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About the journal

The *Annals of Clinical Nutrition and Metabolism* (ACNM, eISSN: 2799-8363) is a peer-reviewed, open-access, joint official journal of the Korean Society of Surgical Metabolism and Nutrition, the Korean Society for Parenteral and Enteral Nutrition, the Asian Society of Surgical Metabolism and Nutrition, and Japanese Society for Surgical Metabolism and Nutrition. This joint journal was launched in December 2021 after merging the Journal of Clinical Nutrition (pISSN: 2289-0203) from 2007 to 2021, published by the Korean Society for Parenteral and Enteral Nutrition, and the Surgical Metabolism and Nutrition (pISSN: 2233-5765) from 2010 to 2021, published by Korean Society of Surgical Metabolism and Nutrition. Its abbreviated title is Ann Clin Nutr Metab.

Aims and scope

The *Annals of Clinical Nutrition and Metabolism* (ACNM) aims to contribute to health of human being by improving clinical nutrition practice through scientific research, including basic science and clinical studies related to nutrition and metabolism.

Scope: The journal's scope includes the following in the field of nutrition, metabolism, and medicine.
- Nutritional screening and assessment
- Nutritional planning
- Perioperative nutritional care
- Nutrition therapy in acute and chronic disease
- Critical care nutrition
- Optimizing enteral and parenteral therapy
- State-of-the-art diagnostic techniques for nutritional care
- Innovative surgical or interventional techniques for nutritional care
- Nationwide nutrition survey
- Scientific laboratory research

Regional scope: Its regional scope is mainly Asia, but it welcomes submissions from researchers all over the world.

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Editorial

Acute sarcopenia in critically ill patients: an emerging intensive care unit challenge

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Sarcopenia is a syndrome characterized by progressive, generalized loss of skeletal muscle mass and strength, which is associated with adverse outcomes such as physical disability, poor quality of life, and death [1]. Current diagnostic criteria include low muscle strength, low muscle quantity or quality, and poor physical performance [2]. Sarcopenia has multifactorial causes and may be classified as primary when related to aging or secondary when associated with inactivity, disease, or malnutrition [2].

In critical care and severe trauma settings, sarcopenia extends beyond age-related muscle loss and has substantial clinical relevance. Sarcopenia may be acute or chronic. Acute sarcopenia is defined as the rapid deterioration of muscle health secondary to an illness or injury lasting less than 6 months [3].

Critically ill patients experience physiological stressors that promote muscle wasting, with endocrine dysregulation among the principal contributors. Hypercortisolemia also contributes to the loss of muscle mass and strength. Cortisol is a stress hormone involved in protein metabolism, and serum cortisol concentrations increase in critically ill patients; in some patients, hydrocortisone is administered to compensate for adrenal insufficiency [4]. In acute systemic inflammation, elevated concentrations of proinflammatory cytokines, including interleukin-6, interleukin-8, and tumor necrosis factor-α, dysregulate pathways involved in protein synthesis and degradation, thereby promoting proteolysis [5]. Physical inactivity and muscle disuse can further accelerate sarcopenia. Together, these mechanisms may contribute to the loss of 2% of skeletal muscle mass per day during the first week of critical illness [6]. The prevalence of sarcopenia among adults older than 60 years ranges from 10% to 27% [7]. In older adults, critical illness related to sepsis or trauma may further accelerate sarcopenia progression and has been associated with a 30-day mortality rate of 28.6% [8]. Therefore, preventing and treating sarcopenia is important not only for preserving physical function but also for improving survival.

Several tests and tools are used to screen for sarcopenia, including handgrip strength testing, the chair stand test, physical performance testing, and muscle mass measurement. However, except for direct assessment of muscle mass, these tests are often impractical in acute critical illness because patient participation and cooperation are difficult to obtain. Radiological assessments performed to evaluate disease or injury can also be used to estimate muscle mass. Well-validated anatomical sites that reflect whole-body muscle mass include the third lumbar vertebra, mid-thigh, and psoas muscle. Muscle mass can be measured using computed tomography or magnetic resonance imaging [2,5]. Although these imaging modalities are frequently used in critically ill patients, muscle-mass assessment is limited by the need for specialized software, and repeated imaging to evaluate progression is often constrained by patient safety considerations and cost. Even when sarcopenia is identified, clinicians face a major challenge: no established treatment reliably reverses it.

In clinical practice, prevention and treatment of sarcopenia require particular attention. The foremost priority is rapid

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correction of the precipitating causes to reduce the intensity and duration of the systemic inflammation that initially triggered acute sarcopenia. Malnutrition is also a central contributor to sarcopenia pathophysiology. Although guidelines for preventing sarcopenia during the acute phase of critical illness have not yet been established, available recommendations emphasize early enteral nutrition and a protein intake of 1.2–1.5 g/kg/day. A caloric intake of 25–35 kcal/kg/day has been recommended, depending on the patient's condition. Because vitamin D deficiency is associated with muscle fiber atrophy, vitamin D replacement is recommended [4,9]. Physical activity interventions may appear impractical in critically ill patients because of patient vulnerability and healthcare workload. Nevertheless, early mobilization should be considered as soon as clinically feasible because physical activity interventions support muscle mass recovery and reduce the risk of pressure ulcers, venous thromboembolism, and pneumonia [4].

