Impact of Nutrition Therapy and Rehabilitation on Acute and Critical Illness: A Systematic Review

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Abstract: There have been no reviews describing the efficacy of the combination of both rehabilitation and nutritional treatments. This systematic review aimed to assess the effects of nutritional therapy on patients with an acute and critical illness undergoing rehabilitation. Online searches using PubMed (MEDLINE), Cochrane Central Register of Controlled Trials, EMBASE (ELSEVIER), and Ichu-shi Web databases identified 986 articles, and 16 additional articles were found through other sources. Each trial assessed for the risk of bias using the Cochrane Collaboration’s tool, and the quality of the body of evidence with The Grading of Recommendations Assessment, Development and Evaluation approach. Two randomized controlled trials were included in this review. Jones et al reported that with an enhanced rehabilitation program, there was no effect of nutritional intervention on quality of life (standardized mean difference [SMD] 0.55, 95% confidence intervals [CI] −0.05 to 1.15; \(P = 0.12\)). However, Hegerova et al reported positive effects of physical therapy and oral supplements on muscle mass (0.65; 95% CI, 0.36 to 0.93; \(P < 0.00001\)) and activities of daily living (SMD 0.28, 95% CI 0.00 to 0.56; \(P = 0.05\)). Strengthened nutritional intervention with enhanced rehabilitation treatment for patients with acute and critical illness may possibly be effective for increasing muscle mass, as well as for improving activities of daily living within a short period after discharge.

Keywords: rehabilitation and nutritional treatment, acute and critical illness, muscle mass, activity of daily living, quality of life.

(Received February 12, 2019, accepted July 26, 2019)

Introduction

In the majority of patients with an acute and critical illness, a skeletal muscle reduction accompanied by nutritional status deterioration may have a great influence on clinical prognosis [1]. A hypermetabolic state induces several catabolic hormones in patients with a critical illness that cause catabolism [2]. As a result, skeletal muscle proteolysis is promoted, and malnutrition progresses [2, 3]. Patients with an acute and critical illness may have reduced physical function and abilities due to invasion or disuse syndrome [4, 5].

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Intensive care unit-acquired weakness (ICU-AW) is a generic term for pathological conditions that cause neuromuscular dysfunction such as respiratory withdrawal difficulty and limb muscle weakness after severe illness, including severe polyneuropathy, severe myopathy, and cases of both pathologies [6]. Early rehabilitation is recommended for the improvement of physical function and the reduction of muscle weakness after acute and critical illness in adult patients [7, 8]. Indeed, while conducting early ambulation or rehabilitation treatment during ICU hospitalization does not affect the short- or long-term mortality rates, such treatment is effective for improving walking ability and muscle strength [9].

According to a systematic review, the malnutrition incidence rate of acute and critical illness patients ranges from 38 to 78% [10]. Undernutrition is an independent predictor of the extension of length of stay in the intensive care unit (ICU), re-entry to the ICU, increased risk of infectious diseases, and increased inhospital mortality [10]. Therefore, for patients with difficult oral intake and high nutritional risk, nutritional screening should be conducted as soon as possible after entering the ICU, and starting enteral or parenteral nutrition within 24 to 48 hours of admission is recommended [11].

There have been suggestions that a combination of rehabilitation and nutritional treatment might be effective instead of rehabilitation treatment or nutritional management alone [12]. However, to our knowledge there have been no reviews describing the effects of combined treatment with nutritional therapy and rehabilitation.

The aim of the current systematic review was to assess the effects of nutritional intervention on patients with an acute and critical illness undergoing rehabilitation.

**Methods**

This study was prospectively registered with the PROSPERO (National Institute for Health Research) database (CRD42017067875), and the systematic review was performed in accordance with the Preferred reporting items for systematic reviews and meta-analyses statement (PRISMA) guidelines [13].

All randomized controlled trials (RCTs), except for cross-over trials, irrespective of publication type, publication status, and publication date, were investigated. Abstracts and non-English-language (except Japanese) publications were excluded.

Acute and critical illness was defined as a life-threatening condition that can result in significant morbidity or mortality. Disuse syndrome was defined as follows: secondary disability caused by physical inactivity, symptoms that occur due to immobilization, inactivity or bedrest; symptoms of systems such as the musculoskeletal, circulatory, respiratory, endocrine metabolic, and psychoneurotic systems; and symptoms that have a negative impact on the activities of daily living (ADL). Rehabilitation treatment refers to a comprehensive or individualized expert program over a certain period, regardless of frequency and amount.

We searched PubMed (MEDLINE), Cochrane Central Register of Controlled Trials, EMBASE, and Ichushi Web, which is a Japanese journal database [14], between the inception of each database and April 2018. Additionally, we performed a manual search of the references and author lists of the relevant reviews and articles included in this review. The key search terms and words to identify eligible studies are listed in Fig. 1.

We also searched articles on adverse effects by nutritional intervention using all published studies, regardless of study type. We defined adverse effects as kidney or liver failure, the development of pneumonia, or sepsis, and searched the MEDLINE from the inception of each database until April 2018 with an additional search strategy to key search terms (Fig. 1), including Mesh terms (Pneumonia, Respiratory Tract Infections, Respiratory Aspiration, Sepsis, Shock, Septic, Renal Insufficiency, and Liver Diseases) and text words (pneumon*, pleuropneumon*, bronchopneumon*, bronchit*, tracheobronchit*, aspirat*, Mendelson, respiratory infect, sepsis, septic, renal insufficienc*, kidney failure, renal failure*, liver, and hepati*).

