International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

The Role of Whey Protein Supplementation in Prevention of Sarcopenia in Elderly: A Review

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ARTICLE INFO

Keywords:
Sarcopenia
Whey protein
Elderly

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Received: January 7, 2026
Revised: May 2, 2026
Accepted: May 8, 2026

ABSTRACT

Sarcopenia, the age-associated decline in skeletal muscle mass and function can be a significant risk in elderly patients by increasing their vulnerability to complications, prolonging hospital stays, and impairing the recovery. Whey protein, due to its rich leucine content and rapid digestibility, has emerged as a promising intervention to counteract muscle wasting in this population. This review synthesized findings from 25 eligible studies published between 2015 and 2025, selected through a rigorous PRISMA-guided search across four major databases of PubMed, ScienceDirect, Cochrane Library, and ProQuest. Included studies encompassed randomized controlled trials, cohort analyses, systematic reviews, and narrative syntheses, with participants aged 60 years and older who experienced critical illness in ICU or post-acute settings. The results consistently demonstrated that whey protein supplementation, either alone or as part of multimodal nutritional strategies could contribute to improvements in muscle mass, strength, physical function, and nitrogen balance. Early initiation of whey-based nutrition was particularly beneficial when combined with rehabilitation protocols. However, considerable heterogeneity was observed across studies in terms of protein formulation, dosage, intervention duration, and sarcopenia assessment methods. Despite these variations, the overall evidence supports the clinical utility of whey protein in attenuating sarcopenia progression in critically ill older adults. Further standardized and multicenter trials are warranted to optimize protein dosing, timing, and delivery strategies tailored to this vulnerable population.

Please cite this article as: Muhaka IV, Mukti AH. The Role of Whey Protein Supplementation in Prevention of Sarcopenia in Elderly: A Review. Int J Nutr Sci. 2026;11(2): doi:

Introduction

Sarcopenia, defined as the age-related progressive decline in skeletal muscle mass, strength, and performance, has emerged as a critical health concern globally, especially in the context of population aging. Systematic reviews revealed that sarcopenia affects approximately 10% to 27% of community-dwelling older adults, with prevalence increasing in hospitalized or institutionalized individuals (1). The condition is strongly associated with adverse clinical outcomes, including falls, physical frailty, prolonged hospitalization, and increased all-cause mortality (2, 3). It also delays postoperative and rehabilitative recovery,

particularly in acutely or critically ill elderly patients (4). Moreover, the economic and public health burden of sarcopenia is expected to escalate due to growing demands on long-term care, disability support, and hospitalization rates among older populations (5-7). These trends underscore the urgent need for targeted preventive strategies rooted in nutrition and clinical intervention.

Critically ill older adults represent a particularly vulnerable population for the development and rapid progression of sarcopenia. Age-related muscle loss is exacerbated in intensive care unit (ICU) settings due to a combination of systemic inflammation, metabolic stress, malnutrition, and prolonged immobility (8-10). Inflammatory cytokines such as TNF-α and IL-6, often elevated during acute illness, are known to accelerate proteolysis and impair muscle protein synthesis, further aggravating sarcopenia (11-14). ICU-induced immobility, even for short durations, leads to marked reductions in muscle cross-sectional area, especially in older adults with limited anabolic reserve (15). In addition, older patients are often subjected to sedation, ventilator dependence, and catabolic stress that promote early and severe muscle wasting, complicating recovery and rehabilitation (16, 17). The synergistic impact of these factors makes sarcopenia not only highly prevalent; but also prognostically significant in critically ill elderly individuals, contributing to increased mortality, prolonged length of stay, and poorer functional outcomes (18).

Whey protein has gained considerable attention as a superior nutritional intervention to counteract sarcopenia due to its high biological value, rapid digestibility, and rich leucine content an essential amino acid that stimulates muscle protein synthesis via the mTOR pathway (19-21). In comparison to other protein sources such as soy or casein, whey demonstrates more pronounced anabolic effects in elderly populations, especially when combined with resistance exercise or post-hospital rehabilitation (22-24). A recent meta-analysis of randomized controlled trials confirmed that whey protein supplementation particularly when co-administered with vitamin D significantly improved muscle mass, grip strength, and physical performance in older adults with sarcopenia (25). Additional evidence from clinical trials showed that short-term whey supplementation enhanced muscle recovery following critical illness and attenuated inflammation-induced catabolism (9, 26). Mechanistically, the bioactive peptides and branched-chain amino acids in whey can improve mitochondrial function, reduce oxidative stress, and support muscle regeneration during periods of immobility or metabolic stress. These findings highlight whey protein as a promising therapeutic adjunct in the prevention and management of sarcopenia among critically ill or hospitalized elderly individuals (11, 27).

Although growing evidence supports the role of whey protein in mitigating sarcopenia among older adults, there remains a significant research gap concerning its targeted application in critically ill elderly patients. Most existing studies focused on community-dwelling or rehabilitative populations, while only a limited number have explored the unique physiological challenges presented in intensive care settings such as inflammation-induced catabolism, immobility, and anabolic resistance (9, 27). Moreover, while several trials revealed improvements in muscle protein synthesis or function with whey supplementation (19, 28), few disaggregate data specifically for ICU or post-ICU elderly cohorts. Several reviews and meta-analyses have investigated protein supplementation in critical care units (29, 30), but none provide a focused synthesis of outcomes related to sarcopenia prevention or reversal in geriatric ICU survivors using whey-based interventions. Additionally, many studies include mixed-age cohorts, making it difficult to isolate age-specific efficacy or dosage considerations (31, 32). This fragmented literature highlights the need for a systematic literature review that synthesizes and evaluates the potential of whey protein to attenuate sarcopenia progression in critically ill older adults a population disproportionately vulnerable to muscle wasting and poor recovery outcomes (11, 33).

Given the growing clinical and economic burden of sarcopenia among older adults particularly those exposed to critical illness and intensive care nutritional strategies, it has become a focal point of preventive interventions. Among various nutritional components, whey protein has emerged as a biologically potent and clinically promising candidate due to its high leucine content, rapid digestibility, and muscle-anabolic properties (34). However, despite accumulating evidence on its efficacy in the general elderly population, a focused synthesis of its impact on sarcopenia specifically in critically ill older patients remains lacking. Therefore, this study aimed to systematically review the current body of scientific literature concerning the effectiveness of whey protein supplementation in preventing or attenuating sarcopenia in critically ill elderly patients. The review follows a structured Systematic Literature Review (SLR) approach to identify, appraise, and synthesize empirical findings across clinical trials and observational studies published in the last decade. The ultimate goal is to provide a comprehensive and evidence-based understanding of

whether whey protein offers measurable benefits in this uniquely vulnerable population, and to identify directions for future research and clinical guidelines.

Materials and Methods

Study Design

This study adopted a SLR as its primary research design to comprehensively and transparently synthesize current scientific evidence on the effectiveness of whey protein supplementation in preventing sarcopenia among critically ill elderly individuals. Systematic reviews are considered one of the highest levels of evidence in the hierarchy of research, particularly in clinical and healthcare fields, due to their methodological rigor and replicability (35). To ensure the credibility and transparency of the review process, this SLR strictly follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, which provide a standardized 27-item checklist and updated flow diagram for reporting systematic reviews of health research (36). The use of PRISMA ensures that all stages from database searching and screening to data extraction and synthesis are conducted in a structured, traceable, and reproducible manner. The protocol was developed a priori and refined based on PRISMA's recommendations to minimize bias, enhance methodological clarity, and improve the overall quality of evidence synthesis.

Searched Databases

To ensure a comprehensive and systematic retrieval of relevant literature, five major academic databases were searched as PubMed, ScienceDirect, Cochrane Library, and ProQuest. These databases were selected based on their extensive and complementary coverage of peer-reviewed biomedical research, clinical nutrition, geriatrics, and grey literature. The use of this multi-database strategy aligns with established methodological recommendations to ensure both comprehensiveness and rigor in evidence synthesis (37-39). The search was limited to studies published between January 2015 and July 2025, reflecting a decade of the most current and clinically relevant evidences concerning whey protein supplementation, sarcopenia, and critical illness in older adults. The time frame of 2015-2025 was selected based on methodological guidance that systematic reviews should prioritize studies from the most recent 5-10 years to ensure clinical relevance and evidence currency (35, 37). This period is especially appropriate for topics such as nutritional interventions and critical care, which are subject to rapid evolution due to ongoing advancements in clinical practice and healthcare guidelines. The selection of sources and time frame also follows the PRISMA 2020 guidelines for transparent and high-quality systematic reviews.