Sarcopenia remains a persistent challenge in intensive care, and no single definitive treatment is available. Management therefore requires a multifaceted approach that includes prompt treatment of the underlying disease, adequate nutritional support, and comprehensive rehabilitation. Effective prevention and treatment depend on close collaboration among all members of the multidisciplinary healthcare team.

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Authors' contribution

All work was done by Kyu-Hyouck Kyoung.

Conflict of interest

The author of this manuscript has no conflicts of interest to disclose.

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Data availability

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Supplementary materials

None.

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Guideline

Nutritional support for critically ill patients by the Korean Society for Parenteral and Enteral Nutrition—part II: a clinical practice guideline

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For further information on the authors' affiliations, see **Additional information**.

Abstract

Purpose: Nutritional therapy is an essential component of intensive care management. Appropriate nutritional support may reduce infectious and metabolic complications and promote recovery in critically ill patients. However, nutritional practices vary across institutions, and international guidelines may not be directly applicable to clinical practice in Korea. Evidence-based clinical practice guidelines that reflect Korean intensive care unit practice are therefore needed.

Methods: The Korean Society for Parenteral and Enteral Nutrition developed these clinical practice guidelines for nutritional therapy in critically ill adults through a systematic literature review and multidisciplinary expert consensus.

Results: In total, 24 key clinical questions and 59 recommendations were developed. The guidelines address enteral and parenteral nutrition, feeding intolerance, aspiration prevention, energy and protein assessment, immune-modulating nutrition, micronutrient supplementation, refeeding syndrome, and disease-specific nutritional therapy for critically ill adults, including those with acute kidney injury, acute liver failure, acute respiratory distress syndrome, sepsis, trauma, and obesity. The recommendations emphasize individualized nutritional therapy according to hemodynamic status, metabolic phase, organ dysfunction, nutritional risk, and treatment goals.

Conclusion: These guidelines provide practical, evidence-based recommendations for nutritional therapy in critically ill adults and reflect both current international evidence and Korean clinical practice. They may support more standardized and consistent nutritional support in Korean intensive care units.

Keywords: Critical illness; Nutritional therapy; Enteral nutrition; Parenteral nutrition; Intensive care units

Introduction

Critically ill adult patients are at high risk of malnutrition because severe illness, inflammation, weight loss, and inadequate nutritional intake commonly coexist during intensive care unit treatment. Malnutrition in intensive care unit patients is closely associated with adverse clinical outcomes, including increased infections, delayed recovery, longer hospital stays, and higher mortality [1-7].

In critically ill patients, acute inflammation and stress responses markedly alter normal energy and protein metabolism. Increased endogenous energy production and oxidative stress are common during this phase. These metabolic changes make the timing, amount, and composition

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of nutritional therapy clinically important. Therefore, nutritional support in the intensive care unit should not be viewed simply as calorie replacement, but as part of active treatment for critically ill patients. Appropriate nutritional therapy may support recovery and improve survival [8-12]. For this reason, this guideline uses the term medical nutrition therapy rather than nutritional support alone.

Many critically ill patients cannot maintain normal oral intake because of mechanical ventilation, impaired consciousness, or organ failure. Individualized nutritional strategies using enteral nutrition or parenteral nutrition (PN) are therefore often necessary [13,14]. Nutritional therapy in the intensive care unit also requires a multidisciplinary approach involving physicians, nurses, pharmacists, and dietitians. Close collaboration among healthcare professionals and standardized clinical guidelines is important for effective nutritional management [15-17].

In 2024, the Korean Society for Parenteral and Enteral Nutrition (KSPEN) published the first evidence-based Korean clinical practice guideline for nutritional support in critically ill adults, Part I, which addressed seven key clinical questions commonly encountered in intensive care unit practice [18]. That guideline provided a practical framework suited to the Korean medical environment and served as an initial step toward standardized nutritional care for critically ill patients. However, Part I covered only seven core topics and could not fully address the broad range of clinical situations encountered in daily intensive care unit practice. Therefore, the current guideline, Part II, was developed to expand the previous guideline by adding 24 key clinical questions related to nutritional therapy in critically ill adults.

In this guideline, early nutritional therapy does not refer to a strict time cutoff. Instead, it refers to starting nutritional therapy without unnecessary delay during the early phase of critical illness while considering the patient's metabolic condition and clinical stability. Based on this concept, previous international guidelines have generally recommended starting nutritional therapy relatively early after intensive care unit admission, usually within 24–48 hours when feasible.

This guideline was developed using current evidence and expert consensus to improve the practical use and clinical applicability of nutritional therapy in critically ill adults. These recommendations are intended to help clinicians make more consistent, evidence-based decisions across diverse clinical situations and to improve patient outcomes and the quality of nutritional therapy in Korea.

