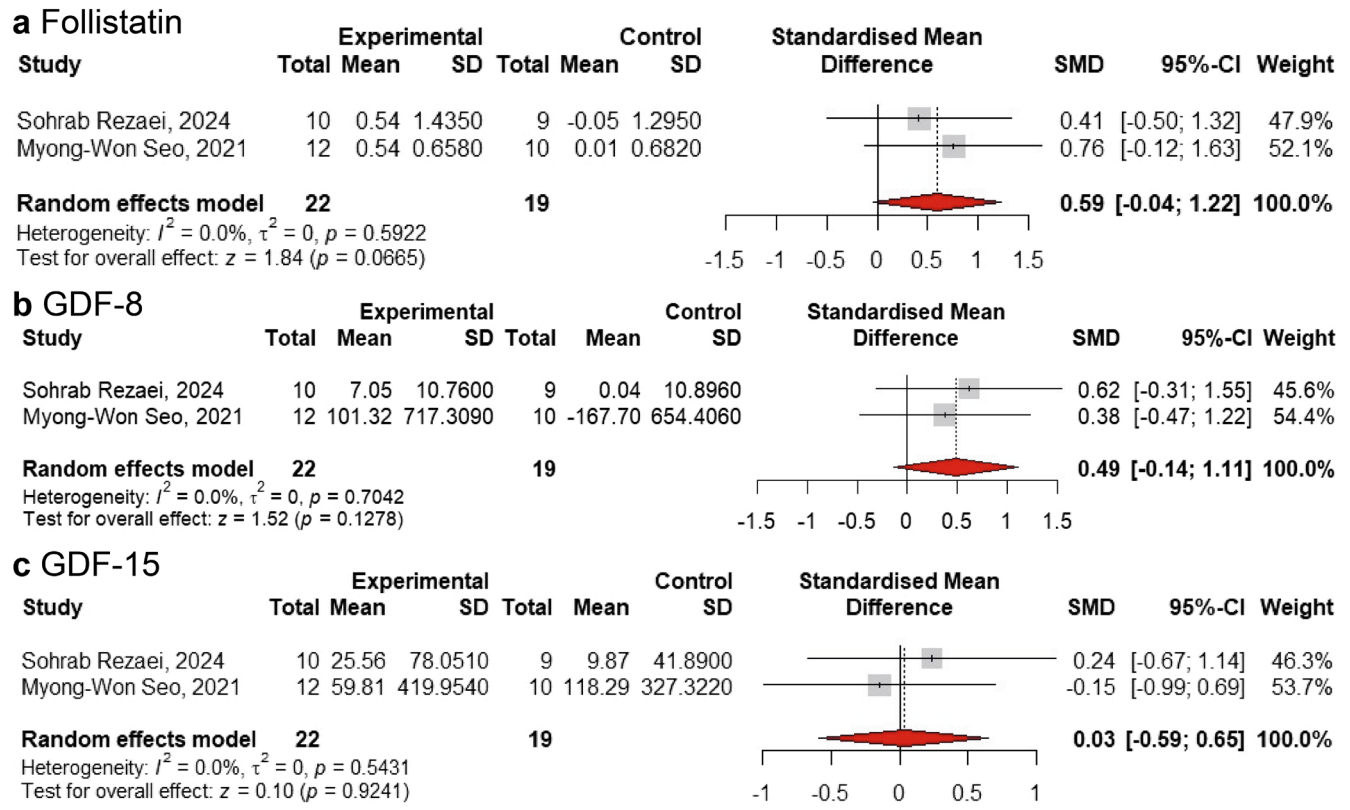

FIGURE 2 | General Forest Plots of the muscle-specific BBM recommended by the ESCEO. Forest plot of (a) follistatin; (b) GDF-8, Growth Differentiation Factor 8; (c) GDF-15, Growth Differentiation Factor 15.