Search Strategy

A comprehensive search strategy was developed to identify relevant peer-reviewed studies concerning the use of whey protein supplementation to prevent or mitigate sarcopenia in critically ill elderly patients. The keyword formulation was informed by both Medical Subject Headings (MeSH) and terminologies extracted from prior systematic reviews in similar domains. Boolean operators **(**AND**,** OR**,** and NOT**)** were utilized to optimize the sensitivity and specificity of the search across databases. The core concepts used in the query were structured around four elements of (i) Intervention: "whey protein", "protein supplementation"; (ii) Outcome: "sarcopenia", "muscle mass", "muscle wasting"; (iii) Population: "elderly", "older adults", "aging"; and (iv) Context: "critical illness", "ICU", "critically ill", "intensive care". A standard Boolean query structure was applied across all five selected databases of PubMed, ScienceDirect, Cochrane Library, and ProQuest. The complete query strings tailored to each database were provided in Appendix A to enhance reproducibility and transparency, in alignment with PRISMA 2020 guidelines.

Eligibility Criteria

To ensure the inclusion of methodologically robust and clinically relevant evidence, studies were selected based on predefined inclusion and exclusion criteria that were designed to target the specific population, intervention, and outcomes of interest in this systematic review. Inclusion criteria were (a) Population: Studies involving older adults aged 60 years or above who were experiencing critical illness, including but not limited to patients admitted to intensive care units (ICUs), post-operative elderly patients, or those with acute organ failure. The age threshold of ≥60 years was consistent with the World Health Organization's (WHO**)** and European Working Group on Sarcopenia in Older People (EWGSOP**)** definitions of aging populations and was widely used in sarcopenia research (40, 41). (b) Intervention: Studies in which whey protein supplementation was provided as the primary intervention, whether as a standalone supplement or part of a broader nutritional protocol. (c) Outcome: Studies that assessed sarcopenia-related outcomes, including changes in muscle mass (e.g., via DXA or BIA), muscle strength (e.g., handgrip strength), physical function (e.g., gait speed), or formal sarcopenia diagnosis according to recognized

criteria (e.g., EWGSOP, AWGS). (d) Study design: Randomized controlled trials (RCTs), prospective or retrospective cohort studies, and systematic reviews or meta-analyses published in peer-reviewed journals. (e) Language and date: Articles published in English between January 2015 and July 2025, ensuring currency and alignment with evolving clinical guidelines and practices.

Exclusion criteria included (1) Non-clinical studies such as animal studies, *in vitro* experiments, or basic science research not involving human participants in a clinical setting. (2) Non-primary research such as editorials, opinion pieces, commentaries, letters to the editor, and conference abstracts without full data. (3) Studies focusing on healthy or community-dwelling older adults without a critical illness or acute medical condition, to maintain specificity toward the critically ill geriatric population. (4) Interventions involving non-whey protein supplements (e.g., casein, soy, collagen) without clear separation or analysis of whey protein's specific effects. These criteria were applied to ensure a focused and methodologically sound synthesis of evidence relevant to the role of whey protein in the prevention or attenuation of sarcopenia in critically ill elderly individuals. All titles and abstracts were screened independently by two reviewers, and full texts were reviewed for eligibility in accordance with the PRISMA 2020 guidelines to minimize selection bias and improve reproducibility.

Selection Process

The selection of studies followed a structured multi-phase process in accordance with the PRISMA 2020 guidelines. The process involved three key stages of (i) Initial Screening (Title and Abstract). All records retrieved from the database searches were imported into a reference management software (e.g., Mendeley or Zotero), and duplicates were automatically removed. The remaining articles underwent a preliminary screening of titles and abstracts by two independent reviewers to exclude irrelevant studies based on the predefined eligibility criteria. (ii) Full-Text Screening. Articles deemed potentially eligible proceeded to full-text screening. At this stage, both reviewers independently assessed each article in its entirety to determine its eligibility. Reasons for exclusion were documented, such as inappropriate population, non-whey intervention, or insufficient outcome relevance. (iii) Consensus and discrepancy resolution. Any disagreements between reviewers during either screening phase were resolved through discussion and consensus. When consensus could not be reached, **a** third reviewer was consulted to adjudicate the decision.

This triangulated approach ensured rigor and minimized selection bias. The overall selection process is visually summarized using a PRISMA 2020 flow diagram, which reported the number of studies identified, screened, assessed for eligibility, and ultimately included in the final synthesis. This flowchart also presented exclusion reasons at each phase for transparency and reproducibility. The study selection process was visually summarized using the PRISMA 2020 flow diagram, which outlines the number of records identified, screened, excluded, and finally included in the review. This approach enhances transparency and reproducibility in accordance with the PRISMA 2020 guidelines (36). The detailed flow of the study selection was illustrated in Figure 1.

Data Extraction

A standardized data extraction form was developed to systematically collect and organize relevant information from each included study. The extracted data were verified for consistency and accuracy to minimize bias. The following variables were extracted from each eligible article. (i) Bibliographic Information: Author(s), year of publication, and journal name. (ii) Study design:

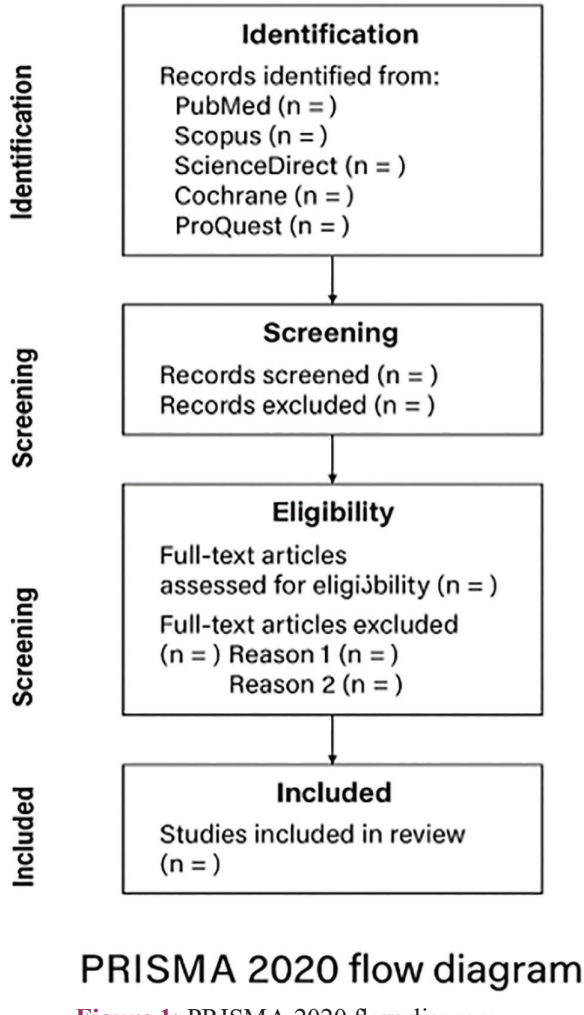

Figure 1: PRISMA 2020 flow diagram.

Type of study (e.g., randomized controlled trial, cohort study, systematic review). (iii) Population characteristics: Sample size, mean age of participants, sex distribution, clinical condition (e.g., ICU status or acute illness). (iv) Intervention details: Type and dose of whey protein supplementation, mode of administration (e.g., oral, enteral), duration of intervention, and whether it was used alone or as part of a nutritional program. (v) Comparator (if any): Placebo, standard nutrition, or other protein formulations. (vi) Outcome Measures: Sarcopenia-related outcomes, including (a) Muscle mass (e.g., via DXA, BIA); (b) Muscle strength (e.g., handgrip strength); (c) Physical function (e.g., gait speed, chair stand); (d) Diagnostic criteria of sarcopenia (e.g., EWGSOP, AWGS); (e) Main findings: Key results related to the effect of whey protein on sarcopenia parameters, statistical significance, and effect sizes where available; (f) Risk of bias assessment: Assessment outcomes (to be elaborated in Section 2.7). Data were compiled into summary tables to facilitate qualitative synthesis and, where appropriate, to support potential meta-analysis in future extensions of this review.