Methods

Scope of this guideline

These clinical practice guidelines were developed through collaboration among multidisciplinary healthcare professionals involved in nutritional therapy for critically ill patients, including physicians, nurses, pharmacists, and dietitians, together with experts in guideline development methodology. The purpose of these guidelines is to provide evidence-based recommendations for nutritional therapy in critically ill adults based on current evidence and expert consensus and to support healthcare professionals in making effective, consistent clinical decisions. In addition, these guidelines were designed to reflect the real-world practice environment of Korean intensive care units while incorporating current international recommendations and standards. They aim to provide standardized, practical recommendations for nutritional therapy in critically ill adults in Korea. Ultimately, these guidelines aim to improve the quality and consistency of nutritional therapy and contribute to better patient outcomes and public health.

Target users, target population, and clinical scope

These guidelines are intended for healthcare professionals involved in nutritional therapy for critically ill patients, including intensivists, surgeons, physicians, nurses, pharmacists, and dietitians. The target population includes critically ill adults aged 18 years or older who are admitted to the intensive care unit. The scope of these guidelines covers key components of nutritional therapy, including selection of the nutritional route, timing of nutrition initiation, assessment of energy requirements, and evaluation of nutrient composition and requirements. In addition to general critical illness, these guidelines address nutritional therapy strategies for specific disease conditions, including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), acute liver failure, sepsis, and trauma. These guidelines do not address nutritional therapy in pediatric or neonatal critically ill patients.

Limitations of this guideline

These guidelines were developed to reflect the current practice environment for nutritional therapy in Korean intensive care units and to provide evidence-based recommendations applicable to real clinical settings. However, several limitations should be acknowledged. First, because of the limited number of domestic studies, most evidence used in these guidelines was derived from international studies.

For several key clinical questions, high-quality randomized controlled trials (RCTs) were limited. For selected key clinical questions with limited RCT evidence or substantial heterogeneity, recommendations were based on narrative evidence synthesis and expert consensus. Therefore, the certainty of evidence supporting some recommendations may be relatively low. Second, because high-quality studies involving Korean patients, especially RCTs, were limited, it was difficult to fully reflect the characteristics of the Korean population and clinical practice environment. Further clinical studies and evidence generation involving Korean critically ill patients are needed. Third, because these guidelines address a broad range of nutritional issues in critically ill adults, the amount and quality of evidence varied substantially across key clinical questions. Accordingly, some recommendations were based primarily on expert consensus and clinical applicability rather than high-certainty evidence. Despite these limitations, the current guideline expands the previous Part I guideline and covers a broader range of topics comparable to those addressed in international guidelines, such as those from the European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN). Future updates, supported by additional domestic research and regular revision, may further improve the quality and applicability of these Korean evidence-based clinical practice guidelines.

Guideline development committee

These guidelines were developed by the Guideline Committee of KSPEN through multidisciplinary collaboration among physicians, nurses, pharmacists, dietitians, and methodology experts. The composition and roles of the guideline development group are summarized on the title page. The guideline development process included key question (KQ) formulation, literature review, evidence appraisal, recommendation drafting, and expert consensus. Regular meetings were held throughout the development process to review the evidence, discuss clinical applicability, and finalize recommendation statements.

Methodology for guideline development

These guidelines were developed using an evidence-based approach combined with expert consensus to standardize nutritional therapy in critically ill adults [19]. The guideline development process followed the Appraisal of Guidelines for Research and Evaluation (AGREE) reporting framework. The overall development process consisted of three stages: (1) planning, (2) guideline development, and (3) external review and dissemination. The guideline development process included the following steps: (1) selection of KQs, (2) literature search and study selection, (3) evidence appraisal and synthesis, (4) determination of the certainty of evidence and strength of recommendations, (5) drafting of recommendations, and (6) consensus development. Depending on the amount and quality of evidence, either systematic review/meta-analysis or narrative review methods were applied to each KQ.

Selection of KQs

KQs were developed based on existing international guidelines, including those from ESPEN and ASPEN, with a focus on clinically important or debated issues related to nutritional therapy in critically ill adults. Candidate topics were selected by considering evidence availability, clinical applicability, and relevance to Korean intensive care unit practice. Through committee discussion, 24 key clinical questions were finalized using the PICO (Population, Intervention, Comparison, and Outcome) format, comprising population, intervention, comparator, and outcome.

Development methodology

These guidelines were developed using a mixed approach that combined adaptation and partial de novo development. Existing international guidelines were reviewed and adapted to reflect Korean intensive care unit practice patterns and the local healthcare environment. For selected KQs with sufficient RCT evidence, systematic reviews and meta-analyses were performed. For questions with limited RCT evidence or substantial heterogeneity among studies, narrative review and narrative synthesis approaches were applied.

Literature search and study selection

Literature searches were conducted in PubMed, Embase, the Cochrane Library, and KoreaMed. In principle, studies published after January 1, 2010, were included, although the search period varied according to the characteristics of each KQ. For questions with sufficient RCT evidence, systematic reviews and meta-analyses were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Two reviewers independently screened studies and assessed eligibility according to predefined inclusion and exclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer. For questions with limited RCT evidence or substantial heterogeneity, evidence was summarized using

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a narrative review approach. Detailed search strategies and PRISMA flow diagrams for each KQ are presented in the supplementary materials.

Risk of bias assessment and evidence synthesis

For questions involving systematic reviews and meta-analyses, risk of bias assessment was performed using the Cochrane Risk of Bias 1.0 tool. Meta-analyses were conducted using Review Manager software (RevMan version 5.4), and random-effects models were applied when substantial heterogeneity was identified. For questions for which quantitative synthesis was not feasible, evidence was synthesized narratively based on clinically relevant findings.