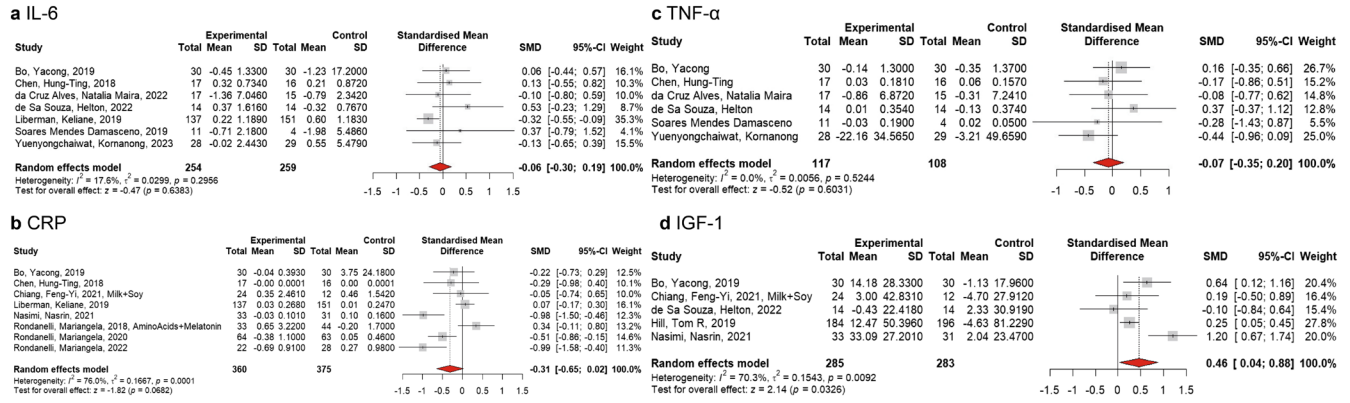

FIGURE 3 | General Forest Plots of the non-muscle-specific BBM recommended by the ESCEO. Forest plot of (a) IL-6, interleukin 6; (b) CRP, C-reactive protein; (c) TNF-α, tumour necrosis factor α; (d) IGF-1, insulin-like growth factor 1.

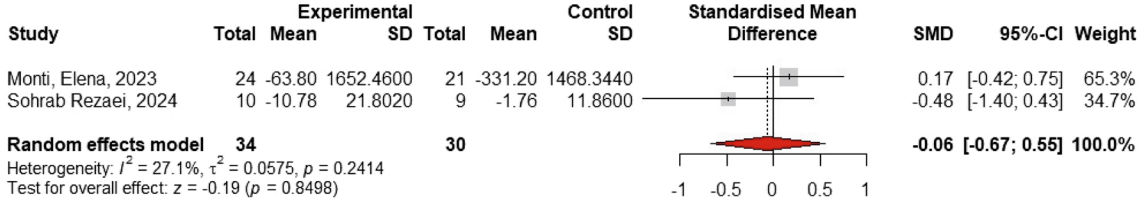

FIGURE 4 | General Forest Plot of the muscle-specific BBM not recommended by the ESCEO. Forest plot of CAF, C-terminal agrin fragment.

In addition to the marked heterogeneity in the numbers of BBMs identified, an important heterogeneity was also observed in the biological relevance to muscle physiology of the BBMs. Only 7 of the 21 trials (33.3%) included at least one muscle-specific biomarker. For instance, creatinine levels were assessed by Rondanelli et al. (2020) and Chiang et al. (2021), while CAF

was reported in the studies of Monti et al. (2023) and Rezaei et al. (2024). Follistatin, GDF-8, and GDF-15 were each investigated in studies by Rezaei et al. (2024) and Seo et al. (2021). Additionally, Hill et al. (2019) assessed PINP, and Moghadam et al. (2020) examined muscle markers such as Myf5, Myog, Pax3 and Pax7. The remaining trials (66.7%) focused exclusively on non-muscle-specific biomarkers.