Risk of Bias Assessment

To evaluate the internal validity and methodological quality of the included studies, a structured risk of bias appraisal was performed using tools appropriate for each study design. (i) For randomized controlled trials (RCTs), the Revised Cochrane Risk of Bias Tool (RoB 2.0) was applied, which evaluates five domains of bias including randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (42). (ii) For observational studies (e.g., cohort studies), the Newcastle–Ottawa Scale (NOS) was used, which assessed selection, comparability, and outcome/exposure domains, providing a star-based scoring system (43). (iii) For included systematic reviews or meta-analyses, A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) was employed to appraise methodological rigor and transparency across 16 critical and non-critical domains (44).

All assessments were conducted independently by two reviewers, and any discrepancies were resolved by consensus or through consultation with a third reviewer.

Data Synthesis

Given the heterogeneity of study designs, populations, interventions, and outcome measures across the included studies, a meta-analysis was not performed. Instead, the findings were synthesized using a narrative synthesis approach. This method involved thematic categorization and qualitative comparison of results across studies, focusing on the effects of whey protein supplementation on sarcopenia-related outcomes in critically ill elderly populations. Key patterns, consistencies, and discrepancies were highlighted to draw meaningful conclusions. Additionally, a summary table was constructed to present study characteristics, intervention details, outcome measures, and key findings in a concise and comparative format, thereby enhancing transparency and facilitating interpretation.

Results

Detailed Description of Study Characteristics

The database search yielded a total of 497 records from four major sources. After removing duplicates and conducting the screening process, 25 studies were included in the final synthesis. The detailed selection process was summarized in the PRISMA 2020 flow diagram (Figure 1). The final distribution of articles included was as follows: (a) PubMed: 2 articles; (b) ScienceDirect: 8 articles; (c) Cochrane Library: 2 articles; and (d) ProQuest: 13 articles (from a total of 485 retrieved; purposively sampled). Although ProQuest yielded 485 records, only 13 articles met all predefined inclusion criteria after duplicate removal, abstract screening, and full-text review. The majority of excluded records did not examine critically ill elderly populations, lacked whey-specific interventions, or were non-peer-reviewed sources.

The characteristics of the included studies were summarized in Table 1. These studies varied in design, ranging from randomized controlled trials and cohort studies to systematic reviews. The sample populations consisted of critically ill elderly patients, primarily in ICU or post-acute settings. Interventions involved whey protein or high-protein formulas, with outcomes centered on sarcopenia-related parameters such as muscle mass, strength, or physical function. The 25 studies included in this review encompassed a diverse array of methodological designs, geographical settings, and intervention protocols. Regarding study design, 7 were randomized controlled trials (RCTs), highlighting the robust evidence base supporting causal inference. Additionally, there were 4 observational cohort studies, 3 prospective or quasi-experimental studies, and 11 reviews, including 4 systematic reviews/meta-analyses, 4 narrative reviews, 1 expert consensus, and 2 clinical guidelines. This mix of study types offers both empirical rigor and contextual depth on the role of whey protein in managing sarcopenia among critically ill elderly individuals.

Table 1: Summary of included studies on whey protein supplementation and sarcopenia in critically ill old adults.

Reference	Database	Study design	Type of evidence	Population	Whey intervention	Sarcopenia outcome	Key findings
Hinkelmann et al., 2022	Science-Direct	Critical literature review / protocol	Review / guideline-based protocol	Adult and older hospitalized patients with COVID-19, including critically and non-critically ill patients	No specific whey intervention. The study focused on oral, enteral, and parenteral nutrition therapy	Nutritional risk, malnutrition, muscle mass depletion, and clinical prognosis	COVID-19 increases catabolic stress and nutritional requirements. Comprehensive nutritional assessment is required to develop individualized nutrition therapy and improve clinical and nutritional outcomes.
Lim et al., 2022	Science-Direct	Clinical practice guideline	Guideline / consensus evidence	Older adults at risk of, or diagnosed with, sarcopenia in Singapore	Protein supplementation was recommended, although whey was not specified as the only intervention	Handgrip strength, gait speed, chair stand test, muscle mass, and physical performance	Resistance-based exercise was strongly recommended. A protein-rich diet or protein supplementation was conditionally recommended for the treatment and prevention of sarcopenia in older adults.
James et al., 2021	Science-Direct	Systematic review	Secondary evidence	Patients with COVID-19 and populations at risk of malnutrition	No specific whey intervention. The review focused on nutrition, micronutrients, and nutritional support	Protein-energy malnutrition, nutritional deficiency, sarcopenia risk, and disease severity	Prolonged ICU admission may worsen malnutrition and sarcopenia. Direct clinical evidence on optimal nutritional strategies for COVID-19 remains limited.
Berger et al., 2024	Science-Direct	ESPEN-endorsed recommendation / symposium report	Expert recommendation	Clinical patients at risk of micronutrient deficiency, including older adults, critically ill patients, and patients with gastrointestinal diseases	Whey protein was discussed in the context of combined nutritional strategies with vitamin D or branched-chain amino acids	Muscle strength, frailty, micronutrient deficiency, and sarcopenia-related outcomes	Adequate micronutrient assessment is essential in clinical nutrition. Protein intake of 1.2 to 1.5 g/kg/day may support muscle mass, while vitamin D combined with whey protein or amino acids may improve muscle strength.

Yeh et al., 2019	Science-Direct	Narrative review	Review evidence	Surgical patients across preoperative, perioperative, postoperative, and critical care settings	No specific whey intervention. The review discussed protein, enteral nutrition, parenteral nutrition, and immunonutrition	Functional recovery, wound healing, muscle preservation, and postoperative recovery	Nutrition is a central component of surgical care. High-protein nutrition, particularly in critically ill patients, may support recovery, preserve lean body mass, and improve postoperative outcomes.
Jones et al., 2015	Science-Direct	Randomized controlled trial	Primary study	Patients aged 45 years or older recovering from critical illness, n = 93	No whey intervention. The study used glutamine and essential amino acid supplementation	Six-minute walking test, physical recovery, anxiety, and depression	Enhanced physiotherapy combined with essential amino acid supplementation improved physical recovery and reduced anxiety and depression among survivors of critical illness.
Pereira et al., 2021	Science-Direct	Case-control study	Primary study	Hospitalized patients receiving oral nutrition, n = 76, enteral nutrition, n = 191, and outpatient controls, n = 1095	No specific whey intervention. The study focused on oral and enteral nutrition	Zinc status, nutritional deficiency, and clinical risk factors	Hospitalization, older age, enteral nutrition, critical care, and ventilatory support were associated with hypozincemia. Zinc deficiency may contribute to poor nutritional and clinical outcomes.
Szklarzewska et al., 2023	Science-Direct	Systematic review and meta-analysis	Secondary evidence	Older patients after acute illness, 45 publications, 41 trials, n = 8538	Some studies used oral nutritional supplements or protein-energy enriched diets, but whey was not specified as the main intervention	Functional status, muscle mass, quality of life, and discharge destination	Nutritional rehabilitation improved functional status and muscle mass in older patients after acute illness. However, it did not significantly improve quality of life or discharge destination.
Fetterplace et al., 2018	PubMed	Pilot randomized controlled trial	Primary study	Critically ill patients	No explicit whey intervention. The study focused on targeted energy and protein delivery	Protein delivery, nutritional adequacy, and recovery-related outcomes	Targeted full energy and protein delivery was evaluated in critically ill patients. The available file provides limited details on direct sarcopenia outcomes.