Studies of patients with an acute and critical illness undergoing rehabilitation treatment and those with deconditioning or disuse syndrome undergoing rehabilitation treatment within a few days from onset to hospitalization, were included. Studies that assessed post-surgical condition, and those that included participants aged under 18 years were excluded.
A.  

| Set# | Search (disuse syndrome* [tiab]) OR (disuse atrophy* [tiab]) OR "Immobilization" [mh] OR "Muscular Atrophy" [mh] OR (deconditioning syndrome [tiab]) OR deconditioning [tiab] OR (deconditioning disorders [tiab]) OR (physical deconditioning [tiab]) OR (muscle deconditioning [tiab]) OR (physical inactivity [tiab]) OR (physiological deconditioning [tiab]) OR (general deconditioning [tiab]) OR (hospital-associated deconditioning* [tiab]) OR (hospitalization-associated disability* [tiab]) OR ("low activity" [tiab]) OR inaction [tiab] OR ("low exercise" [tiab]) OR "inpatient rehabilitation" [tiab] OR ward-based [tiab] | Results |
|------|----------------------------------|---------|
| 1    | Search (disuse syndrome* [tiab]) OR (disuse atrophy* [tiab]) OR "Immobilization" [mh] OR "Muscular Atrophy" [mh] OR (deconditioning syndrome [tiab]) OR deconditioning [tiab] OR (deconditioning disorders [tiab]) OR (physical deconditioning [tiab]) OR (muscle deconditioning [tiab]) OR (physical inactivity [tiab]) OR (physiological deconditioning [tiab]) OR (general deconditioning [tiab]) OR (hospital-associated deconditioning* [tiab]) OR (hospitalization-associated disability* [tiab]) OR ("low activity" [tiab]) OR inaction [tiab] OR ("low exercise" [tiab]) OR "inpatient rehabilitation" [tiab] OR ward-based [tiab] | 57730    |
| 2    | Search "Hospitalization" [mh] OR hospitalization [tiab] OR hospitalized [tiab] OR hospital [tiab] OR "Inpatient" [mh] OR inpatient [tiab] OR ("bed rest" [mh]) OR ("bed rest" [tiab]) OR bedrest [tiab] OR "Acute Disease" [mh] OR acute [tiab] OR "acute illness" [tiab] OR acute* [tiab] OR "Critical Illness" [mh] OR "critical illness" [tiab] OR "critically ill" [tiab] | 2081091  |
| 3    | Search ("Feeding Methods" [mh]) OR ("Nutrition Therapy" [mh]) OR ("Enteral Nutrition" [mh]) OR ("Parenteral Nutrition" [mh]) OR ("Protein Hydrolysates" [mh]) OR ("Nutritional Support" [mh]) OR ("Nutritional Requirements" [mh]) OR ("Energy Intake" [mh]) OR ("Dietary Protein" [mh]) OR ("Dietary Supplements" [mh]) OR alimentation [tiab] OR "branched chain amino acids" [tiab] OR BCAA [tiab] OR (dietary disorder* [tiab]) OR (dietary protein* [tiab]) OR (dietary supplement* [tiab]) OR (energy intake [tiab]) OR (enteral nutrition [tiab]) OR enterostomy* [tiab] OR (fat emulsion [tiab]) OR (formulated food* [tiab]) OR gastrostomy [tiab] OR hyperalimentation* [tiab] OR (hypocaloric alimentation* [tiab]) OR (hypocaloric nutrition [tiab]) OR (intragastric feed* [tiab]) OR (intragastric nutrition [tiab]) OR nutrition [tiab] OR (nutrition diseases [tiab]) OR (nutrition disorders [tiab]) OR (nutritional intervention* [tiab]) OR (nutritionalsupport [tiab]) OR (nutritional support [tiab]) OR (parenteral nutrition [tiab]) OR (percutaneous endoscopic gastrostomy* [tiab]) OR (peripheral parenteral nutrition [tiab]) OR (permissive underfeeding [tiab]) OR (post-pyloric feeding [tiab]) OR (post-pyloric nutrition [tiab]) OR (protein hydrolysate [tiab]) OR (supplemental feed* [tiab]) OR (total parenteral nutrition [tiab]) | 702598   |
| 4    | Search ("nutrition" [mh]) OR ("exercise" [mh]) OR ("Physical Therapy Modalities" [mh]) OR ("Early Ambulation" [mh]) OR ("Walking" [mh]) OR ("Nursing Care" [mh]) OR rehabilitation [tiab] OR exercise* [tiab] OR training [tiab] OR (physical therapy [tiab]) OR kinesiotherapy [tiab] OR mobilization [tiab] OR walking [tiab] OR ambulation [tiab] OR (nursing care [tiab]) OR workout [tiab] | 1148158  |
| 5    | Search ("Randomized Controlled Trial" [pt]) OR ("Controlled Clinical Trial" [pt]) OR randomized [tiab] OR placebo [tiab] OR "Drug Therapy" [sh] OR randomized [tiab] OR trial [tiab] OR groups [tiab] NOT ("Animal" [mh] NOT "Humans" [mh]) | 3670933  |
| 6    | Search #1 OR #2 OR #3 OR #4 OR #5 | 92      |
| 7    | Search ("Infant" [mh] OR "Child" [mh]) NOT "Adult" [mh] | 1546823  |
| 8    | Search #6 NOT #7 | 85      |

