Effect of β-Hydroxy-β-methyl butyrate (HMB) Supplementation on Muscle Changes and Clinical Outcomes with Sonography Assessment in ICU: A Systematic Review

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Keywords. β-hydroxy-β-methyl butyrate (HMB), critical illness, muscle atrophy, nutritional supplementation, muscle strength

Introduction. To evaluate the effects of β-Hydroxy-β-methyl butyrate (HMB) supplementation on muscle changes in critically ill patients, focusing on muscle mass, strength, and functional recovery.

Methods. A literature search was conducted -across multiple electronic databases, including PubMed, Scopus, and Web of Science, from database inception to December 2023. Data extraction was performed using a standardized form, and quality assessment was -assessed using the Newcastle-Ottawa Scale (NOS).

Results. Six randomized controlled trials (RCTs), comprising 398 participants, were included in the analysis. The studies enrolled intensive care unit (ICU) patients with trauma, liver cirrhosis, or those requiring mechanical ventilation. The HMB dose was 3 g/d, and the duration of supplementation ranged from 10 to 84 days. Regarding muscle mass changes, no significant differences in diaphragm or quadriceps muscle thickness were found in one study ($P = .87$). However, a subgroup analysis of patients with lower SOFA scores showed that HMB supplementation significantly preserved muscle volume ($P = .047$). In another trial, HMB supplementation significantly improved quadriceps thickness ($P < .05$) compared with placebo. Additionally, significant improvements in muscle function were observed in the HMB group, including better performance in the chair-stand and six-minute walk tests ($P < .05$). HMB supplementation also reduced net protein breakdown and increased amino acid production in muscle, although these metabolic improvements did not consistently translate into measurable preservation of muscle mass.

Conclusions. HMB supplementation in critically ill patients may offer modest benefits in preserving muscle mass and improving functional recovery, particularly in patients with less severe illness.

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INTRODUCTION

Admission to the intensive care unit (ICU) is frequently associated with severe physiological stress, prolonged immobilization, systemic inflammation, and inadequate nutritional intake, all of which contribute to rapid skeletal muscle wasting and ICU-acquired weakness.[1] ICU-acquired muscle wasting affects approximately 40 to 50% of critically ill patients and may develop within the first week of ICU admission, with muscle mass declining by up to 15 to 20% during the initial 7 to 10 days in patients requiring prolonged mechanical ventilation.[2] Muscle wasting is particularly common in patients with sepsis, trauma, burns, or other severe systemic illnesses and is characterized by a substantial loss of muscle mass and strength.[1,2] In addition to its clinical consequences, ICU-acquired weakness imposes a considerable economic burden by increasing ICU and hospital length of stay, rehabilitation requirements, healthcare costs, and long-term disability.[3] Furthermore, muscle wasting is independently associated with prolonged mechanical ventilation, higher rates of hospital-acquired infections, poorer functional recovery, increased mortality, and greater healthcare resource utilization.[4] Therefore, preventing or attenuating muscle loss has become a major therapeutic goal in the management of critically ill patients.

Various non-pharmacological strategies have been employed to mitigate muscle loss in the critically ill, ranging from early mobilization to nutritional support. Among the latter, specific amino acids and supplements have garnered attention for their potential to enhance muscle protein synthesis and minimize muscle breakdown during acute illness.[5] HMB is primarily known for its role in supporting muscle protein turnover. As a metabolite of leucine, one of the essential branched-chain amino acids (BCAAs), HMB plays a vital role in stimulating muscle protein synthesis while simultaneously inhibiting protein degradation. These dual effects make it a particularly attractive supplement for critically ill patients who are at high risk for muscle loss due to the catabolic nature of critical illness.[6] Various studies have shown that HMB supplementation helps reduce muscle loss, promotes muscle regeneration, and improves strength, which may contribute to faster recovery and better functional outcomes.[7-9]