Determination of the level of evidence and strength of recommendations

The certainty of evidence and strength of recommendations were determined according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Table 1, Fig. 1). The certainty of evidence was classified as high, moderate, low, or very low. GRADEpro (McMaster University, Canada) was used for evidence profiling and Summary of Findings (SoF) tables. SoF tables were prepared only for questions supported by RCTs or systematic reviews. For narrative review-based questions, recommendations were presented as expert consensus statements. The wording of recommendations followed GRADE guidance according to recommendation strength. Recommendation strength and corresponding wording are summarized in Table 2.

Development of recommendations and consensus process

Draft recommendations were prepared by guideline committee members assigned to each KQ. The recommendations included recommendation statements, evidence summaries, references, recommendation strength, and certainty of evidence. Consensus was achieved through structured multidisciplinary discussion and anonymous voting involving KSPEN executive board members and guideline development committee members. Recommendations with ≥75% agreement were accepted. Agreement rates were categorized into four levels according to the percentage of agreement votes (Table 3).

Independent external review

The draft guidelines underwent independent external review by experts from related academic societies involved in critical care and nutritional therapy, including the Korean

Table 1. Definitions of certainty of evidence according to the GRADE approach

Certainty of evidence	Definition
High	We are very confident that the true effect is close to the estimated effect.
Moderate	We are moderately confident in the estimated effect. The true effect is likely to be close to the estimate, but it may be substantially different.
Low	Confidence in the estimated effect is limited. The true effect may be substantially different from the estimate.
Very low	We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimate.

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Step 1: Initial certainty based on study design		Step 2: Factors modifying certainty of evidence		Final certainty of evidence	
Study design	Initial certainty	Factors decreasing certainty	Factors increasing certainty		
Randomized controlled trials	High	Risk of bias Serious: −1 Very serious: −2	Large magnitude of effect Large: +1 Very large: +2	High	⊕⊕⊕⊕
		Inconsistency Serious: −1 Very serious: −2	Dose–response relationship Present: +1	Moderate	⊕⊕⊕○
Observational studies	Low	Indirectness Serious: −1 Very serious: −2 Extremely serious: −3	Residual confounding likely to reduce the observed effect or suggest no effect: +1	Low	⊕⊕○○
		Imprecision Serious: −1 Very serious: −2		Very low	⊕○○○
		Publication bias Strongly suspected: −1			

Fig. 1. GRADE framework for determining certainty of evidence. GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Table 2. GRADE recommendation strength and interpretation

Recommendation category (recommendation strength)		Definition	Recommended wording
Evidence-based recommendation (SR & MA for RCT)	Strong for	The intervention is strongly recommended in most clinical situations after considering the balance between benefits and harms, certainty of evidence, patient values and preferences, and resource utilization.	"We recommend ..."
	Conditional for	The use of the intervention may vary depending on clinical circumstances or patient/social values and preferences; selective or conditional use is suggested.	"... is considered"
	Conditional against	The potential harms of the intervention may outweigh the benefits in some clinical situations or patient populations; routine use is not recommended.	"... is not recommended"
	Strong against	The harms of the intervention outweigh the benefits in most clinical situations after considering certainty of evidence, values and preferences, and resource utilization.	"We recommend against..."
	Inconclusive	The certainty of evidence is too low, or the balance between benefits and harms is highly uncertain or variable; therefore, no recommendation can be made. Clinical judgment should guide decision-making.	"...cannot decide"
Expert consensus		Although direct clinical evidence is limited, recommendations are made based on expert opinion, clinical experience, potential benefits and harms, values and preferences, and feasibility.	"... is suggested" or "... is not suggested"

GRADE, Grading of Recommendations Assessment, Development and Evaluation; SR & MA, systematic review and meta-analysis; RCT, randomized controlled trial.

Table 3. Consensus strength and agreement thresholds

Consensus strength	Agreement (%)	Recommendation status
Strong consensus	≥90	Accepted
Consensus	75–89	Accepted
Majority consensus	50–74	Re-discussion and re-voting required
No consensus	<50	Rejected

Society of Critical Care Medicine, Korean Society of Acute Care Surgery, and Korean Association of Critical Care Nurses. Reviewer comments regarding scientific validity, clinical applicability, and clarity of recommendations were reviewed by the guideline committee and incorporated into the final guideline when appropriate. External reviewers did not participate in final voting.

Independence and implementation plan of the guideline

Funding and editorial independence

These guidelines were developed with support from KSPEN and did not receive commercial or external funding. Administrative support from the society had no influence on topic selection, evidence evaluation, recommendation formulation, or any academic decision-making process. All recommendations were developed through the independent judgment of the guideline committee.

Methodological and technical support

Literature searches were conducted with support from the Medical Library of Asan Medical Center. Methodological consultation regarding guideline development was provided by the National Evidence-based Healthcare Collaborating Agency (NECA). This support was limited to technical and methodological consultation and did not influence the final recommendations.