Despite the wide array of BBMs assessed across studies, none of the included studies align with the recommendations recently issued by the CARES SPRL (Ladang et al. 2023). These recommendations propose a minimum panel of biomarkers to standardise outcome reporting in sarcopenia trials, distinguishing between muscle-specific BBMs (e.g., myostatin–follistatin, BDNF, PIIINP and the Sarcopenia Index) and markers of systemic pathophysiological processes (e.g., IGF-I, DHEA, cortisol, CRP, IL-6 and TNF-α) (Ladang et al. 2023; Woodman and Mangoni 2023). The BBMs proposed by the ESCEO and CARES SPRL were not all retrieved in the literature published when the guidelines were issued. The lack of adherence to these guidelines observed in our analysis was expected as many of the included RCTs were conducted before the publication of these recommendations. Secondly, the guidelines were specifically designed for RCTs evaluating new chemical entities for the treatment of sarcopenia, whereas none of the RCTs included in our analysis investigated such interventions.

In the present meta-analysis, we also conducted a preliminary investigation into the effect of interventions on the changes in BBMs. For this purpose, BBMs were classified as either muscle-specific or non-muscle-specific BBMs, in accordance with ESCEO guideline classifications (Ladang et al. (2023)). The muscle-specific BBMs recommended by the ESCEO guidelines that were included in this meta-analysis are GDF-15, GDF-8 and follistatin. Based on data availability, follistatin and GDF-8 were included separately in this group even if the ESCEO recommendations advise to measure them as a couple. The meta-analysis performed for each of these BBMs did not demonstrate a significant impact of sarcopenia interventions on their concentrations in this preliminary investigation. Among the non-muscle-specific BBMs recommended by the ESCEO guidelines, IGF-1, CRP, IL-6 and TNF-α were included in this meta-analysis. IGF-1 concentration was significantly impacted by sarcopenia interventions while CRP, IL-6 and TNF-α concentrations were not. These results are in general contradiction with other papers assessing inflammation BBMs in sarcopenia (Bano et al. 2017; Picca et al. 2022). However, unlike this study, in the papers of Bano et al. (2017) and of Picca et al. (2022), the biomarkers concentrations were statistically different between individuals with sarcopenia and controls without sarcopenia. Several other BBMs recommended by ESCEO were not assessed in any of the included RCTs, including adiponectin, leptin, dehydroepiandrosterone sulphate (DHEAS), and cortisol, whereas testosterone was measured in only one RCT (de Sa Souza et al. 2022). Similarly, no RCT in our analysis measured the amino terminal peptide of type III procollagen (PIIINP), brain-derived neurotrophic factor (BDNF) or the sarcopenia index (Ladang et al. 2023). This highlights the need to further assess these BBMs in sarcopenia RCTs.

Different factors should be taken into account when interpreting the results of the meta-analyses. Indeed, some meta-analytical models may lack statistical power due to the limited number of included studies and, consequently, the small number of participants. Consequently, the quality of the included RCTs was considered as some concerns to high risk of bias in 9 out of 21 RCTs. Yet, sensitivity analyses demonstrated that the RCTs of poorer quality were not driving the meta-analytical models. In addition, high heterogeneity was observed across models, which may be attributed to variations in intervention protocols, differences in BBM measurement methods, the differences in RCTs' duration, and disparities in the efficacy of the interventions on sarcopenia-related health outcomes. Moreover, the large number of primary endpoints reported per study further complicated the interpretation of BBM-specific effects.

Nevertheless, to further explore this aspect, we conducted a secondary analysis that restricted the body of evidence to studies demonstrating significant improvements in key clinical parameters of sarcopenia, namely, those showing at least a significant improvement in muscle strength or muscle mass. Among the 14 RCTs reporting improvements in muscle mass and/or strength, several biomarkers displayed distinct patterns. Concentrations of GDF-8, TWEAK, CRP and IL-2 were found to decrease following intervention, while GDF-15, follistatin, CAF, Myf5, Myog, Pax3, Pax7, 25-(OH)-vitamin D, LDL, vitamin E and IGF-1 increased in association with clinical improvements. Still, the increase in 25-(OH)-vitamin D concentration may only reflect an effective supplementation of vitamin D in RCTs' participants. Findings regarding albumin were inconsistent. Finally, when performing a meta-analysis of ESCEO-recommended BBMs within RCTs that demonstrated significant improvement in muscle mass and/or muscle strength, IL-6, CRP, TNF-α remained unaffected by interventions specific to sarcopenia. Furthermore, although IGF-1 showed significant response when considering all included RCTs, this effect was no longer significant when the analysis was restricted to only those reporting improvements in muscle mass and/or muscle strength. This difference might be explained by the loss of RCTs with large sample sizes when including only RCTs that demonstrated significant improvement in muscle mass and/or muscle strength in the meta-analysis. Further evidence is needed to better understand the diagnostic accuracy of IGF-1 for sarcopenia.