B.  

| Set# | Search (disuse syndrome*) OR (disuse atrophy*) OR (deconditioning syndrome) OR deconditioning OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | Results |
|------|----------------------------------|---------|
| 1    | (disuse syndrome*) OR (disuse atrophy*) OR (deconditioning syndrome) OR deconditioning OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 939      |
| 2    | (disuse syndrome*) OR (disuse atrophy*) OR (deconditioning syndrome) OR deconditioning OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 2062     |
| 3    | (disuse syndrome*) OR (disuse atrophy*) OR (deconditioning syndrome) OR deconditioning OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 2960     |
| 4    | (disuse syndrome*) OR (disuse atrophy*) OR (deconditioning syndrome) OR deconditioning OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 21952    |
| 5    | (disuse syndrome*) OR (deconditioning syndrome) OR (disuse atrophy*) OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 192011   |
| 6    | (disuse syndrome*) OR (deconditioning syndrome) OR (disuse atrophy*) OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 193364   |
| 7    | (disuse syndrome*) OR (deconditioning syndrome) OR (disuse atrophy*) OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 32322    |
| 8    | (disuse syndrome*) OR (deconditioning syndrome) OR (disuse atrophy*) OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 41195    |
| 9    | (disuse syndrome*) OR (deconditioning syndrome) OR (disuse atrophy*) OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 53444    |
| 10   | (disuse syndrome*) OR (deconditioning syndrome) OR (disuse atrophy*) OR (deconditioning disorders) OR (physical deconditioning) OR (muscle deconditioning) OR (physical inactivity) OR (physiological deconditioning) OR (general deconditioning) OR (hospital-associated deconditioning) OR (hospitalization-associated disability) OR ("low activity") OR inaction OR ("low exercise") OR "inpatient rehabilitation" OR ward-based | 45242    |
| 11   | rehabilitation OR exercise* OR training OR (physical therapy) OR kinesiotherapy OR mobilization OR walking OR ambulation OR (nursing care) OR workout | 45242    |
| 12   | rehabilitation OR exercise* OR training OR (physical therapy) OR kinesiotherapy OR mobilization OR walking OR ambulation OR (nursing care) OR workout | 140023   |
| 13   | rehabilitation OR exercise* OR training OR (physical therapy) OR kinesiotherapy OR mobilization OR walking OR ambulation OR (nursing care) OR workout | 150051   |
| 14   | rehabilitation OR exercise* OR training OR (physical therapy) OR kinesiotherapy OR mobilization OR walking OR ambulation OR (nursing care) OR workout | 79       |
| 15   | rehabilitation OR exercise* OR training OR (physical therapy) OR kinesiotherapy OR mobilization OR walking OR ambulation OR (nursing care) OR workout | 14018    |

Fig. 1. Search strategy. A: PubMed (MEDLINE), B: Cochrane Central Register of Controlled Trials, C: Embase®, D: ICHU-SHI Web (Japan Medical Abstracts Society). *The number of search results is the number before duplicate elimination. **The number of search results is the number after duplicate elimination.
### C.