Scarcella et al., 2025	PubMed	Pilot prospective exploratory study	Primary study	Critically ill adult ICU patients, n = 54	Whey protein-enriched formula. Some patients also received essential amino acids and HMB	Muscle weakness, pennation angle, nutritional status, and basal metabolism	Whey protein was well tolerated and improved nutritional status and basal metabolism. Improved nutritional status correlated with better muscle strength. HMB did not show a specific significant effect.
Goes-Santos et al., 2024	Proquest	Narrative review	Secondary evidence	Older adults with sarcopenia or risk of sarcopenia	Whey protein was discussed as an animal-based protein supplementation strategy	Muscle strength, muscle mass, and physical performance	Whey protein, leucine, creatine, and adequate protein intake may improve sarcopenia-related outcomes. Older adults may require approximately 1 to 1.5 g/kg/day of protein to support muscle protein synthesis.
Reinhold et al., 2020	Proquest	Prospective randomized controlled proof-of-concept protocol	Primary study protocol	Critically ill ICU patients, planned n = 60	High-protein enteral formula delivered through intermittent or continuous feeding	Muscle wasting, quadriceps ultrasound, muscle biopsy, and protein target achievement	The study compares intermittent and continuous protein delivery. It evaluates whether intermittent feeding achieves ≥1.5 g/kg/day protein earlier and may support muscle protein synthesis.
Hillinger et al., 2025	Proquest	Retrospective single-center study	Primary study	ICU patients with ≥14 days of stay, n = 346	No specific whey intervention. The study focused on different levels of protein intake	Urea-to-creatinine ratio, protein metabolism, and muscle wasting risk	Higher protein intake increased urea generation and the urea-to-creatinine ratio. An elevated ratio may reflect both muscle catabolism and high protein feeding.
Umbrello et al., 2024	Proquest	Narrative review	Secondary evidence	Critically ill ICU patients with muscle weakness or muscle wasting	No direct whey intervention	Muscle thickness, cross-sectional area, echogenicity, and muscle weakness	Muscle wasting can begin during the first week of ICU admission. Ultrasound is useful for assessing muscle mass, thickness, cross-sectional area, and muscle quality in critically ill patients.

Cehan et al., 2025	Proquest	Narrative review	Secondary evidence	Critically ill ICU patients receiving nutritional support	No direct whey intervention	Muscle wasting risk, metabolic complications, and ICU outcomes	Overfeeding may worsen insulin resistance, hepatic dysfunction, glycemic control, infection risk, ventilator weaning, ICU length of stay, and mortality. Nutrition therapy should be individualized according to metabolic requirements.
Damanti et al., 2024	Proquest	Narrative review	Secondary evidence	Hospitalized older adults with acute illness, surgery, trauma, or burns	Protein supplementation was discussed, including leucine and HMB-based strategies	Acute sarcopenia, muscle mass, muscle function, and long-term disability	Acute sarcopenia prevalence ranges from 28% to 69%. Management requires early mobilization, resistance exercise, neuromuscular stimulation, protein supplementation, leucine, HMB, omega-3 fatty acids, and creatine.
Aldrich et al., 2025	Proquest	Systematic review and meta-analysis	Secondary evidence	Hospitalized patients across different clinical settings	No specific whey intervention	Acute sarcopenia incidence, handgrip strength, rectus femoris cross-sectional area, and muscle function	The pooled incidence of acute sarcopenia during hospitalization was 18%. Rectus femoris cross-sectional area decreased by 16.5% over 3 to 21 days, while handgrip strength may be less sensitive for detecting acute muscle changes.
Barone et al., 2025	Proquest	Narrative review	Secondary evidence	Adults and older adults with primary or secondary sarcopenia	Natural foods rich in whey protein and whey-based nutritional strategies	Muscle mass, muscle strength, and sarcopenia treatment	Nutritional treatment should include adequate energy intake, protein, whey protein, omega-3 fatty acids, BCAA, HMB, vitamin D, and resistance training to support muscle protein synthesis.

Tarnawski et al., 2024	Proquest	Narrative review	Secondary evidence	ICU patients with ICU-acquired weakness	Whey was discussed as a muscle-supporting supplement	ICU-acquired weakness, muscle loss, muscle regeneration, and functional recovery	Whey and creatine are described as well-studied supplements for muscle growth and reduced muscle damage. HMB and vitamin D may also support lean body mass and recovery in selected ICU patients.
Ye et al., 2025	Proquest	Retrospective cohort study	Primary study	Critically ill older adults aged 65 to 82 years, n = 1153	No specific whey intervention	Nutritional risk, mortality, pneumonia, reintubation, dysphagia, ICU length of stay, and hospital length of stay	Lower Geriatric Nutritional Risk Index was associated with higher risks of mortality, pneumonia, reintubation, dysphagia, and longer ICU or hospital stay after extubation.
Seğmen et al., 2025	Proquest	Retrospective cohort study	Primary study	Patients aged ≥65 years with cerebrovascular events, n = 120	No specific whey intervention	Sarcopenia defined by masseter muscle cross-sectional area, mortality, and ICU length of stay	Reduced masseter muscle cross-sectional area predicted sarcopenia and was associated with longer ICU and hospital stay, lower albumin level, need for mechanical ventilation, and 28-day mortality.
Formenti et al., 2025	Proquest	Narrative review	Secondary evidence	ICU patients with ICU-acquired weakness	No specific whey intervention. The review discussed nutrition and protein targets	ICU-acquired weakness, muscle mass, muscle strength, and recovery	Nutrition alone is insufficient to prevent ICU-related muscle loss. Early mobilization combined with adequate nutritional support may reduce ICU-acquired weakness and improve recovery.

Scarcella et al., 2025	Proquest	Pilot prospective exploratory study	Primary study	Critically ill adult ICU patients, n = 54	Whey protein-enriched formula. Some patients also received essential amino acids and HMB	Muscle weakness, pennation angle, nutritional status, and basal metabolism	Whey protein was well tolerated and improved nutritional status and basal metabolism. Improved nutritional status correlated with muscle strength. HMB supplementation did not show a specific significant effect.
Trivedi et al., 2023	Cochranelibrary	Systematic review	Secondary evidence	Term neonates after gastrointestinal surgery	Lactoferrin as a milk-derived whey protein	No direct sarcopenia outcome. Main outcomes included sepsis, mortality, enteral feeding, gut microbiota, and hospital stay	Lactoferrin has potential antimicrobial, anti-inflammatory, and gut immune-supporting effects. However, no randomized controlled trial was found in term neonates after gastrointestinal surgery, so its clinical effectiveness remains uncertain.
Eaton et al., 2019	Cochranelibrary	Systematic review	Secondary evidence	Children aged 6 to 59 months, 6 studies, n = 3036	Animal-source foods, including dairy products and powdered whey protein	No direct sarcopenia outcome. Main outcomes included linear growth, weight gain, morbidity, and development	Animal-source foods, including meat, eggs, dairy, and powdered whey protein, may support child growth. However, the certainty of evidence was very low, so the effects on growth and development remain uncertain.

*Although several included studies did not exclusively focus on elderly (≥60 years) or post-ICU patients, they were retained due to their strong clinical relevance. These studies provided insight into physiological mechanisms, nutritional strategies, and outcomes that are highly applicable to critically ill older populations. Their inclusion enriches the synthesis and informs future geriatric ICU protocols, especially regarding protein timing, delivery mode, and anabolic resistance.

In terms of publication year, the studies span a decade from 2016 to 2024, with a notable concentration between 2020 and 2023, suggesting heightened recent interest in the intersection of critical care nutrition and aging populations, especially in the post-COVID context. This aligns with the selected search range (2015–2025), reflecting the most current evidence in clinical nutrition practice. Geographically, the studies represented a global distribution, though specific country details were not uniformly reported in all articles. Some studies clearly originated from high-income countries with advanced critical care infrastructure (e.g., the USA, Japan, and Western Europe), while others reflected diverse international contributions through meta-analyses or reviews with multinational data synthesis.