An important aspect of this work to take into account is the fact that it was often unclear whether certain biomarkers were measured for safety or efficacy purposes. Among the RCTs included in this review, only the study of Yang et al. (2023) explicitly reported the use of biomarkers for safety monitoring. This lack of clarity is particularly notable for renal and hepatic biomarkers, which are generally expected to remain stable when measured for safety purposes. Creatinine serves as a pertinent example. While it is conventionally used to assess renal function in clinical settings, it may also be used as a marker of muscle mass in the context of sarcopenia. This highlights the challenge of distinguishing safety and efficacy biomarkers in studies on sarcopenia, especially in non-pharmacological interventions. Furthermore, none of the included RCTs evaluated pharmacological interventions, which may explain the absence of biomarkers classification related to safety outcomes.

5 | Limitations

This study presents several methodological limitations that must be acknowledged. First, as already discussed, a substantial heterogeneity was observed in the measurement of blood-based biomarkers across studies, arising from differences in assay techniques, analytical platforms, reporting units and RCTs duration. To address this, we applied SMD in our meta-analytical models to facilitate cross-study comparisons. A GRADE analysis assessment was not feasible due to the low number of RCTs included in the meta-analyses, which applies also for publication bias assessment. Second, the interpretation of biomarker responsiveness is complicated by the fact that many included RCTs failed to demonstrate significant improvements in their primary clinical endpoints. Moreover, biomarkers were frequently reported as secondary outcomes, raising concerns about whether these trials were sufficiently powered to detect changes in biomarker levels. Although surrogate endpoints should ideally be included in adequately powered analyses, the limited reporting and variability in BBM measurement likely undermined statistical sensitivity. Furthermore, it appears to be a considerable challenge to demonstrate a significant change in key measures of sarcopenia with a median length of RCTs intervention of 12 weeks. No subgroup analyses were performed on this parameter. Lastly, our analyses did not establish the responsiveness of BBMs to sarcopenia-targeted interventions, which may reflect a combination of inadequate biomarker selection, heterogeneous study designs or limited efficacy of the interventions themselves.

6 | Conclusions

This systematic review and meta-analysis underscore the limitations in the use of BBMs in current sarcopenia research. None of the evaluated biomarkers demonstrated consistent sensitivity or specificity sufficient to support their routine use as surrogate efficacy endpoints or as a reliable outcome measure or diagnostic tool for sarcopenia (Beaudart et al. 2025). We therefore importantly advocate for further well-designed RCTs incorporating muscle-specific biomarkers to refine our understanding of their relevance and ultimately improve biomarker-driven approaches in the management of sarcopenia. Our findings emphasise the need to operationalise existing biomarkers guidelines and develop a harmonised Core Outcome Set (COS) for sarcopenia intervention trials. Such standardisation efforts are essential to enhance inter-study comparability, support regulatory alignment and facilitate the identification of robust biomarker signatures predictive of meaningful clinical outcomes. Ultimately, improving the methodological rigour in biomarker research will accelerate the development of targeted interventions and contribute to more effective and resource-efficient management of sarcopenia.