| Set# | Search for                                                                 | Results  |
|------|-----------------------------------------------------------------------------|----------|
| #1   | (EMB. EXACT. EXPLODE ("muscle atrophy") OR EMB. EXACT. EXPLODE ("immobilization")) | 118503*  |
| #2   | (TI, AB (disuse syndrome*) OR TI, AB (disuse atrophy*) OR TI, AB (deconditioning syndrome) OR TI, AB (deconditioning disorder) OR TI, AB (physical deconditioning) OR TI, AB (muscle deconditioning) OR TI, AB (physical inactivity) OR TI, AB (physiological deconditioning) OR TI, AB (early ambulation) OR TI, AB (general deconditioning) OR TI, AB (hospital-associated deconditioning*) OR TI, AB (hospitalization-associated disability*) OR TI, AB ("low activity") OR TI, AB (inaction) OR TI, AB ("low exercise") OR TI, AB ("inpatient rehabilitation") OR TI, AB (ward-based)) | 36561*  |
| #3   | (S1 or S2)                                                                  | 150356*  |
| #4   | (EMB. EXACT. EXPLODE ("hospitalization") OR EMB. EXACT. EXPLODE ("hospital patient") OR EMB. EXACT ("bed rest") OR EMB. EXACT ("acute disease") OR EMB. EXACT ("critical illness") | 749660*  |
| #5   | (TI, AB (hospitalization) OR TI, AB (hospitalized) OR TL, AB (hospital) OR TI, AB ("bed rest") OR TI, AB (acute) OR TI, AB (acutely) OR TI, AB ("critical illness") OR TI, AB ("critically ill")) | 3035973* |
| #6   | (S4 or S5)                                                                  | 3295674* |
| #7   | (EMB. EXACT. EXPLODE ("artificial feeding") OR EMB. EXACT. EXPLODE ("diet therapy") OR EMB. EXACT. EXPLODE ("enterostomy") OR EMB. EXACT. EXPLODE ("liped emulsion") OR EMB. EXACT. EXPLODE ("elemental diet") OR EMB. EXACT. EXPLODE ("gastrostomy") OR EMB. EXACT. EXPLODE ("nutritional disorder") OR EMB. EXACT. EXPLODE ("protein hydrolysate") OR EMB. EXACT. EXPLODE ("nutritional requirement") OR EMB. EXACT. EXPLODE ("dietary intake") OR EMB. EXACT. EXPLODE ("diet supplementation") ) | 1508070* |
| #8   | (TI, AB (alimentation) OR TI, AB (branched chain amino acid) OR TI, AB (BCAA) OR TI, AB (dietary NEAR disorder*) OR TI, AB (dietary NEAR protein*) OR TI, AB (NEAR supplement*) OR TI, AB (energy NEAR intake) OR TI, AB (enteral NEAR nutrition) OR TI, AB (enterostomy*) OR TI, AB (fat NEAR emulsion) OR TI, AB (formulated NEAR food*) OR TI, AB (gastrostomy*) OR TI, AB (hyperalimentation) OR TI, AB (hypocaloric NEAR nutrition) OR TI, AB (hypocaloric NEAR protein*) OR TI, AB (intragastric NEAR feeding*) OR TI, AB (intragastric NEAR nutrition) OR TI, AB (nutrition NEAR diseases) OR TI, AB (nutrition NEAR disorders) OR (nutrition NEAR intervention*) OR TI, AB (nutrition NEAR requirement*) OR TI, AB (nutrition NEAR support) OR TI, AB (parenteral NEAR nutrition) OR TI, AB (peripheral parental nutrition) OR TI, AB (permissive NEAR underfeeding) OR TI, AB (post-pyloric NEAR feeding) OR TI, AB (post-pyloric NEAR nutrition) OR TI, AB (protein NEAR hydrolysate) OR TI, AB (supplemental NEAR feed*) OR TI, AB (total parenteral nutrition)) | 298961*  |
| #9   | (S7 or S8)                                                                  | 1619536* |
| #10  | (EMB. EXACT. EXPLODE ("rehabilitation") OR EMB. EXACT. EXPLODE ("exercise") OR EMB. EXACT. EXPLODE ("physiotherapy") OR EMB. EXACT. EXPLODE ("mobilization") OR EMB. EXACT. EXPLODE ("walking") OR EMB. EXACT. EXPLODE ("nursing care") | 942889*  |
| #11  | (TI, AB (rehabilitation) OR TI, AB (exercise*) OR TI, AB (training) OR TI, AB (physical NEAR therapy) OR TI, AB (kinesitherapy) OR TI, AB (mobilization) OR TI, AB (walking) OR TI, AB (ambulation) OR TI, AB (nursing NEAR care) OR TI, AB (workout)) | 1102416* |
| #12  | (S10 or S11)                                                                 | 1537421* |
| #13  | (EMB. EXACT. EXPLODE ("randomized controlled trial (topic)") OR EMB. EXACT. EXPLODE ("randomized controlled trial") OR EMB. EXACT. EXPLODE ("controlled clinical trial (topic)") OR EMB. EXACT. EXPLODE ("controlled clinical trial") OR TI, AB (placebo) OR QU (DT) OR TI, AB (randomly) OR TI, AB (trial) OR TI, AB (groups)) | 8373015* |
| #14  | (ANIMAL (YES) NOT HUMAN (YES))                                               | 5070152* |
| #15  | (S13 not S14)                                                                | 7427151* |
| #16  | (S3 and S6 and S9 and S12 and S15)                                            | 670*     |
| #17  | (EMB. EXACT. EXPLODE ("child") NOT EMB. EXACT. EXPLODE ("adult")           | 2091177* |
| #18  | (S16 not S17)                                                                | 636**    |

### D.

| Set# | Search for                                                                 | Results  |
|------|-----------------------------------------------------------------------------|----------|
| #1   | (EMB. EXACT. EXPLODE "(original language") | 34,341   |
| #2   | (TI, AB (disuse syndrome*) OR TI, AB (disuse atrophy*) OR TI, AB (deconditioning syndrome) OR TI, AB (deconditioning disorder) OR TI, AB (physical deconditioning) OR TI, AB (muscle deconditioning) OR TI, AB (physical inactivity) OR TI, AB (physiological deconditioning) OR TI, AB (early ambulation) OR TI, AB (general deconditioning) OR TI, AB (hospital-associated deconditioning*) OR TI, AB (hospitalization-associated disability*) OR TI, AB ("low activity") OR TI, AB (inaction) OR TI, AB ("low exercise") OR TI, AB ("inpatient rehabilitation") OR TI, AB (ward-based)) | 1723,309 |
| #3   | (EMB. EXACT. EXPLODE ("muscle atrophy") OR EMB. EXACT. EXPLODE ("immobilization")) | 865,735  |
| #4   | (TI, AB (disuse syndrome*) OR TI, AB (disuse atrophy*) OR TI, AB (deconditioning syndrome) OR TI, AB (deconditioning disorder) OR TI, AB (physical deconditioning) OR TI, AB (muscle deconditioning) OR TI, AB (physical inactivity) OR TI, AB (physiological deconditioning) OR TI, AB (early ambulation) OR TI, AB (general deconditioning) OR TI, AB (hospital-associated deconditioning*) OR TI, AB (hospitalization-associated disability*) OR TI, AB ("low activity") OR TI, AB (inaction) OR TI, AB ("low exercise") OR TI, AB ("inpatient rehabilitation") OR TI, AB (ward-based)) | 163,272  |
| #5   | (EMB. EXACT. EXPLODE "(original language") | 190      |
| #6   | (EMB. EXACT. EXPLODE "(original language") | 158      |