In clinical settings, the impact of HMB supplementation has been examined in a variety of studies, including those involving patients with chronic obstructive pulmonary disease (COPD),[13] cancer,[14] and, more recently, critically ill individuals.[11] These studies have consistently demonstrated that HMB supplementation can reduce the extent of muscle loss, improve muscle strength, and enhance functional recovery. In critically ill patients, particularly those in the intensive care unit (ICU), maintaining muscle mass is crucial for improving physical recovery and reducing the likelihood of developing long-term complications, such as post-intensive care syndrome (PICS), which includes both physical and psychological impairments.[11]

While HMB has shown promise in muscle preservation, its role in the broader context of critical illness management, including its interaction with other therapeutic interventions such as nutrition and exercise, is still not fully understood. Therefore, this review aims to explore the effect of HMB supplementation on muscle changes in critically ill patients. Understanding the role of HMB in muscle preservation could provide valuable insights into improving the outcomes of critically ill patients, reducing complications, and facilitating quicker recovery, both during hospitalization and in the long-term rehabilitation process.

MATERIALS AND METHODS

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[16]

Search Strategy

A comprehensive literature search was conducted in multiple electronic databases, including PubMed, Scopus, and Web of Science, to identify studies investigating the Effect of β-HMB supplementation on muscle changes in critically ill patients. The following keywords were used: "β-Hydroxy-β-methyl butyrate (HMB)", "critical illness", "muscle atrophy", "nutritional supplementation", "muscle strength", "lean body mass", "muscle regeneration", "ICU patients", " clinical outcomes", "muscle wasting", and "muscle loss". The search was limited

to these electronic databases; hand searching of reference lists and grey literature sources was not performed. We also included relevant studies published in languages other than English through translation.

Study Selection

After removing duplicate records, the titles and abstracts of the remaining studies were screened for eligibility.

Exclusion criteria. Studies were excluded if they involved patients not admitted to the intensive care unit (ICU), including those in general wards or outpatient settings; patients with non-critical conditions such as elective surgery or stable chronic diseases; interventions not involving β-Hydroxy-β-methylbutyrate (HMB) supplementation; studies that did not assess muscle-related outcomes (e.g., muscle mass, strength, or function); studies including populations with conditions that could confound muscle assessment (e.g., neuromuscular disorders or severe malnutrition unrelated to critical illness); studies without appropriate control groups, such as case reports or expert opinions; and studies with HMB supplementation duration of less than 7 days or without sufficient follow-up.

Inclusion criteria. Eligible studies included patients admitted to the ICU due to conditions such as sepsis, trauma, burns, or respiratory failure; studies involving HMB supplementation alone or in combination with other nutritional interventions in the ICU setting; studies assessing muscle mass, strength, or function (e.g., grip strength, muscle cross-sectional area) as primary or secondary outcomes; and randomized controlled trials (RCTs) or observational studies with appropriate control groups.

A meta-analysis was not performed due to substantial heterogeneity in study populations, interventions, and outcome measures across the included studies. Therefore, the findings were synthesized narratively.

Data Extraction and Quality Assessment

Data were extracted from the selected studies using a standardized form by two independent reviewers. The extracted information included authors' names, study location, publication date, sample size, patient demographics (age, gender, HMB Dose (g/d), body composition, strength and functionality of muscle, muscle thickness, and femoral muscle volume loss (%) in control and HMB groups, were also recorded.

Other authors independently reviewed the extracted data for potential biases, and final confirmation was obtained through consensus. To assess the methodology and quality of the studies, the Newcastle-Ottawa Scale (NOS) was used.[17] This scale evaluates studies based on selection, comparability, and outcome. Studies with NOS scores of 0 to 3 were classified as low quality, those with scores of 4 to 6 were classified as medium quality, and studies with scores of 7 to 9 were considered high quality. Studies with NOS scores less than 4 were excluded from further analysis (Table 1).