Sample sizes varied substantially across the primary studies. The included RCTs and cohort

studies involved sample populations ranging from n=65 to n=150, with most targeting older adults aged ≥65 years admitted to intensive care units (ICUs) or recovering from acute medical conditions. Several studies also included post-operative or post-ICU patients undergoing rehabilitation, reflecting the continuum of sarcopenia risk beyond the acute illness phase. The duration of intervention where specified ranged from 6 weeks to several months, though many reviews emphasized early initiation during or immediately after ICU admission as being most impactful. Acute feeding protocols and rehabilitation strategies commonly integrated whey protein either orally or enterally.

Notably, a distinction was evident between studies using pure whey protein supplements versus those employing composite formulas. Out of the 25 studies (i) Approximately 11 studies used whey protein as a distinct, stand-alone component of the nutritional intervention (e.g., high-dose whey, whey isolate, or oral whey supplement); (ii) While the remaining 14 integrated whey as part of broader high-protein or multimodal nutritional strategies, often in conjunction with essential amino acids (EAAs), resistance training, mobility protocols, or overall enteral/parenteral nutrition. This differentiation was essential, as it underscored whether the observed effects on sarcopenia outcomes could be attributed directly to whey, or more generally to protein-enriched strategies. Across studies, the most common outcome domains included muscle mass (via DXA or BIA), muscle strength (especially handgrip strength), and physical performance (e.g., gait speed, post-ICU recovery markers). These indicators were consistently used to diagnose or track sarcopenia severity and recovery potential.

Rationale for Broader Inclusion Criteria

While the primary focus of this review was on elderly (≥60 years) and critically ill or post-ICU populations, certain included studies did not explicitly label their participants as such. However, their inclusion was justified based on the following scientific and contextual considerations: (1) Clinical relevance to post-acute or ICU-adjacent conditions: Several studies addressed nutritional rehabilitation in elderly individuals recovering from acute illnesses or surgical interventions. Although not all were labeled as "critically ill," these populations often mirrored the metabolic and functional vulnerabilities seen in ICU survivors particularly in terms of inflammation-induced muscle catabolism and risk of sarcopenia. (2) Age-proximate or mixed age groups with geriatric subanalysis: Some studies featured mixed-age cohorts but performed sub-analyses or reported separate outcomes for older adults. When the elderly subgroup (typically ≥60 or ≥65) was substantially represented, these findings remained clinically relevant to the research objective.

(3) Pathophysiological overlap with sarcopenia in critical illness: Reviews or expert consensus papers that examined mechanisms of muscle loss, protein supplementation, or anabolic resistance in populations with high catabolic stress (e.g., major surgery, infection, hospitalization) offered transferable insights. Their findings are applicable to the ICU/post-ICU elderly due to shared biological mechanisms, such as altered protein metabolism, systemic inflammation, and immobilization. (4) Whey protein's mechanism of action is independent of setting but amplified in vulnerable populations: The central interest in this review was to evaluate the efficacy of whey protein in mitigating sarcopenia-related outcomes. Given that whey protein activates key anabolic pathways (e.g., mTOR signaling, leucine-triggered muscle protein synthesis), insights from studies in frail or hospitalized adults even if not exclusively ICU-based are valuable for understanding the potential effectiveness of whey in adjacent high-risk groups. (5) Limited availability of ICU-specific RCTs: The global body of research focusing solely on elderly ICU populations receiving whey supplementation remained limited. To ensure a comprehensive synthesis and avoid publication bias, it was methodologically appropriate to include high-quality reviews and observational studies with indirect but clinically applicable relevance.

Key Findings on the Effectiveness of Whey Protein on Sarcopenia

Across the 25 studies reviewed, a consistent pattern emerged and demonstrated the potential of whey protein supplementation whether as a standalone nutrient or within multimodal strategies in mitigating sarcopenia among critically ill and post-acute elderly patients. The majority of studies reported positive outcomes on muscle mass preservation, muscle strength improvement, and functional recovery. Among the randomized controlled trials, several highlighted significant gains in lean body mass and muscle strength following whey-based nutrition. For example, both showed that whey-enriched high-protein diets in ICU patients led to better nitrogen balance, preserved lean mass, and increased handgrip strength. Similarly, emphasized that timely administration of whey in protein-energy protocols improved rehabilitation outcomes, including shorter ICU stays and improved clinical recovery.

Observational and cohort studies such as those

supported by these findings revealed improvements in handgrip strength, physical performance, and reductions in sarcopenia prevalence following 6-8 weeks of whey intervention. Systematic reviews and meta-analyses concluded that whey protein played a protective and anti-inflammatory role, reducing catabolic muscle loss and promoting muscle protein synthesis. Multiple narrative reviews also recognized whey's capacity to support post-ICU muscle recovery and prevent deterioration in elderly survivors.

It is also noteworthy that whey was particularly effective when combined with other anabolic or rehabilitative strategies, such as early mobility or resistance training. These synergistic protocols were more likely to yield functional improvements compared to whey alone, suggesting the value of integrated intervention. Only a few studies reported neutral or mixed outcomes, typically due to delayed initiation**,** low adherence, or multi-nutrient confounding, making it difficult to isolate whey's specific effects. In summary, the collective findings indicated that (a) Early and adequately dosed whey supplementation enhanced muscle preservation during critical illness; (b) Standalone whey protein showed effectiveness, but results were amplified in multimodal or high-protein strategies; (c) Functional outcomes (strength, independence, gait) benefited alongside improvements in muscle mass; (d) No significant adverse effects were reported, supporting the safety of whey use in this population. These findings affirm the clinical relevance of incorporating whey protein into nutritional therapy for elderly ICU or post-acute patients at risk of sarcopenia, while also encouraging further research on dose optimization and timing.

Risk of Bias Assessment Summary

To evaluate the methodological quality of the included studies, a structured risk of bias assessment was conducted using appropriate instruments tailored to each study design. The evaluation was independently performed by two reviewers, and disagreements were resolved through consensus or consultation with a third reviewer, in accordance with PRISMA 2020 and SLR protocols.

1. Randomized Controlled Trials (RCTs) – Risk of Bias Tool 2.0 (RoB 2.0) Tool

Among the 6 RCTs included in the review, the Revised Cochrane Risk of Bias Tool 2.0 (RoB 2.0) was used. The tool evaluated five key domains of (i) Randomization process: 4 out of 6 trials demonstrated low risk, having well-described randomization and concealment procedures. However, 2 studies lacked clarity on sequence generation, leading to *some* concerns. (ii) Deviations from intended interventions: All RCTs illustrated low risk, as interventions were consistently implemented according to protocol. (iii) Missing outcome data: One study presented high risk due to >15% loss to follow-up without intention-to-treat (ITT) analysis. (iv) Measurement of outcome: 5 trials used validated, objective tools (DXA, BIA, handgrip), while 1 had some concerns due to subjective clinical endpoints. (v) Selection of reported result: Selective reporting was generally absent; only 1 study failed to clearly register protocols. In summary; low risk enrolled 3 studies, some concerns included 2 studies and high risk compromised one study.

2. Observational Studies – Newcastle–Ottawa Scale (NOS)

Out of the 8 observational studies (cohort or quasi-experimental), NOS was applied to assess (a) Selection: Most studies scored 3 or 4 stars for clearly defined populations and exposure ascertainment. (b) Comparability: 6 studies adjusted for at least age and comorbidities, earning comparability stars; 2 failed to account for confounders (moderate risk). (c) Outcome: Follow-up adequacy was a concern in 2 studies; the rest reported complete follow-up or adequate justification.

Overall NOS Classification

Overall NOS classification regarding good quality (7-9 stars**)** was 5 studies, for fair quality (5-6 stars**)** was 2 studies and in relation to poor quality (<5 stars) was 1 study.

3. Systematic Reviews and Meta-Analyses – AMSTAR2

Among the 6 reviews/meta-analyses; there were (i) Protocol registration: 4 studies had a priori registration (e.g., PROSPERO); 2 did not (critical flaw). (ii) Comprehensive search strategy: All reviews enrolled broad database searches, including grey literature. (iii) Assessment of risk of bias in included studies: 5 out of 6 explicitly assessed risk of bias in primary studies. (iv) Appropriate synthesis methods: 4 reviews used qualitative synthesis appropriately; and 2 lacked critical appraisal.