**Note:** The table includes search terms and results for specific topics, such as rehabilitation, exercise, physiotherapy, and various clinical conditions. The results are expressed in asterisks (*) with numerical counts.
The intervention group was defined as subjects who had received nutritional treatment such as nutritional lectures, counseling, fortified foods, oral nutritional supplements, or parenteral/enteral nutrition. Parenteral or enteral nutrition, regardless of calories and elements, were included in the intervention group. Interventions of micronutrients alone (i.e. vitamin or mineral supplements alone) were excluded, because the present study focused on the nutritional intervention of energy and/or protein. The control group included subjects who had undergone sham interventions or no intervention.

The primary outcome was activities of daily living (ADL) measured on validated scales such as the Barthel Index (BI) [15]. The secondary outcomes were all-cause mortality, quality of life (QOL) measured on any validated scale, complications (falling or pneumonia), and muscle strength, such as hand grip strength at a certain period following intervention.

All included articles were reviewed by two review authors (SM and HS). Titles and/or abstracts of the studies were retrieved and screened independently by the review authors to identify studies that potentially met the inclusion criteria outlined above. The full text of these potentially eligible studies were retrieved and independently assessed for eligibility by the review authors. Any disagreement between them over the eligibility of the studies were resolved through discussion. The review authors independently extracted study characteristics and outcome data from the included trials. If there were unclear data, we contacted the trial authors and received more detailed data by email.

The review authors independently assessed risk of bias of each trial using the Cochrane Collaboration’s tool [16]. We used the following characteristics: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases. Any differences in opinion were resolved through discussion, and each judgement was based on consensus. We judged the risk of bias for each item as ‘low risk’, ‘high risk’ or ‘unclear risk’.

Statistical analysis was performed using Review Manager version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) to pool results with the random effects model and calculate risk ratios (RR) with 95% confidence intervals (CI). The effect sizes were represented by the standardized mean difference (SMD), because the studies assessed the primary or secondary outcomes using a variety of measurements. We used the differences between the mean and standard deviation of continuous data in each study for SMD calculation. The threshold for significance was set at \( P < 0.05 \).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [17] was used to assess the quality of the body of evidence relating to the primary and secondary outcomes. We graded the evidence of each outcome as “very low”, “low”, “moderate”, or “high” according to the GRADE working group criteria.

Results

There was a total of 986 articles from MEDLINE (n=113), the Cochrane Library (n=79), EMBASE (n=636), and Ichu-shi Web (n=158) that were searched in all databases. Sixteen studies were identified through other sources. After removing duplicate articles, 864 studies were screened. Fig. 2 shows the PRISMA flow chart of the articles included in this review.

Two RCTs were included for systematic review [18, 19]. One was reported by Hegerova et al, who examined the effects of the provision of physical therapy and oral supplements on acute and critical illness patients over the age of 78 early after hospitalization [18]. The other was by Jones et al, who investigated the combined effects of a dietary supplement containing glutamine and an essential amino acid, and a 6-week enhanced physical therapy and exercise program on acute and critical illness patients over the age of 45 [19].

The details of the two RCTs are provided in Table 1. Neither RCT study investigated all mortality and complications (falling or pneumonia) in the outcomes. Meanwhile, ADL and QOL were investigated by BI [18] and the physical function scores of the Short Form 36 [20], or European quality of life 5 dimensions [21] (SF-36 / EQ-5D) [19], respectively. Although muscle strength was not measured, 6-minute walk test (6MWT) was conducted [19], and lean body mass (LBM) with bioelectrical impedance analysis [18], indirectly involved in the muscle strength, was measured.
We determined the allocation, which included sequence generation and concealment, of the Jones study, as low risk of bias [19], while the Hegerova study was determined as unclear risk of bias, because of insufficient information [18]. In blinding, the Hegerova study was determined to be high risk of bias, because the research participants were not blinded for nutritional intervention [18], and the Jones study was determined as unclear risk of bias due to insufficient information [19]. As for the outcome data, the Hegerova study was determined as low risk of bias [18], but the Jones study was judged as high risk of bias, due to not reaching sufficient recruitment by power calculation, a lack of follow-up for over 20% of the participants, and some study outcomes that were not included in the article [19]. Regarding other sources of bias, the Jones study was assessed as low risk of bias [19], whereas the Hegerova study was high risk, because the intensity of the rehabilitation program during hospitalization varied among the participants [18].

The subject characteristics of the RCT by Hegerova et al [18] are shown in Table 1. Their study demonstrated that oral supplements and rehabilitation programs by ergometer and physiotherapy might result in a difference in BI from the normal diet and rehabilitation program at 6 months after discharge (SMD 0.28, 95% CI 0.00 to 0.56; \( P = 0.05 \) at 3 month, 0.30; 95%CI, 0.02 to 0.58; \( P = 0.03 \) at 6 months), but there were no differences at 9 and 12 months after discharge (Fig. 3).