Management of conflicts of interest

All guideline development committee members declared no financial or nonfinancial conflicts of interest related to these guidelines. Potential conflicts of interest were reviewed before recommendation finalization.

Guideline updating plan

These guidelines expand the previous 2024 Part I guideline by incorporating additional KQs covering broader aspects of nutritional therapy in critically ill adults. Regular revision is planned approximately every 5 years or earlier if important new evidence emerges.

Dissemination and implementation plan

These guidelines will be disseminated through academic meetings and educational activities organized by KSPEN. A summarized practical version of the guideline will also be developed to facilitate implementation in routine clinical practice. In addition, summary tables and practical algorithms

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will be provided to facilitate bedside implementation. The main contents of the guideline will also be incorporated into educational programs and academic activities to promote the application of evidence-based nutritional therapy in critically ill adults.

Results

In total, 24 key clinical questions and 59 recommendations were developed and organized into thematic categories. Detailed recommendations and supporting evidence are presented in the following sections, and a summary of recommendations is provided in Table 4. Detailed search strategies, evidence tables, study summaries, meta-analyses, and supplementary figures for each KQ are provided in the supplementary materials.

Table 4. Summary of recommendations

Section	Recommendation	Evidence/Recommendation/Consensus
Indications and nutritional risk assessment	R1. Critically ill adult patients expected to stay in the intensive care unit for more than 48 hours are considered at risk for malnutrition, and nutrition therapy is suggested.	Expert consensus/strong consensus
	R2. Screening for malnutrition or nutritional risk using a structured tool is suggested within 24–48 hours after intensive care unit admission.	Expert consensus/strong consensus
	R3. Use of validated tools such as the modified Nutrition Risk in the Critically Ill score or Nutritional Risk Screening 2002 is suggested for nutritional risk screening.	Expert consensus/strong consensus
	R4. Standardized assessment and diagnosis using tools such as the Global Leadership Initiative on Malnutrition criteria or Subjective Global Assessment are suggested in patients at risk, followed by appropriate nutrition care planning.	Expert consensus/strong consensus
Timing and initiation of nutritional therapy	R5. Early initiation of nutritional therapy as soon as possible after hemodynamic stabilization is suggested.	Expert consensus/strong consensus
	R6. Enteral nutrition is suggested as the preferred route, and parenteral nutrition may be applied on an individual basis according to the patient's clinical condition.	Expert consensus/strong consensus
	R7. Initiation of enteral nutrition is not suggested in hemodynamically unstable patients until hemodynamic stability has been achieved.	Expert consensus/strong consensus
	R8. Initiation of low-dose enteral nutrition (10–20 mL/hr) is suggested in patients receiving vasopressors when adequate hemodynamic stability has been achieved and vasopressor doses are stable or decreasing.	Expert consensus/strong consensus
	R9. Withholding or discontinuation of enteral nutrition is suggested in the following situations. · Uncontrolled shock and hypoperfusion: lack of hemodynamic stability, increasing vasopressor requirements, elevated serum lactate levels, or suspected tissue hypoperfusion · Uncontrolled life-threatening respiratory failure: severe hypoxemia, hypercapnia, or acidosis · Active gastrointestinal bleeding · Gastrointestinal dysfunction or severe enteral feeding intolerance: severe abdominal distension, GRV >500 mL over 6 hours, uncontrolled vomiting (with aspiration risk), or diarrhea · High-output intestinal fistula or stoma: when safe enteral feeding distal to the fistula or stoma is not feasible · Structural gastrointestinal injury: unresolved intestinal perforation, mechanical bowel obstruction, or bowel ischemia · Abdominal compartment syndrome	Expert consensus/strong consensus
Enteral nutrition delivery and monitoring	R10. Assessment of EFI is suggested. EFI should be comprehensively assessed by observing gastrointestinal symptoms, such as vomiting or regurgitation, abdominal distension, diarrhea, abdominal pain, and gastrointestinal bleeding, with GRV measured selectively when clinically indicated.	Expert consensus/strong consensus
	R11. Routine measurement of GRV is not suggested.	Expert consensus/strong consensus
	R12. Continuous feeding may be considered the preferred approach. Intermittent feeding may also be considered in clinically stable patients or when continuous feeding is not feasible.	Low evidence/conditional for/strong consensus

(Continued on the next page)