Author Contributions

This study was developed and designed by Charlotte Beaudart and Jonathan Douxfils, with Charlotte Beaudart and Dolores Sanchez-Rodriguez contributing to the bibliographic search. The screening process and study selection were conducted by Yoke Mun Chan, Dolores Sanchez-Rodriguez and Charlotte Beaudart. The protocol was established by Emma Boretti, Emma Calluy, Jean-Yves Reginster, Jonathan Douxfils and Charlotte Beaudart, ensuring a structured approach to data collection and analysis. Data extraction was carried out by Emma Boretti, Emma Calluy and Yveline Malrechauffé, with Yoke Mun Chan, Emma Calluy and Sophie Van Heden responsible for the quality assessment of included studies. Emma Calluy performed the statistical analyses, ensuring the robustness and reliability of the findings. The manuscript was drafted by Emma Calluy, Sophie Van Heden and Charlotte Beaudart, incorporating the study's key findings and interpretations. All authors revised the article for important intellectual content and provided their final approval for the submitted manuscript. All authors read and agreed to the final version of the manuscript. Screening: Yoke Mun Chan, Dolores Sanchez-Rodriguez, Charlotte Beaudart. Selection: Yoke Mun Chan, Dolores Sanchez-Rodriguez, Charlotte Beaudart. Protocol: Emma Boretti, Emma Calluy, Jean-Yves Reginster, Etienne Cavalier, Aurélie Ladang, Jonathan Douxfils, Charlotte Beaudart. Extraction: Emma Boretti, Emma Calluy, Yveline Malrechauffé. Quality assessment: Yoke Mun Chan, Emma Calluy, Sophie Van Heden. Statistical analyses: Emma Calluy. Redaction of the manuscript: Emma Calluy. Review of the manuscript: All authors read, reviewed, and agreed to the final version of the manuscript.

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The authors have nothing to report.

Ethics Statement

For systematic reviews and meta-analyses, Ethics Committee approval is not required.

Conflicts of Interest

J.D. is the Director of the Board, the Chief Scientific Officier and the Founder of QUALIblood, a contract research organisation that received funding from several pharmaceutical industries. He also reports personal fees from Daiichi Sankyo, Diagnostica Stago, DOASense, Gedeon Richter, GyneBioPharma, LiBBMs, Mayne Pharma, Portola, Roche, Roche Diagnostics, Synlab, YHLO and Werfen.

Data Availability Statement

The protocol has been published on Prospero (CRD42024603238), and all data are registered on OSF (https://osf.io/wtv5z/).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** PRISMA 2020 checklist. **Data S2:** Search strategies used for Medline (via Ovid), Cochrane Central Register of Controlled Trials (via Ovid) and Embase. **Data S3:** Assessment of the risk of bias of the included randomised controlled trials using the Cochrane RoB2.0 tool. **Data S4:** Leave-one-out analysis of the BBMs recommended by the ESCEO (Ladang et al. 2023). (a) IL-6, interleukin 6; (b) CRP, C-reactive protein; (c) TNF-α, tumour necrosis factor α; (d) IGF-1, Insulin-like growth factor 1. **Data S5:** Subgroup analysis of the BBMs recommended by the ESCEO (Ladang et al. 2023). (a) IL-6, interleukin 6; (b) CRP, C-reactive protein; (c) TNF-α, tumour necrosis factor α; (d) IGF-1, Insulin-like growth factor 1. **Data S6:** Funnel plot (publication bias) of the BBMs recommended by the ESCEO by type of intervention (Ladang et al. 2023). (a) IL-6, interleukin 6; (b) CRP, C-reactive protein; (c) TNF-α, tumour necrosis factor α; (d) IGF-1, Insulin-like growth factor 1. **Data S7:** Forest plot of the BBMs recommended by the ESCEO (Ladang et al. 2023) in RCTs demonstrating a significant improvement in muscle mass and/or muscle strength. (a) IL-6, interleukin 6; (b) CRP, C-reactive protein; (c) TNF-α, tumour necrosis factor α; (d) IGF-1, Insulin-like growth factor 1. **Data S8:** Subgroup analysis of the BBMs recommended by the ESCEO (Ladang et al. 2023) in RCTs demonstrating a significant improvement in muscle mass and/or muscle strength. (a) IL-6, interleukin 6; (b) CRP, C-reactive protein; (c) TNF-α, tumour necrosis factor α.