**Table 1. Basic characteristics of randomized controlled trials enrolled in the systematic review**

| Author/Year | Sample Size | Age | Randomization | Blinding | Design | Intervention | Control | Intervention duration | Outcome | Observation duration |
|-------------|-------------|-----|---------------|----------|--------|--------------|---------|----------------------|---------|---------------------|
| Hegerova et al 2015 | 200 | 78 or older | Not described | Not described | Parallel | 1. Standard diet + Nutritional supplement 2. Physiotherapy (initiated on day 1 of hospitalization) | 1. Standard diet 2. Physiotherapy (after improvement of the underlying disease) | Entire hospital stay | LBM | 12 months |
| Jones et al 2015 | 93 | 45 or older | Computed random generation | Double for nutrient randomization | 2 × 2 factorial | 1. Standard diet + GEAA 2. PEPSE+ward based physiotherapy | 1. Standard diet 2. Ward based physiotherapy | Entire hospital stay | 6 MWT | 3 months |

LBM: lean body mass, BI: Barthel index, GEAA: supplementary glutamine and essential amino acids mixture, PEPSE: early physiotherapy and program of enhanced physiotherapy and structured exercise, 6MWT: 6-minute walk test distance, SF-36: the short form 36, EQ-5D: European quality of life 5 dimensions, HADS: the hospital anxiety and depression scale
Health-related quality of life was assessed using the SF-36 and EQ-5D by Jones et al [19], and nutritional intervention had no significant effect on QOL (SMD 0.55, 95% CI -0.05 to 1.15; \( P = 0.12 \) with early physiotherapy and program of enhanced physiotherapy and structured exercise [PEPSE], SMD -0.46, 95% CI -1.04 to 0.12; \( P = 0.07 \) without PEPSE), regardless of whether an enhanced rehabilitation program was implemented at 3 months after ICU discharge (Fig. 4).

Intervention group had a certain positive effect on LBM (0.65; 95% CI, 0.36 to 0.93; \( P < 0.00001 \) at 3 months), evaluated by bioimpedance every 3 months for 12 months after discharge [19]. On the other hand, intervention group did not have a favorable effect on 6MWT [18] (Fig. 5).

We judged the outcomes of LBM and BI as very low due to very serious indirectness of evidence, as well as serious imprecision and risk of bias. We also judged the outcomes of 6 MWT, SF-36, EQ-5D as low due to serious imprecision and risk of bias. Consequently, the grade for the quality of evidence was defined as very low. No studies reported adverse effects by nutritional intervention.

### Discussion

Only two RCTs were included in the present systematic review. It was suggested that early nutritional intervention might be useful for increasing muscle mass and ADL, but not for improving QOL in patients with an acute and critical illness undergoing rehabilitation treatment. Most past RCTs have reported the effects of intervention focused only on nutritional therapy or rehabilitation treatment. Therefore, there have been very few trials that evaluated the effects of combined rehabilitation treatment and nutritional therapy. Previous systematic reviews, which analyzed the effects of nutritional therapy only or rehabilitation treatment

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**Fig. 3. Forest plot of effect size in activities of daily living.** Activities of daily living was measured by the Barthel Index (BI).
In the current systematic review, among the outcomes, “all mortality rate” and “complications” could not be analyzed, because no corresponding study exists. In accordance with the GRADE approach, the body of evidence for each outcome was assessed as very low or low, following quality assessments such as risk of bias, directness, and precision.

The current systematic review suggested that the intervention of rehabilitation treatment and nutritional therapy may have shown positive effects on muscle mass and ADL. Meanwhile, only nutritional intervention without PEPSE (enhanced rehabilitation program) might have a negative effect on QOL [19]. Although this result is paradoxically very important, it is difficult to present this as evidence with only the outcome of this systematic review, due to the small sample size and number of trials. It might be difficult to design a relevant and rational protocol to verify the effect of nutritional intervention [25]. In previous studies, early energy/protein administration after ICU admission did not necessarily prevent ICU-AW, or improve physical function [26] or mortality [27]. In future trials, a well-verified protocol that takes into account nutrient requirements, nutrient amount, administration method, administration timing, and time period is necessary.

The effects of intervention confirmed in this review may be limited, because levels of nutritional and rehabilitation intervention that both studies require were higher than the standard. Patients might be burdened by the continuation of reinforced rehabilitation and nutritional treatment using protein-enhanced supplements not only during hospitalization but also after discharge. An individual setting might be, of course,
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required for intervention period and load. However, the combination of rehabilitation and nutritional treatment may improve ADL at the individual level and lead to cost-effectiveness at the social level, regarding the prevention of mortality and readmission [28, 29].

A direct undesirable effect of intervention could not be determined because it has not been reported in previous RCTs or observational studies. Feinberg et
al’s study, concerning the nutrition-only intervention, did not report adverse effects of nutrition support [22]. However, as they suggested that the result might be due to an underestimation of the adverse effects of nutrition support [22], a future observational study, concerning the harm of nutrition support, may be necessary.