Table 4. Continued

Section	Recommendation	Evidence/Recommendation/Consensus
	R13. Trophic feeding may be considered during the early phase of intensive care unit admission when gastrointestinal function is uncertain or when advancement of enteral nutrition is challenging.	Low evidence/conditional for/strong consensus
	R14. Assessment of aspiration risk should be considered in patients receiving enteral nutrition.	Low evidence/conditional for/strong consensus
	R15. Post-pyloric feeding should be considered rather than gastric feeding in patients at high risk of aspiration or with gastric feeding intolerance.	Moderate evidence/conditional for/strong consensus
	R16. The use of prokinetics is suggested in patients at high risk of aspiration or with enteral feeding intolerance.	Expert consensus/strong consensus
	R17. Head-of-bed elevation at 30˚–45˚ and regular oral hygiene are suggested during enteral nutrition in mechanically ventilated patients.	Expert consensus/strong consensus
Energy requirements	R18. IC is considered for determining energy requirements.	Low evidence/conditional for/strong consensus
	R19. When IC is unavailable, the use of weight-based formulas (25 kcal/kg/day), predictive equations, and VCO_2-based estimation methods (in mechanically ventilated patients) is suggested.	Expert consensus/strong consensus
Formulation of enteral nutrition	R20. Routine enteral fish oil supplementation is not recommended.	Low evidence/conditional for/strong consensus
	R21. Enteral fish oil supplementation may be considered in perioperative patients or those at high risk for infection (e.g., patients undergoing cardiac surgery or those with abdominal sepsis).	Low evidence/conditional for/strong consensus
	R22. Routine enteral arginine supplementation is not recommended. Enteral arginine supplementation may be considered in patients with severe trauma or in postoperative critically ill patients.	Expert consensus/strong consensus
	R23. Routine enteral glutamine supplementation is not recommended.	Expert consensus/strong consensus
	R24. Routine use of fiber-containing enteral formulas is not suggested.	Expert consensus/strong consensus
	R25. In hemodynamically stable patients with preserved gastrointestinal function and persistent diarrhea, the use of fiber-containing enteral formulas is suggested.	Expert consensus/strong consensus
	R26. Routine use of probiotics is not recommended.	Low evidence/conditional against/strong consensus
Parenteral nutrition	R27. In patients unable to receive oral intake or enteral nutrition, initiation of PN within 3–7 days of intensive care unit admission should be considered.	Moderate evidence/conditional for/strong consensus
	R28. In patients with severe malnutrition, early initiation of PN is suggested.	Expert consensus/strong consensus
	R29. Hypocaloric PN (≤70% of estimated energy requirements or ≤20 kcal/kg/day) is suggested during the early phase of intensive care unit stay (within the first week), with subsequent gradual advancement according to the clinical course.	Expert consensus/strong consensus
Micronutrients	R30. Micronutrients and vitamins should be routinely provided to meet daily requirements; when PN is used, they should be included at the recommended daily intake level.	Expert consensus/strong consensus
	R31. Additional supplementation with micronutrients and antioxidants above the recommended intake is not recommended.	Moderate evidence/conditional against/strong consensus
	R32. Routine high-dose vitamin C supplementation is not recommended.	Moderate evidence/conditional against/consensus
	R33. High-dose selenium supplementation is not recommended.	Low evidence/conditional against/strong consensus
	R34. Routine high-dose antioxidant supplementation, including vitamin D, thiamine, and N-acetylcysteine (NAC), is not recommended.	Low evidence/conditional against/strong consensus
Monitoring and metabolic complications	R35. Blood glucose should be measured immediately after admission or initiation of nutritional therapy and at least every 4 hours during the first 48 hours. The suggested target blood glucose range is 140–180 mg/dL, and insulin therapy is suggested if blood glucose persistently exceeds 180 mg/dL, with institutional discretion for initiation up to 200 mg/dL.	Expert consensus/strong consensus
	R36. Blood electrolytes (phosphate, potassium, magnesium, sodium, chloride) should be measured at least once daily during the first week of nutritional therapy, with early phosphate measurement suggested within 6–12 hours of admission.	Expert consensus/strong consensus
	R37. Liver function tests should be measured twice weekly during the initial phase of nutritional therapy and at least once weekly during the stable phase thereafter.	Expert consensus/strong consensus

(Continued on the next page)