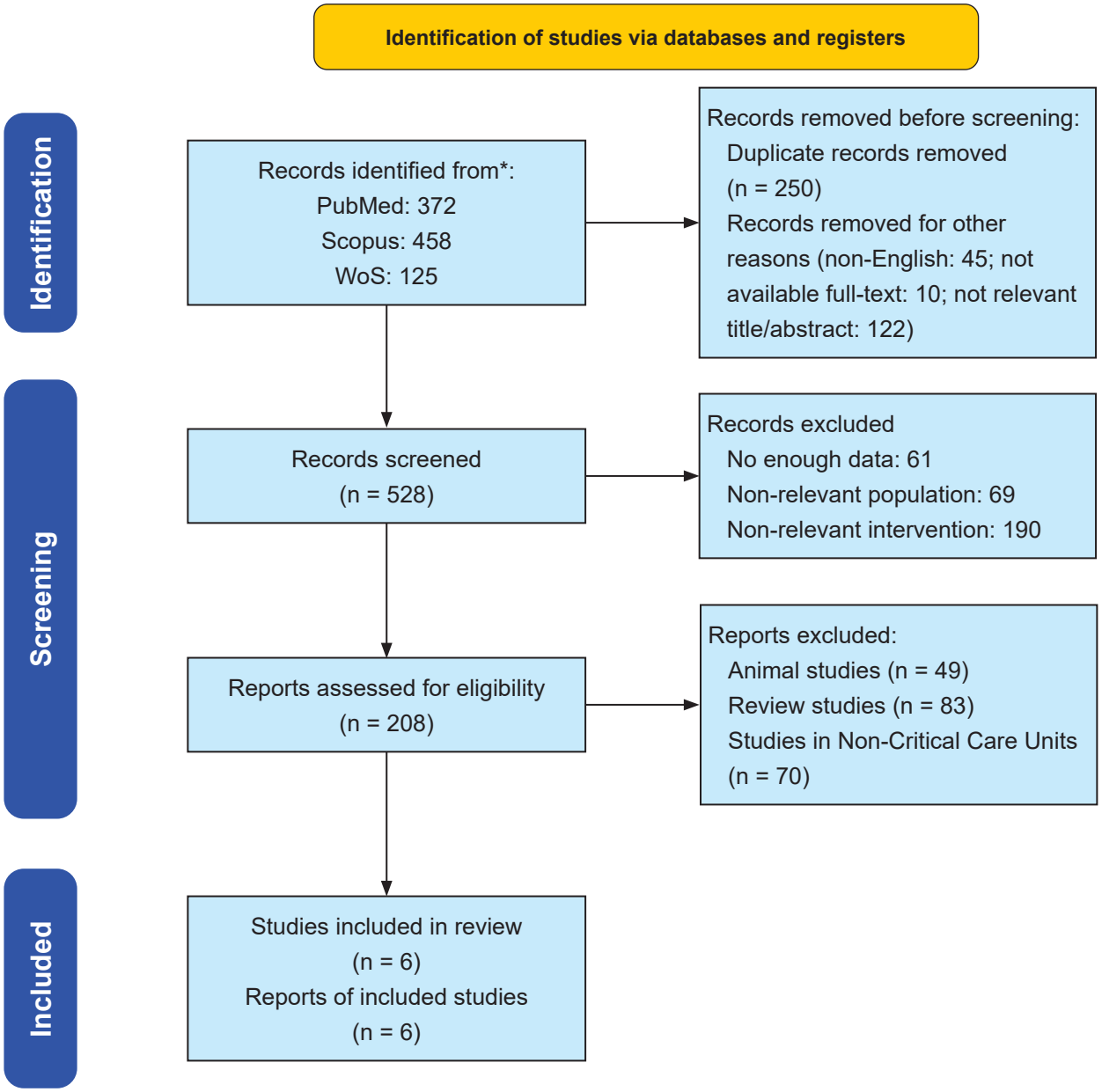
RESULTS

Patient Demographics and the Selection of Studies

Database searches yielded a total of 955 records: 372 from PubMed, 458 from Scopus, and 125 from Web of Science. After removing 250 duplicate records and 177 for various reasons (non-English language, 45; lack of full text, 10; irrelevant titles/abstracts, 122), 528 records remained for screening. During the screening process, 320 studies were excluded due to insufficient data (61), non-relevant populations (69), and non-relevant interventions (190). Of the 208 reports assessed for eligibility, an

Table 1. Quality Assessment of the Included Studies

Study ID	Selection	Comparability	Outcome	Total
Supinski et al. (2021)[18]	4	2	3	9
Lattanzi et al. (2021)[19]	4	2	3	9
Nakamura et al. (2020)[20]	4	1	3	8
Viana et al. (2021)[21]	4	1	3	8
Kuhls et al. (2007)[22]	4	2	3	9
Witthol et al. (2023)[23]	4	1	2	7



PRISMA Flow Diagram Illustrating the Selection of Articles

additional 202 studies were excluded, including animal studies (49), review articles (83), and studies conducted in non-critical care units (70). Ultimately, 6 studies were included in the final review and analysis (Figure).