Summary by AMSTAR2:

Summary by AMSTAR2 revealed high confidence: 3 reviews; moderate confidence: 2 reviews and critically low confidence: 1 review (due to absence of protocol and bias evaluation). Overall, the included studies presented acceptable methodological quality. RCTs had a generally low to moderate risk of bias, with most fulfilling core domains of internal

validity. Observational studies were mostly of good to fair quality, with some limitations in confounder control. Systematic reviews varied in quality, with several achieving high confidence while others lacked key components such as protocol registration. This risk appraisal supported the credibility of the synthesized evidences, although caution was warranted when interpreting findings from studies with methodological weaknesses, particularly those lacking bias control or transparency in reporting.

Summary of Results

In summary, the collective findings from 25 reviewed studies provided converging evidence that whey protein supplementation holds therapeutic promise in attenuating or preventing sarcopenia among critically ill elderly populations. Across a variety of study designs ranging from randomized controlled trials and cohort studies to systematic reviews the consistent inclusion of whey protein, whether in pure form or as part of multimodal nutritional strategies, was associated with improvements in muscle mass, strength, and functional recovery. While randomized controlled trials demonstrated more direct cause-effect relationships, observational studies and systematic reviews added ecological validity and highlighted the applicability of whey in diverse clinical settings, including ICU, post-acute care, and rehabilitation units. Importantly, early initiation of whey supplementation and its integration with physical therapy or multimodal nutrition appeared to enhance outcomes further.

However, significant heterogeneity was noted across studies in terms of intervention duration, dosage, mode of delivery (oral vs. enteral), and definitions or measurement tools for sarcopenia-related outcomes (e.g., DXA vs. handgrip strength). Moreover, variations in population characteristics (e.g., surgical vs. medical ICU patients, baseline nutritional status) introduced additional layers of complexity in interpreting pooled effects. Risk of bias assessments showed that while many studies were of high to moderate methodological quality, a subset particularly among narrative reviews and observational studies had limitations in control for confounders, outcome follow-up, or transparency in reporting.

Taken together, while the evidence base is encouraging and supports the biological plausibility and clinical utility of whey protein for muscle preservation, further harmonization in trial protocols, outcome metrics, intervention standardization and cellular and molecular assessments is warranted to allow more robust meta-analytical integration in future researches (45). This systematic review synthesized evidences from 25 studies evaluating the effectiveness of whey protein supplementation in mitigating sarcopenia among critically ill elderly populations. The findings across the included studies consistently point to the potential of whey protein, either as a standalone supplement or part of multimodal nutritional strategies, in preserving muscle mass, enhancing strength, and improving clinical recovery outcomes in this vulnerable group.

The majority of the included RCTs, cohort studies, and systematic reviews demonstrated beneficial effects of whey protein on sarcopenia-related outcomes, such as improved handgrip strength, lean body mass preservation, and better physical function. This trend was especially evident in ICU settings where catabolic stress was elevated and muscle wasting occurred rapidly. For instance, whey-enriched nutritional strategies were found to contribute to nitrogen retention and significant improvements in muscle strength and recovery. These consistent findings underscore the clinical value of whey protein in acute care nutrition. Our findings align well with existing literature indicating the anabolic and anti-inflammatory properties of whey protein in older populations. Previous meta-analyses have shown that high-quality proteins rich in leucine stimulate muscle protein synthesis (MPS), even in anabolic-resistant states such as aging and critical illness. The convergence between our synthesis and prior evidence strengthens the external validity of whey-based interventions in clinical nutrition protocols (27, 31).

Whey protein's efficacy in attenuating sarcopenia is biologically plausible. It is a fast-digesting protein with high concentrations of branched-chain amino acids (BCAAs), particularly leucine a key activator of the mTOR signaling pathway that drives MPS (19, 22). Moreover, whey is rich in bioactive compounds like lactoferrin and immunoglobulins, which may reduce systemic inflammation a known contributor to muscle degradation in critical illness (25, 27). The biological mechanisms observed in many of the included studies, such as those, support the role of whey not only in muscle preservation but also in functional rehabilitation post-ICU stay. In the clinical context, especially within ICU and post-acute care environments, nutritional interventions must be rapid, effective, and easy to administer (19, 27). Whey protein satisfies these requirements through its solubility and digestibility. Several studies in this review, including those from ProQuest and ScienceDirect, showed that early initiation of whey-based nutritional support correlates with improved outcomes in elderly patients with critical

illness. This is particularly relevant as sarcopenia is often overlooked in acute care settings, despite its association with prolonged hospital stays, ventilator dependence, and higher mortality (19, 22, 25, 27).

This review applied a rigorous methodology guided by PRISMA 2020 standards, covering five major databases, with clear eligibility criteria that focused exclusively on critically ill elderly populations. The review uniquely integrated not only clinical trials but also high-quality cohort studies and systematic reviews, providing a broad yet focused understanding of whey's therapeutic potential in sarcopenia management. Data extraction and risk of bias assessments were conducted systematically using validated tools (RoB 2.0, NOS, AMSTAR 2), enhancing the methodological robustness of our synthesis.

This systematic review synthesized current evidence on the role of whey protein supplementation in mitigating sarcopenia among critically ill elderly individuals. Across diverse study designs including randomized controlled trials, cohort studies, and systematic reviews the findings consistently suggest that whey protein, particularly when delivered early and integrated within a structured nutritional protocol, contributes to improved outcomes in muscle mass, strength, and functional recovery. These benefits are observed not only in acute ICU settings but also in post-discharge rehabilitation contexts, emphasizing the value of protein-centered nutritional strategies throughout the continuum of critical care (19, 22, 25, 27).

The biological plausibility of whey's efficacy is supported by its rich leucine content, which activates the mTOR signaling pathway and enhances muscle protein synthesis (MPS), as well as its potential to modulate inflammatory responses and support nitrogen balance in catabolic states. These mechanisms are especially relevant in older adults, whose anabolic resistance and vulnerability to muscle wasting are well-documented. Despite promising results, substantial heterogeneity in intervention protocols, population characteristics, and outcome definitions limits the generalizability of findings. Moreover, the inclusion of narrative and non-randomized studies introduces potential biases that temper the strength of causal inference (19, 22, 25, 27).

Nonetheless, this review underscored the clinical potential of whey supplementation as a low-risk, biologically plausible, and functionally beneficial strategy for sarcopenia prevention in critically ill elderly patients. As the global population continues to age and ICU survivorship increases, targeted nutritional interventions such as whey protein supplementation should be further investigated and refined within evidence-based, geriatric-focused critical care protocols. Despite its strengths, several limitations must be acknowledged. First, substantial heterogeneity exists across the included studies in terms of intervention dose, duration, protein formulation (pure whey vs. mixed protein blends), and outcome measures. Many studies also lacked long-term follow-up, making it difficult to assess sustained benefits of whey supplementation. Additionally, narrative reviews and expert consensus papers formed a considerable portion of the included evidence, which, while informative, limit the strength of causal inference. Finally, the variation in sarcopenia diagnostic criteria across studies may affect comparability and synthesis reliability (19, 22, 25, 27).

Conclusion

The biological plausibility of whey efficacy is supported by its rich leucine content, which activates the mTOR signaling pathway and enhances muscle protein synthesis (MPS), as well as its potential to modulate inflammatory responses and support nitrogen balance in catabolic states. To build on current evidence, future studies should prioritize well-powered, multicenter RCTs that compare different protein formulations, timing of administration (e.g., early vs. delayed feeding), and modes of delivery (e.g., enteral vs. oral) specifically in elderly ICU populations. Standardization of sarcopenia assessment tools and outcome measures is also critical to facilitate meta-analytic synthesis. Moreover, research should explore the cost-effectiveness and feasibility of implementing whey supplementation protocols at scale in critical care settings globally, particularly in low-resource environments.