Both muscle mass and ADL had a very low certainty of evidence due to very serious indirectness, and serious imprecision and risk of bias. In addition, QOL had a low certainty of evidence due to imprecision and risk of bias. We added 6MWT to the outcome as a complement, but considered that 6MWT had a very low certainty of evidence because it was not an originally selected outcome. Since 6MWT shows walking ability and exercise tolerance, and might directly be associated with ADL, it is necessary to consider exercise tolerance as an outcome in a future systematic review.

To our knowledge, this is the first systematic review to confirm the simultaneous intervention effects of the combination of rehabilitation and nutritional treatment. Although the quality of evidence in each outcome was judged to be low, the possibility of obtaining certain positive effects on muscle mass and ADL was demonstrated. Because ICU-AW is considered to be a similar condition to sarcopenia in the ICU [30], the combination of rehabilitation and nutritional treatment may produce positive effects on patients with an acute and critical illness, regarding the prevention and treatment of sarcopenia [12, 31, 32].

There are several limitations in this review. First, only two RCTs could be included. We could not obtain information on all of the originally selected outcomes and perform a meta-analysis due to the small number of preceding RCTs. Therefore, the quality of evidence across all outcomes was low. Second, acute and critical illness as defined in this review included various clinical conditions and diseases. It is also worth noting that the two RCTs included in this review were premised on restarting oral intake after admission. Previous studies have already reported that early resumption of oral intake after hospitalization has a positive impact on physical function improvement and disease treatment [33, 34]. Therefore, further studies are necessary to confirm whether the results of the current systematic review can be applied to all acute and critical illnesses. It is also assumed that negative outcomes were not announced, so there is a possibility that the publication bias has not been verified. Furthermore, the search restriction was a possible limitation. We were unable to obtain trials that were still unpublished or in press or were not published in the English language. Based on this information, critical outcomes may be overturned by future studies, like an ongoing RCT [35]. Continuous surveys and monitoring are required. In conclusion, we suggest implementation of strengthened nutritional intervention for patients with an acute and critical illness who undergo rehabilitation treatment, based on the premise of an enhanced rehabilitation program.

Acknowledgements

We would like to thank Dr. Yuu Tanaka, Mr. Takaaki Suzuki, Dr. Eishu Nango, and Dr. Hidemichi Yuasa.

Conflict of Interest

Drs. Kou, Momosaki, Miyazaki, Wakabayashi have no conflicts of interest to declare. Department of Disaster and Comprehensive Medicine, Fukushima Medical University is an endowment department (Corresponding author, Dr. Shamoto, works as a lecturer), which was established from a source other than the university itself; KOWA YAKUHIN (the present Alfresa Holdings Corporation), TOSHIBA CORPORATION, THE TOHO BANK, LTD., FUKUSHIMA-MINPO CO., LTD., FUKUSHIMA-MINPO Education Welfare Agency, NAGAO CLINIC, Johnson & Johnson, Kyowa Hakko Kirin Co., Ltd., and Yasuda Urology Clinic.

References

1. Barker LA, Gout BS & Crowe TC (2011): Hospital malnutrition: Prevalence, identification and impact on patients and the healthcare system. Int J Environ Res Public Health 8: 514–527
2. Puthucheary ZA, Rawal J, McPhail M et al (2013): Acute skeletal muscle wasting in critical illness. JAMA 310: 1591–1600
3. Ndahimana D & Kim EK (2018): Energy requirements in critically ill patients. Clin Nutr Res 7: 81–90
4. Truong AD, Fan E, Brower RG & Needham DM (2009): Bench-to-bedside review: Mobilizing patients in the intensive care unit—from pathophysiology to clinical trials. Crit Care 13: 216
5. TEAM Study Investigators, Hodgson C, Bellomo R et al (2015): Early mobilization and recovery in mechanically ventilated patients in the ICU: A bi-national, multi-centre, prospective cohort study. Crit Care 19: 81
6. Kress JP & Hall JB (2014): ICU-acquired weakness and recovery from critical illness. N Engl J Med 370: 1626–1635
7. Gosselink R, Bott J, Johnson M, Dean E, Nava S, Norrenberg M, Schönhofer B, Stiller K, van de Leur H & Vincent JL (2008): Physiotherapy for adult patients with critical illness: Recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. Intensive Care Med 34: 1188–1199
8. National Institute for Health and Care Excellence (UK) (NICE) (2017): Rehabilitation after critical illness in adults (QS158). http://www.nice.org.uk/guidance/qs158/ (Accessed May 5, 2018)
9. Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T & Hodgson CL (2017): The effects of active mobilisation and rehabilitation in ICU on mortality and function: A systematic review. Intensive Care Med 43: 171–183
10. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF & Miller M (2017): Association between malnutrition and clinical outcomes in the intensive care unit: A systematic review. JPEN J Parenter Enteral Nutr 41: 744–758
11. McClave SA, Taylor BE, Martindale RG et al (2016): Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 40: 159–211
12. Wakabayashi H & Sakuma K (2014): Rehabilitation nutrition for sarcopenia with disability: A combination of both rehabilitation and nutrition care management. J Cachexia Sarcopenia Muscle 5: 269–277
13. Moher D, Liberati A, Tetzlaff J & Altman DG; PRISMA Group (2009): Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 339: b2535
14. Japan Medical Abstracts Society: Ichu-shi Web. http://search.jamas.or.jp/ (Accessed April 29, 2018)
15. Mahoney FI & Barthel DW (1965): Functional evaluation: The Barthel index. Md State Med J 14: 61–65
16. Higgins JPT & Sally G (2011): Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration, Oxford. https://training.cochrane.org/handbook/ (Accessed April 29, 2018)
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P & Schünemann HJ; GRADE Working Group (2008): GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336: 924–926
18. Hegerova P, Dedkova Z & Sobotka L (2015): Early nutritional support and physiotherapy improved long-term self-sufficiency in acutely ill older patients. Nutrition 31: 166–170
19. Jones C, Eddleston J, McCairn A, Dowling S, McWilliams D, Coughlan E & Griffiths RD (2015): Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: A randomized controlled trial. J Crit Care 30: 901–907
20. Ware JE Jr & Sherbourne CD (1992): The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30: 473–483
21. EuroQol Group (1990): EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 16: 199–208
22. Feinberg J, Nielsen EE, Korang SK et al (2017): Nutrition support in hospitalised adults at nutritional risk. Cochrane Database Syst Rev 5: CD011598
23. Lambell KJ, King SJ, Forsyth AK & Tierney AC (2018): Association of energy and protein delivery on skeletal muscle mass changes in critically ill adults: A systematic review. JPEN J Parenter Enteral Nutr 42: 1112–1122
24. Fuke R, Hifumi T, Kondo Y, Hatakeyama J, Takei T, Yamakawa K, Inoue S & Nishida O (2018): Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: A systematic review and meta-analysis. BMJ Open 8: e019998
25. Wang CY, Huang CT, Chen CH, Chen MF, Ching SL & Huang YC (2017): Optimal energy delivery, rather than the implementation of a feeding protocol, may benefit clinical outcomes in critically ill patients. nutrients 9: pii: E527
26. Casaer MP (2015): Muscle weakness and nutrition
therapy in ICU. Curr Opin Clin Nutr Metab Care 18: 162–168

27. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR & Oudemans-van Straaten HM (2014): Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care 18: 701

28. Yang M, Hu X, Wang H, Zhang L, Hao Q & Dong B (2017): Sarcopenia predicts readmission and mortality in elderly patients in acute care wards: A prospective study. J Cachexia Sarcopenia Muscle 8: 251–258

29. Sulo S, Feldstein J, Partridge J, Schwander B, Sriram K & Summerfelt WT (2017): Budget impact of a comprehensive nutrition-focused quality improvement program for malnourished hospitalized patients. Am Health Drug Benefits 10: 262–270

30. Kizilarslanoglu MC, Kuyumcu ME, Yesil Y & Halil M (2016): Sarcopenia in critically ill patients. J Anesth 30: 884–890

31. Glover EI & Phillips SM (2010): Resistance exercise and appropriate nutrition to counteract muscle wasting and promote muscle hypertrophy. Curr Opin Clin Nutr Metab Care 13: 630–634

32. Molnár A, Jónásné Sztruhár I, Csontos ÁÁ, Ferencz C, Várbiro S & Székács B (2016): Special nutrition intervention is required for muscle protective efficacy of physical exercise in elderly people at highest risk of sarcopenia. Physiol Int 103: 368–376

33. Koyama T, Maeda K, Anzai H, Koganei Y, Shamoto H & Wakabayashi H (2015): Early commencement of oral intake and physical function are associated with early hospital discharge with oral intake in hospitalized elderly individuals with pneumonia. J Am Geriatr Soc 63: 2183–2185

34. Maeda K, Koga T & Akagi J (2016): Tentative nil per os leads to poor outcomes in older adults with aspiration pneumonia. Clin Nutr 35: 1147–1152

35. Gade J, Beck AM, Bitz C, Christensen B, Klausen TW, Vinther A & Astrup A (2018): Protein-enriched, milk-based supplement to counteract sarcopenia in acutely ill geriatric patients offered resistance exercise training during and after hospitalisation: Study protocol for a randomised, double-blind, multicentre trial. BMJ Open 8: e019210
急性疾患におけるリハビリテーションと栄養療法の併用－システマティックレビュー－

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要 旨：急性疾患に対するリハビリテーションと栄養療法の併用効果検証を目的としたシステマティックレビューを行った。MEDLINE, CENTRAL, EMBASEと医中誌データベース検索の986件と他ソース16件の論文からリハビリテーション治療中の急性疾患症例に対する栄養介入効果を検証した2件のランダム比較試験を抽出した。

コクランrisk of bias評価とランダム効果モデルを用いた解析。GRADEアプローチでエビデンスの質評価を行った。Jonesらの研究ではQOL改善効果がなかった（標準化平均差[SMD] 0.55, 95%信頼区間[CI] -0.05 - 1.15; P=0.12）が、Hegerovaらの研究では筋肉量（SMD 0.65, 95%CI 0.36 - 0.93; P<0.00001）とADL（SMD 0.28, 95%CI 0.00 - 0.56; P=0.05）に改善効果を認めた。急性疾患に対するリハビリテーション栄養療法は筋肉量増加とADL改善に効果的な可能性がある。しかしアウトカム全般にわたる全体的エビデンスの質は低く、さらに研究が必要である。

キーワード：リハビリテーション治療, 栄養療法, 急性疾患, 筋肉量, 日常生活動作。

J UOEH（産業医大誌）41（3）：303 - 315（2019）