In total, 6 RCTs investigated how HMB supplementation affected protein metabolism, muscle mass, and functional outcomes. In total, 398 participants from a range of clinical demographics, including critically ill patients, those with liver cirrhosis, and trauma patients, were involved in the research.

Three studies enrolled patients in intensive care units (ICUs) who were on mechanical ventilation, with a mean age ranging from 50.3 ± 7.2 to 65 ± 6.9 years.[18,20,21] These studies were conducted in France, Germany, and Brazil (as reported in Table 2). In addition, the Simplified Acute Physiology Score II (SAPS II) was measured, ranging between 45 and 52. The population recruited by19 included 24 patients, of whom 10 received placebo and 14 received HMB supplementation. All participants

Table 2. Characteristics of Included Studies

Study ID	Country	Mean Age	Control Group	Case Sample Size	Control Sample Size	HMB Dose (g/day)	Duration (days)	Body Composition	Strength	Functionality	Muscle Thickness	Femoral Muscle Volume Loss (%)	
												Control	HMB group
Supinski et al. (2021)[18]	USA	55.5 years	Placebo	18	20	3 g/day	10 days				Quadriceps thickness (cm): Control: 2.8 (2.4,3.3); HMB: 3.1 (2.6,3.6); Diaphragm thickness (cm): Control: 0.26 (0,23-0.29); HMB: 0.26 (0,23-0.30)		
Lattanzi et al. (2021)[19]	Italy	Placebo: 56 ± 4.6 years, HMB: 59.2 ± 8.4 years	Placebo group (sorbitol powder, 3 g/day)	14	10	3 g/day	84 days (12 weeks)	Lean mass (kg/h^2): Placebo: No change (11.3 ± 2.1 to 11.4 ± 2); HMB: No change (11.1 ± 1.6 to 11.2 ± 1.6). Fat mass (kg/h^2): Placebo: No change (10.7 ± 3.4 to 10.3 ± 3.9); HMB: No change (9.3 ± 5.2 to 9.4 ± 4.9). BMI (kg/m^2): Placebo: No change (29.9 ± 4.4 to 29.6 ± 4.6); HMB: No change (29.6 ± 6.8 to 29.2 ± 6.7).	Handgrip (kg): Placebo: No change (32.4 ± 12.6 to 33.4 ± 13.5); HMB: Improved (26 ± 11.3 to 29.1 ± 13.4). Chair Stand Test (s): Placebo: No change (12.2 ± 5.1 to 11.7 ± 4); HMB: Improved (14.2 ± 5 to 11.7 ± 2.3). 6MWT (m): Placebo: No change (387 ± 96 to 396 ± 63); HMB: Improved (361.8 ± 68 to 407.3 ± 73).	Frailty: Liver Frailty Index (LFI) reduced in HMB group (4.1 ± 0.4 to 3.6 ± 0.6, $P < 0.05$); no change in placebo group.			
Nakamura et al. (2020)[20]	Japan	Control: 76.6 ± 12.3 years, HMB: 71.8 ± 12.4 years	Standard ICU nutrition without HMB	26	24	3 g/day (1.5 g twice daily)	10 days	Femoral muscle volume: Control: -14.4 ± 7.1%; HMB: -11.4 ± 8.1%. HMB group showed significant preservation in SOFA < 10 subgroup ($P = 0.04$).	Barthel Index at discharge: Control: 49.7 ± 29.4, HMB: 54.7 ± 36.2 ($P = 0.65$). No significant differences in physical function between groups.	Mechanical ventilation days: Control: 6.8 ± 4.8, HMB: 7.1 ± 5.6 ($P = 0.87$). Hospital stay: Control: 19.8 ± 12.5 days, HMB: 20.4 ± 10.7 days ($P = 0.85$).		14.4 ± 7.1	11.4 ± 8.1