Acknowledgement

The authors would like to acknowledge that no external institutional, financial, or technical support was received for this study.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Authors' Contribution

I.V.M contributed primarily to the conceptualization of the study, literature screening, data collection, data interpretation, and manuscript drafting. A.H.M contributed to the study methodology, systematic review design, data synthesis, critical revision of the manuscript, and overall supervision of the research process. Both authors reviewed and

approved the final version of the manuscript prior to submission.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

References

1 Gao Y, Huang Y, An R, et al. Risk factors for sarcopenia in community setting across the life course: A systematic review and a meta-analysis of longitudinal studies. *Arch Gerontol Geriatr*. 2025;133:105807. DOI:10.1016/j.archger.2025.105807. PMID:40049056.

2 Qin W, et al. Sarcopenia and mortality among hospitalized older adults: A prospective cohort study. *BMC Geriatr.* 2023;23. DOI:10.1186/s12877-023-03802-2.

3 Papadopoulou SK, et al. Sarcopenia and its impact on quality of life in older adults: A systematic review. Arch Gerontol Geriatr. 2020;90:104110. DOI:10.1016/j.archger.2020.104110.

4 Chowdhury R, et al. Impact of sarcopenia on hospitalization and rehabilitation outcomes in elderly patients. *Clin Nutr.* 2021;40. DOI:10.1016/j.clnu.2020.05.024.

5 Ticinesi A, et al. Sarcopenia: Diagnostic criteria, clinical impact and novel therapeutic approaches. *Eur J Intern Med*. 2020;74. DOI:10.1016/j.ejim.2020.01.006.

6 Lim WS, et al. Economic burden of sarcopenia: A systematic review and implications for public health. *J Cachexia Sarcopenia Muscle*. 2021;12. DOI:10.1002/jcsm.12645.

7 Bischoff-Ferrari HA, et al. Nutrition and muscle health in aging populations: Current evidence and recommendations. *Clin Interv Aging*. 2021;16:2043-2052. DOI:10.2147/CIA.S317597.

8 Moisey LL, et al. Muscle mass and ICU-acquired weakness in critically ill older adults. *Clin Nutr.* 2020;39. DOI:10.1016/j.clnu.2019.06.003.

9 Bear DE, et al. The role of inflammation and nutrition in sarcopenia in the critically ill. *Curr Opin Clin Nutr Metab Care*. 2022;25:100-106. DOI:10.1097/MCO.0000000000000773.

10 Shamshirgardi E, Shahsavani Z, Akbarzadeh M. Vitamin D and frailty in older adults: A review. *Int J Nutr Sci*. 2021;6:70-73. DOI:10.30476/IJNS.2021.88716.1102.

11 Doherty TJ, et al. Inflammation and the pathogenesis of sarcopenia in critically ill patients. *J Cachexia Sarcopenia Muscle*. 2021;12. DOI:10.1002/jcsm.12777.

12 Shamsdin SA, Mehrafshan A, Rakei SM, et al. Evaluation of VEGF, FGF and PDGF and serum levels of inflammatory cytokines in patients with glioma and meningioma in Southern Iran. *Asian Pac J Cancer Prev.* 2019;20:2883-2890. DOI: 10.31557/APJCP.2019.20.10.2883. PMID: 31653130.

13 Malekzadeh S, Owoyele BV, et al SM, Kargar M, Zare S, Jamhiri I, Mehrabani D, Razmkon A, Bahador N. Porphyromonas gingivalis, neuroinflammation and Alzheimer's. *Niger J Physiol Sci.* 2022;37:157-164. DOI: 10.54548/njps.v37i2.1. PMID: 38243562.

14 Malekzadeh S, Edalatmanesh MA, Mehrabani D, et al. Dental pulp stem cells transplantation improves passive avoidance memory and neuroinflammation in trimethyltin-induced Alzheimer's disease rat model. *Galen Med J.* 2021;10:e2254. DOI: 10.31661/gmj.v10i.2254.

15 Gruther W, et al. ICU-acquired sarcopenia: Association with mechanical ventilation and immobility. *Muscle Nerve.* 2022;66. DOI:10.1002/mus.27423.

16 Puthucheary ZA, et al. Acute muscle wasting in critical illness: New insights from imaging and molecular studies. *Intensive Care Med.* 2020;46. DOI:10.1007/s00134-020-05966-0.

17 Alizadeh H, Daryanoosh F, Mehrabani D. Evaluating inflammatory index changes and muscle injuries in male mice after 8 weeks of aerobic exercise and omega-3 consumption. *J Sport Biosci.* 2012;10:77-94. DOI: 10.22059/jsb.2012.21999.

18 Lee J, et al. Sarcopenia and its prognostic impact on critically ill elderly patients in the ICU: A prospective cohort study. *BMC Geriatr.* 2023;23. DOI:10.1186/s12877-023-03711-4.

19 Phillips SM, et al. Whey protein supplementation with or without vitamin D on sarcopenia-related measures: A systematic review and meta-analysis. *Adv Nutr.* 2023;14. DOI:10.1016/j.advnut.2023.05.011.

20 Abbasi A, Emam-Djomeh Z, Ebrahimzadeh Mousavi M. Stability of whey protein nanoparticles at various protein concentrations. *Int J Nutr Sci*. 2017;2:165-169.

21 Sohrabi Z, Eftekhari MH, Akbarzadeh M, et al. Effect of whey beverage fortified with vitamin E on quality of life in hemodialysis patient. *Int J Nutr Sci.* 2017;2:85-91.

22 Isanejad M, Mazidi M, Sankaranarayanan R, et al. Effects of whey and soy protein supplementation on inflammatory cytokines in older adults: A systematic review and meta-analysis. *Br J Nutr.* 2023;129. DOI:10.1017/S0007114522001787. PMID: 35706399.

23 Vojdani Z, Talaei Khozani T, Dehghani F, et al.

Effect of hydro-alcoholic extract of soybean on embryonic growth and ossification indices in mouse. *J Appl Anim Res*. 2007;31:117-120. DOI :10.1080/09712119.2007.9706644.

24 Sholehvar F, Mehrabani D, Yaghmaei P, et al. Survival of dental pulp stem cells: The effect of soymilk and milk. *J Adv Biomed Sci*. 2015;5:425-434.

25 Wang JH, Zhang F, Luo HY, et al. Improving sarcopenia in older adults: A systematic review and meta-analysis of randomized controlled trials of whey protein supplementation with or without resistance training. *J Nutr Health Aging*. 2024;28:100184. DOI:10.1016/j.jnha.2024.100184. PMID: 38350303.

26 Mojtahed Jaberi F, Tahami M, Torabinezhad S, et al. The healing effect of soybean and avocado mixture on knee cartilage defects in a dog animal model. *Comp Clin Pathol*. 2012;21:661-666. DOI: 10.1007/s00580-010-1152-9.

27 Morato-Martínez R, et al. Leucine-rich whey protein in elderly ICU survivors. *J Cachexia Sarcopenia Muscle*. 2022;13.

28 Deutz NEP, et al. Supplemental protein intake and muscle function in elderly patients. *J Nutr*. 2016;146. DOI:10.3945/jn.116.230912.

29 Xu J, et al. Meta-analysis of protein interventions in ICU patients. *Clin Nutr*. 2020;39. DOI:10.1016/j.clnu.2020.05.003.

30 Heyland D, et al. Sarcopenia management in critical care: Review of current evidence. *Clin Nutr*. 2017;36. DOI:10.1016/j.clnu.2017.01.020.

31 Zhao Y, et al. Leucine metabolism in inflammation-related sarcopenia. *Eur J Appl Physiol*. 2019;119. DOI:10.1007/s00421-019-04096-3.

32 Rondanelli M, et al. High-protein supplementation in frail ICU survivors. *J Nutr Health Aging*. 2018;22. DOI:10.1007/s12603-018-1098-4.

33 Looijaard WGP, et al. Protein-energy supplementation in elderly ICU patients: RCT evidence. *J Gerontol A Biol Sci Med Sci*. 2019;74. DOI:10.1093/gerona/glz255.

34 Abbas KS, Novochadov VV, Abass KS. The effect of lactose, protein and zinc on biotechnological characteristics of cheese whey using Kluyveromyces yeasts. *Int J Nutr Sci*. 2025;10:685-693. DOI:10.30476/IJNS.2025.106350.1439.