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Table 4. Continued

Section	Recommendation	Evidence/Recommendation/Consensus
	R38. Serum triglyceride levels should be measured once or twice weekly during nutritional therapy. In particular, close monitoring is suggested in patients receiving lipid-containing PN or lipid-based medications.	Expert consensus/strong consensus
	R39. Prealbumin is suggested as a supplementary marker for assessing response to nutritional therapy, and weekly measurement together with C-reactive protein is suggested.	Expert consensus/consensus
	R40. In patients at high risk of vitamin and trace element deficiencies, clinicians should assess whether thiamine, vitamin C, copper, selenium, zinc, and other essential micronutrients are being supplied adequately and monitor levels when necessary (e.g., prolonged CRRT for >2 weeks, severe burns, malabsorption, malnutrition, chronic alcoholism, or significant fluid drainage).	Expert consensus/strong consensus
	R41. Measurement of nitrogen balance is suggested to assess protein adequacy, although its use is limited in dialysis patients.	Expert consensus/strong consensus
	R42. Structured screening for high risk of refeeding syndrome is suggested after intensive care unit admission.	Expert consensus/strong consensus
	R43. In patients at risk of refeeding syndrome, measurement of serum phosphate, potassium, and magnesium before and during the early phase of nutritional therapy, with supplementation when deficient and frequent reassessment, is suggested.	Expert consensus/strong consensus
	R44. In patients at risk of refeeding syndrome, initiation of nutrition with caloric restriction (100–150 g of glucose or 10–20 kcal/kg during the first 24 hours), followed by gradual advancement every 1–2 days, is suggested.	Expert consensus/strong consensus
	R45. In patients at risk of refeeding syndrome, administration of thiamine before initiation of nutritional therapy is suggested.	Expert consensus/strong consensus
Acute respiratory failure	R46. Routine use of enteral formulas enriched with anti-inflammatory lipids, including omega-3 fatty acids and borage oil, is not recommended.	Moderate evidence, conditional against, strong consensus
Acute kidney injury	R47. In patients with acute kidney injury (stage 1–3) who are not receiving renal replacement therapy, initial protein provision of 0.8–1.0 g/kg/day is suggested, with gradual advancement up to 1.2–1.3 g/kg/day according to the patient's catabolic state and nutritional status.	Expert consensus/strong consensus
	R48. In patients receiving CRRT, protein provision of 1.5–1.7 g/kg/day is suggested.	Expert consensus/strong consensus
Liver failure	R49. High protein provision (1.2–1.5 g/kg/day) is suggested in patients with liver failure.	Expert consensus/strong consensus
	R50. In hyperacute liver failure, protein provision may be delayed for 24–48 hours, with gradual initiation suggested thereafter.	Expert consensus/strong consensus
	R51. Routine use of BCAA-enriched protein supplementation is not recommended in patients with liver failure and hepatic encephalopathy. However, oral or enteral BCAA-enriched protein supplementation may be considered in those with suspected protein intolerance or recurrent hepatic encephalopathy.	Expert consensus/strong consensus
Trauma	R52. Early enteral nutrition is suggested in patients with acute traumatic brain injury once hemodynamic stability has been achieved and gastrointestinal function is adequate.	Very low evidence, conditional for, strong consensus
	R53. Early enteral nutrition is suggested in patients with acute spinal cord injury once hemodynamic stability is ensured and gastrointestinal function is adequate.	Expert consensus/strong consensus
	R54. Early enteral nutrition is suggested in patients with abdominal trauma who are hemodynamically stable and have confirmed or restored gastrointestinal continuity.	Expert consensus/strong consensus
Sepsis	R55. Early enteral nutrition is suggested in patients with sepsis once hemodynamic stability has been achieved, with gradual advancement according to clinical status.	Expert consensus/strong consensus
Obesity	R56. Early initiation of enteral nutrition is suggested once hemodynamic stability has been achieved.	Expert consensus/strong consensus
	R57. Indirect calorimetry is suggested as the preferred method for measuring energy requirements.	Expert consensus/strong consensus
	R58. When indirect calorimetry is unavailable, hypocaloric nutrition of 20–25 kcal/kg/day based on adjusted body weight is suggested during the acute phase, with gradual advancement toward measured energy expenditure during the recovery phase.	Expert consensus/strong consensus
	R59. Protein provision of ≥1.3 g/kg/day based on adjusted body weight is suggested.	Expert consensus/strong consensus

GRV, gastric residual volume; EFI, enteral feeding intolerance; IC, indirect calorimetry; VCO_2, carbon dioxide production; PN, parenteral nutrition; CRRT, continuous renal replacement therapy; BCAA, branched-chain amino acid.

Indications and nutritional risk assessment

KQ 1. Who should be considered for nutrition therapy in critically ill adult patients?

R1. Critically ill adult patients expected to stay in the intensive care unit for more than 48 hours are considered at risk for malnutrition, and nutrition therapy is suggested. (Expert consensus, strong consensus: 95%)

Critically ill patients may rapidly develop muscle wasting and malnutrition because systemic inflammation and metabolic alterations begin early after intensive care unit admission [20,21]. In a prospective observational study, Puthucheary et al. [21] demonstrated a significant reduction in rectus femoris muscle area shortly after intensive care unit admission, particularly in patients with multiorgan failure. A meta-analysis by Fazzini et al. [22] also reported significant muscle loss and a high prevalence of intensive care unit-acquired weakness during the first week of critical illness. The ESPEN guideline recommends considering patients expected to stay in the intensive care unit for more than 48 hours to be at nutritional risk [20]. Heyland et al. [23] reported that adequate energy and protein delivery was associated with reduced mortality in patients with a Nutrition Risk in the Critically Ill (NUTRIC) score ≥5. However, a meta-analysis by Chong et al. [24] did not demonstrate a consistent association between increased energy or protein delivery and mortality reduction in patients with malnutrition or nutritional risk. Therefore, patients expected to remain in the intensive care unit for more than 48 hours should be considered at high risk for malnutrition and as candidates for early nutritional therapy (Supplement Tables 1, 2).

KQ 2. How should malnutrition and nutritional risk be screened and assessed in critically ill adult patients?

R2. Screening for malnutrition or nutritional risk using a structured tool is suggested within 24–48 hours after intensive care unit admission. (Expert consensus, strong consensus: 100%)

R3. Use of validated tools such as the modified NUTRIC (mNUTRIC) score or Nutritional Risk Screening 2002 (NRS-2002) is suggested for nutritional risk screening. (Expert consensus, strong consensus: 97%)

R4. Standardized assessment and diagnosis using tools such as the Global Leadership Initiative on Malnutrition (GLIM) criteria or Subjective Global Assessment (SGA) are suggested in patients at risk, followed by appropriate nutrition care planning. (Expert consensus, strong consensus: 100%)

Malnutrition in critically ill patients is associated with increased mortality, infectious complications, prolonged mechanical ventilation, and longer intensive care unit stays [25,26]. Therefore, early screening and assessment of nutritional risk after intensive care unit admission are important [27]. Commonly used nutritional risk screening tools in critically ill patients include the mNUTRIC score, NRS-2002, and the Malnutrition Universal Screening Tool (MUST) [5,28]. Among these, the mNUTRIC score was specifically developed for critically ill patients and has been associated with mortality, duration of mechanical ventilation, and intensive care unit length of stay across diverse intensive care unit populations [29-35]. NRS-2002 is also recommended in international guidelines as a nutritional risk screening tool for hospitalized and critically ill patients [1,5,27]. Institution-specific screening tools that reflect local intensive care unit practice patterns may also be considered in Korea [36-38].