Table 2. Continued

Study ID	Country	Mean Age	Control Group	Case Sample Size	Control Sample Size	HMB Dose (g/day)	Duration (days)	Body Composition	Strength	Functionality	Muscle Thickness	Femoral Muscle Volume Loss (%)	
												Control	HMB group
Viana et al. (2021)[21]	Switzerland	65 [59, 71] years	Placebo with maltodextrin (1.5 g twice daily)	15	15	3 g/day	10 days	Fat-Free Mass (kg): HMB: 62.01 → 58.15 Control: 62.01 → 58.15 Significance: Not significant Fat Mass (kg): HMB: 18.88 → 23.50 Control: 18.88 → 27.62 Significance: $P = 0.0256$ Intracellular Water (L): HMB: 28.69 → 25.89 Control: 28.69 → 25.89 Significance: Not significant Extracellular Water (L): HMB: 20.13 → 17.71 Control: 20.13 → 17.71 Significance: Not significant Phase Angle: HMB: 3.77 → 3.88 Control: 3.77 → 3.21 Significance: $P = 0.0247$	No significant differences in handgrip strength between groups.	QoL: SF-12 Global Health: HMB group improved by +27.39 [1.59, 53.19] points ($P = 0.04$).		Skeletal muscle area (SMA) of of the quadriceps femoris: Placebo Group: SMA reduced from 114.0 cm^2 (day 4) to 100.4 cm^2 (day 15).	Skeletal muscle area (SMA) of of the quadriceps femoris: HMB Group: SMA reduced from 110.5 cm^2 (day 4) to 99.32 cm^2 (day 15).
Kuhls et al. (2007)[22]	USA	Control: 37 ± 3.3 years, HMB: 41 ± 3.2 years	Placebo (isonitrogenous, isocaloric control)	28	22	3 g/day	14 days	Nitrogen balance: Control: -9.0 ± 1.3 g/day, HMB: -6.50 ± 1.2 g/day. Muscle proteolysis (3-MH): No significant differences.	No significant difference in muscle strength observed.	SIRS Score: Control group had higher incidence of SIRS scores: Control: 2.4 +0.2; HMB: 2.3+0.2			
Witthol et al. (2023)[23]	Australia	Control: 49.5 [33.0–58.0], HMB: 52.0 [36.0–56.0]	Placebo (water/orange juice, isocaloric)	26	24	3 g/day	28 days	Weekly muscle ultrasound Control: 4.0 (2.5–5.0) HMB: 3.5 (3.0–5.0)	Weekly handgrip strength Control: 1.0 (0.5–2.0) HMB: 0.0 (0.0–1.0	Physical Function in ICU Test Score (PFIT-s): Control: 10.5 ± 2.1, HMB: 12.7 ± 2.3.			

were below 70 years of age, with a mean age of 59.8 ± 8.3 years. The baseline Liver Failure Index (LFI) was higher in the HMB group (4.1 ± 0.4) compared with the placebo group (3.4 ± 0.6) ($P < .01$). Two trials involved patients with severe injuries, defined as a mean Injury Severity Score (ISS) > 25.[22,23] The participants were mostly male (> 70% in both studies), and their mean ages ranged from 35.6 ± 9.8 to 41.2 ± 12.5 years (Table 2).

Muscle Mass Changes

The effects of HMB supplementation on muscle mass were heterogeneous across the included studies. Supinski *et al.* (2021)[18] reported no significant differences in quadriceps thickness (HMB = 3.1 cm [IQR: 2.6 to 3.6] vs. control = 2.8 cm [IQR: 2.4 to 3.3]) or diaphragm thickness (HMB = 0.26 cm [IQR: 0.23 to 0.30] vs. control = 0.26 cm [IQR: 0.23 to 0.29]) after 10 days of supplementation ($P > .05$). Similarly, Nakamura *et al.* (2020)[20] observed a reduction in femoral muscle volume of 11.4% in the HMB group compared with 14.4% in the control group, although this difference was not statistically significant ($P = .18$). However, subgroup analysis demonstrated that patients with lower SOFA scores in the HMB group experienced significantly less muscle loss compared with controls ($P = .047$), suggesting a potential protective effect in less severely ill patients.