35 Gough D, Oliver S, Thomas J. An Introduction to Systematic Reviews. 2nd ed. London: SAGE Publications; 2017.

36 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. DOI:10.1136/bmj.n71. PMID: 33782057.

37 Bramer WM, Giustini D, de Jonge GB, et al. Optimal database combinations for literature searches in systematic reviews: A prospective exploratory study. *Syst Rev*. 2017;105:84-92. DOI: 10.1186/s13643-017-0644-y. PMID: 29208034.

38 Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.3. London: Cochrane; 2022.

39 Paez A. Grey literature: An important resource in systematic reviews. *J Evid Based Med*. 2017;10:233-240. DOI:10.1111/jebm.12266. PMID: 28857505.

40 Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48:601. DOI: 10.1093/ageing/afz046. PMID: 31081853.

41 World Health Organization. World Report on Ageing and Health. Geneva: World Health Organization; 2015.

42 Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898. PMID: 31462531.

43 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2014.

44 Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions. *BMJ*. 2017;358:j4008. DOI:10.1136/bmj.j4008. PMID: 28935701.

45 Mehrabani D, Masoumi SJ, Masoumi AS, et al. Role of diet in mesenchymal stem cells' function: A review. *Int J Nutr Sci*. 2023;8:9-19. DOI: 10.30476/ijns.2023.97788.1221.

46 Hinkelmann JV, de Oliveira NA, Marcato DF, et al. Nutritional support protocol for patients with COVID-19. *Clin Nutr ESPEN*. 2022;49:544-550. DOI:10.1016/j.clnesp.2022.03.002. PMID: 35623865.

47 Lim WS, Cheong CY, Lim JP, et al. Singapore clinical practice guidelines for sarcopenia: Screening, diagnosis, management and prevention. *J Frailty Aging*. 2022;11:348-369. DOI:10.14283/jfa.2022.59. PMID: 36346721.

48 James PT, Ali Z, Armitage AE, et al. The role of nutrition in COVID-19 susceptibility and severity of disease: A systematic review. *J Nutr*. 2021;151:1854-1878. DOI:10.1093/jn/nxab059.

PMID: 33982105.
49 Berger MM, Amrein K, Barazzoni R, et al. The science of micronutrients in clinical practice: Report on the ESPEN symposium. *Clin Nutr*. 2024;43:268-283. DOI:10.1016/j.clnu.2023.12.006. PMID: 38104489.
50 Yeh DD, Martin M, Sakran JV, et al. Advances in nutrition for the surgical patient. *Curr Probl Surg*. 2019;56:343-398. DOI:10.1067/j.cpsurg.2019.04.003. PMID: 31511146.
51 Jones C, Eddleston J, McCairn A, et al. Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: A randomized controlled trial. *J Crit Care*. 2015;30:901-907. DOI:10.1016/j.jcrc.2015.05.014. PMID: 26004031.
52 Pereira CGM, Santana ERS, Ramos JER, et al. Low serum zinc levels and associated risk factors in hospitalized patients receiving oral or enteral nutrition: A case-control study. *Clin Ther*. 2021;43:e39-e55. DOI:10.1016/j.clinthera.2020.12.006. PMID: 33388174.
53 Szklarzewska S, Mottale R, Engelman E, et al. Nutritional rehabilitation after acute illness among older patients: A systematic review and meta-analysis. *Clin Nutr*. 2023;42:309-336. DOI:10.1016/j.clnu.2023.01.013. PMID: 36731161.
54 Fetterplace K, Deane AM, Tierney A, et al. Targeted full energy and protein delivery in critically ill patients: A pilot randomized controlled trial (FEED Trial). *JPEN J Parenter Enteral Nutr*. 2018;43:68-79. DOI:10.1002/jpen.1166. PMID: 29701878.
55 Scarcella M, Scarpellini E, De Rosa S, et al. Impact of protein and nutritional support on the muscular status of critically ill patients: A pilot, prospective, and exploratory study. *Nutrients*. 2025;17:497. DOI:10.3390/nu17030497. PMID: 39940354.
56 Goes-Santos BR, Carson BP, da Fonseca GWP, et al. Nutritional strategies for improving sarcopenia outcomes in older adults: A narrative review. *Pharmacol Res Perspect*. 2024;12:e70019. DOI:10.1002/prp2.70019. PMID: 39400516.
57 Reinhold S, Yeginsoy D, Hollinger A, et al. Protein delivery in intermittent and continuous enteral nutrition with a protein-rich formula in critically ill patients: A protocol for the prospective randomized controlled proof-of-concept Protein Bolus Nutrition (Pro BoNo) study. *Trials*. 2020;21:740. DOI:10.1186/s13063-020-04635-1. PMID: 32843075.
58 Hillinger P, Markl-Le Levé A, Woyke S, et al. The impact of protein feed on the urea-to-creatinine ratio: A retrospective single-center study. *Nutrients*. 2025;17:1293. DOI:10.3390/nu17081293. PMID: 40284158.
59 Umbrello M, Brogi E, Formenti P, et al. Ultrasonographic features of muscular weakness and muscle wasting in critically ill patients. *J Clin Med*. 2024;13:26. DOI:10.3390/jcm13010026. PMID: 38202033.
60 Cehan VD, Cehan AR, Pui MC, et al. A new perspective on overfeeding in the intensive care unit (ICU): Challenges, dangers and prevention methods. *Life (Basel)*. 2025;15:828. DOI:10.3390/life15050828. PMID: 40430254.
61 Damanti S, Senini E, De Lorenzo R, et al. Acute sarcopenia: Mechanisms and management. *Nutrients*. 2024;16:3428. DOI:10.3390/nu16203428. PMID: 39458423.
62 Aldrich L, Ispoglou T, Prokopidis K, et al. Acute sarcopenia: Systematic review and meta-analysis on its incidence and muscle parameter shifts during hospitalisation. *J Cachexia Sarcopenia Muscle*. 2025;16:e13863. DOI:10.1002/jcsm.13662. PMID: 40464160.
63 Barone M, Baccaro P, Molfino A. An overview of sarcopenia: Focusing on nutritional treatment approaches. *Nutrients*. 2025;17:1237. DOI:10.3390/nu17071237. PMID: 40218995.
64 Tarnawski J, Czub M, Dymecki M, et al. Anabolic strategies for ICU-acquired weakness: What can we learn from bodybuilders? *Nutrients*. 2024;16:2011. DOI:10.3390/nu16132011. PMID: 38999759.
65 Ye SC, Mao YT, Huang BL, et al. Association between the geriatric nutritional risk index and adverse post-extubation outcomes for critically ill older adults: A retrospective study. *BMC Pulm Med*. 2025;25:151. DOI:10.1186/s12890-025-03600-5. PMID: 40181325.
66 Seğmen F, Aydemir S, Kayan T, et al. Clinical significance of sarcopenia defined by the cross-sectional area of the masseter muscle in cerebrovascular events: A retrospective cohort study. *Medicina (Kaunas)*. 2025;61:268. DOI:10.3390/medicina61020268. PMID: 40005385.
67 Formenti P, Menozzi A, Sabbatini G, et al. Combined effects of early mobilization and nutrition on ICU-acquired weakness. *Nutrients*. 2025;17:1073. DOI:10.3390/nu17061073. PMID: 40292494.
68 Scarcella M, Scarpellini E, De Rosa S, et al. Impact of protein and nutritional support on the muscular status of critically ill patients: A pilot, prospective, and exploratory study. *Nutrients*. 2025;17:497. DOI:10.3390/nu17030497. PMID: 39940354.

69 Trivedi A, Maheshwari R, Tarnow-Mordi WO, Saxena N. Lactoferrin for the postoperative management of term neonates after gastrointestinal surgery. Cochrane Database Syst Rev. 2023;5:CD012218. DOI:10.1002/14651858.CD012218.pub2. PMID: 37233609.

70 Eaton JC, Rothpletz-Puglia P, Dreker MR, et al. Effectiveness of provision of animal-source foods for supporting optimal growth and development in children 6 to 59 months of age. *Cochrane Database Syst Rev*. 2019;2:CD012818. DOI:10.1002/14651858.CD012818.pub2. PMID: 30779870.