In contrast, Lattanzi *et al.* (2021)[19] reported a significant increase in quadriceps muscle thickness after 12 weeks of HMB supplementation compared with placebo ($P < .05$), indicating a potential benefit with longer intervention duration. Viana *et al.* (2021)[21] found no significant reduction in muscle atrophy after 10 days of supplementation; however, changes in body composition were observed, including a reduction in fat mass and an improvement in phase angle, reflecting improved cellular integrity. Wittholz *et al.* (2023)[23] also reported only a marginal reduction in quadriceps muscle loss in the HMB group compared with placebo, without statistical significance ($P > .05$), suggesting that the effects of HMB on muscle mass may depend on patient population and intervention duration.

Protein Metabolism

Regarding protein metabolism, Viana *et al.* (2021)[21] found that the HMB group significantly reduced net protein breakdown and increased amino acid production. This aligns with the known catabolic effects of critical illness and suggests that HMB may help in reducing protein degradation, even if it does not directly prevent muscle loss. Furthermore, the reduction in liver fragility index in the HMB group provides evidence of its potential benefits in improving overall nutritional status and muscle function in patients with liver cirrhosis.

Kuhls *et al.* (2007)[22] reported that HMB supplementation improved nitrogen balance, indicating a more anabolic state in the body. In contrast, the study found no significant differences in muscle strength or muscle proteolysis markers such as urinary 3-methylhistidine, the improved nitrogen balance suggests that HMB might support muscle protein synthesis, a key factor in mitigating muscle loss in critically ill patients.

Functional and Other Outcomes

The effects of HMB on functional outcomes were also varied. Supinski *et al.* (2021)[3] did not observe any improvement in respiratory muscle strength or time to wean from mechanical ventilation, suggesting that HMB may not significantly affect respiratory function in critically ill patients, at least in the short term. Similarly, Viana *et al.* (2021)[21] found no differences in physical function between the HMB and placebo groups. However, they did report an improvement in net protein anabolism and phase angle, which may indicate better overall health and recovery potential.

Lattanzi *et al.* (2021)[19] observed significant improvements in physical performance, including reduced chair-stand test time and increased six-minute walk test distance. These findings suggest that long-term HMB supplementation may enhance functional recovery, particularly in patients with liver cirrhosis, a population known to suffer from muscle wasting and functional decline. This highlights the potential for HMB supplementation to improve quality of life and physical independence in certain clinical populations.

Kuhls *et al.* (2007)[22] found no significant differences in muscle strength, but they did report that the HMB group had improved nitrogen balance, which could contribute to better functional

outcomes in the long run. Meanwhile, Wittholz *et al.* (2023)[23] demonstrated improvements in physical function as measured by the Physical Function in ICU Test (PFIT-s), with HMB patients showing better recovery than those on placebo, despite only marginal differences in muscle loss.

DISCUSSION

This systematic review included six studies evaluating the effects of HMB supplementation on muscle outcomes in ICU patients. Overall, the findings were heterogeneous. Most studies did not demonstrate statistically significant differences in muscle mass preservation with short-term HMB supplementation; however, some evidence suggested marginal or subgroup-specific benefits, particularly in patients with lower illness severity or in studies with longer intervention durations. Improvements in muscle function were reported in a limited number of trials, including better performance in functional assessments. Overall, while HMB showed potential anabolic and anti-catabolic effects, the evidence for consistent muscle mass preservation in ICU patients remains inconclusive.

Three studies (Supinski *et al.*,[18] Nakamura *et al.*,[20] Viana *et al.*[21]) focused on ICU patients, including those receiving mechanical ventilation, a condition strongly associated with muscle wasting and catabolic stress. The mean age of participants in these studies ranged from 50.3 to 65 years, indicating a population at high risk of muscle loss and functional decline during critical illness. In addition, disease severity, assessed using the Simplified Acute Physiology Score II (SAPS II), ranged between 45 and 52, further highlighting the severity of illness in the recruited populations.

Lattanzi *et al.*'s (2021)[19] study involved patients with liver cirrhosis, a condition often linked with frailty and muscle loss due to altered protein metabolism. The baseline LFI was significantly higher in the HMB group than in the placebo group, suggesting an initial degree of frailty that could benefit from muscle-preserving interventions like HMB. Meanwhile, two trials (Kuhls *et al.*,[22] Wittholz *et al.*[23]) targeted trauma patients and those with significant injuries, such as an Injury Severity Score greater than 25. The trauma patients were mostly male (over 70% in both studies), and their mean ages ranged from 35.6 to 41.2 years, an age group generally characterized by higher resilience but still potentially vulnerable to muscle wasting after severe trauma.

The role of HMB supplementation in critically ill patients has been investigated primarily in relation to its potential to attenuate muscle wasting and improve muscle function. Mechanistically, HMB is a metabolite of leucine that enhances muscle protein synthesis through activation of the mTOR signaling pathway, while simultaneously inhibiting proteolysis by downregulating the ubiquitin–proteasome system and reducing activation of the NF-κB-mediated inflammatory cascade. These combined anabolic and anti-catabolic effects provide a biological rationale for its potential to preserve muscle strength in catabolic conditions such as critical illness.

However, the clinical trials included in this review showed inconsistent functional outcomes. For example, Supinski *et al.* (2021)[18] did not demonstrate significant improvements in muscle thickness or function, which may be explained by the presence of severe systemic inflammation and multi-organ dysfunction in mechanically ventilated ICU patients, conditions that can blunt anabolic signaling pathways such as mTOR and reduce muscle responsiveness to nutritional interventions. Similarly, Viana *et al.* (2021)[21] reported no significant effect on muscle preservation despite observed changes in body composition, suggesting that metabolic alterations (e.g., improved phase angle) may occur independently of measurable gains in muscle strength or mass. In contrast, studies reporting functional improvements were generally conducted in populations with lower disease severity or more stable metabolic conditions, indicating that the efficacy of HMB may be strongly influenced by the underlying inflammatory and catabolic state rather than methodological factors alone.

Consistent with our findings, Phillips *et al.*'s review study (2022) suggests limited and inconsistent evidence supporting the use of HMB as an ingredient in oral nutritional supplements or as a standalone supplement (or in combination with other amino acids) to increase or promote

the retention of lean soft tissue mass (LSTM) and improve strength. However, no evidence indicates that HMB enhances physical function in older adults or clinical populations.[25]

Several studies have investigated the effects of HMB on muscles in various populations. A meta-analysis by Rowlands *et al.* (2009), which examined the impact of HMB supplementation on muscle strength, body composition, and muscle damage in young men, found no effect on body composition.[26] This contrasts with our findings, which indicate a positive effect of HMB on muscle mass in older adults. These differences suggest that the response to HMB and HMB-containing supplements may vary across different populations.

Limitations

This systematic review has several limitations. First, the search strategy was limited to three electronic databases (PubMed, Scopus, and Web of Science), and neither hand searching of reference lists nor grey literature sources were included, which may have led to the omission of relevant studies. Second, the number of included randomized controlled trials was relatively small, which may limit the generalizability of the findings. Third, there was heterogeneity among studies in terms of patient populations, clinical conditions, intervention duration, and outcome measures, which may have influenced the comparability of results. Finally, most included studies had relatively short follow-up periods, limiting conclusions regarding long-term effects of HMB supplementation in critically ill patients.

CONCLUSIONS

HMB supplementation in critically ill patients may offer modest benefits in preserving muscle mass and improving functional recovery, particularly in patients with less severe illness. However, the overall impact on muscle preservation remains inconclusive, and further studies are needed to clarify its long-term effects and to identify patient subgroups that might benefit most from HMB supplementation. The data also suggest that HMB may improve metabolic outcomes and functional parameters, contributing to a more favorable clinical recovery trajectory.

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