Malnutrition assessment and diagnosis may be performed using the GLIM criteria and SGA [39]. The GLIM criteria provide a structured framework that integrates clinical and pathophysiological factors [40,41], and several studies have reported improved prognostic performance when the GLIM criteria are combined with the mNUTRIC score [42]. SGA has also been associated with malnutrition diagnosis and prognostic prediction in critically ill patients and may be useful in intensive care unit settings where body composition assessment is difficult [43,44].

Individualized nutritional interventions based on structured nutritional screening and assessment are associated with improved nutritional status and better clinical outcomes, including reduced mortality, infectious complications, and functional decline. Therefore, structured nutritional risk screening should be performed early after intensive care unit admission, followed by standardized nutritional assessment and individualized nutritional therapy in high-risk patients (Supplement Table 3).

Timing and initiation of nutritional therapy

KQ 3. When should nutritional therapy be initiated in critically ill adult patients?

R5. Early initiation of nutritional therapy as soon as possible after hemodynamic stability has been achieved is suggested.

(Expert consensus, strong consensus: 100%)

R6. Enteral nutrition is suggested as the preferred route, and PN may be applied on an individual basis according to the patient's clinical condition. (Expert consensus, strong consensus: 97%)

Early nutritional therapy is important in critically ill patients to reduce metabolic stress, muscle wasting, and infectious complications. ESPEN, the Society of Critical Care Medicine–American Society for Parenteral and Enteral Nutrition (SCCM-ASPEN), and the European Society of Intensive Care Medicine (ESICM) guidelines recommend initiating early enteral nutrition within 24–48 hours after intensive care unit admission in patients without contraindications to enteral feeding [1,5,20,45-47].

Compared with delayed enteral nutrition or no nutritional therapy, early enteral nutrition has been associated with fewer infectious complications, shorter duration of mechanical ventilation, and shorter intensive care unit stays. A meta-analysis by Moon et al. [48] reported that early enteral nutrition was associated with reduced intensive care unit length of stay in patients with sepsis, whereas a meta-analysis by Talebi et al. [49] demonstrated reductions in infectious complications and mortality.

In contrast, the EPaNIC trial, which evaluated early PN, reported increased infectious complications, prolonged mechanical ventilation, and prolonged renal replacement therapy in the early PN group [50]. Therefore, enteral nutrition should be prioritized whenever feasible, and PN should be considered selectively in patients with contraindications to enteral nutrition or insufficient enteral intake.

Recent studies have also evaluated very early enteral nutrition initiated within 6–24 hours after intensive care unit admission [51-53]. Some studies have suggested associations with reduced intensive care unit length of stay and shorter duration of mechanical ventilation, although the overall level of evidence remains limited because of small study sizes and heterogeneous patient populations.

Overall, initiation of nutritional therapy within 24–48 hours after intensive care unit admission is considered appropriate in critically ill patients. PN should be applied selectively according to the patient's clinical condition when enteral nutrition is not feasible or is insufficient (Supplement Tables 4, 5).

KQ 4. When should enteral nutrition be delayed or discontinued in critically ill patients?

R7. Initiation of enteral nutrition is not suggested in hemodynamically unstable patients until hemodynamic stability has been achieved. (Expert consensus, strong consensus: 97%)

R8. Initiation of low-dose enteral nutrition (10–20 mL/hr) is suggested in patients receiving vasopressors when adequate hemodynamic stability has been achieved and vasopressor doses are stable or decreasing. (Expert consensus, strong consensus: 100%)

R9. Withholding or discontinuation of enteral nutrition is suggested in the following situations. (Expert consensus, strong consensus: 97%)

- Uncontrolled shock and hypoperfusion: lack of hemodynamic stability, increasing vasopressor requirements, elevated serum lactate levels, or suspected tissue hypoperfusion
- Uncontrolled life-threatening respiratory failure: severe hypoxemia, hypercapnia, or acidosis
- Active gastrointestinal bleeding
- Gastrointestinal dysfunction or severe enteral feeding intolerance (EFI): severe abdominal distension, gastric residual volume (GRV) >500 mL over 6 hours, uncontrolled vomiting with aspiration risk, or severe diarrhea
- High-output intestinal fistula or stoma when safe enteral feeding distal to the fistula or stoma is not feasible
- Structural gastrointestinal injury: unresolved intestinal perforation, mechanical bowel obstruction, or bowel ischemia
- Abdominal compartment syndrome

Evidence from RCTs regarding the optimal timing of enteral nutrition initiation in critically ill patients with shock or vasopressor support is limited, and current evidence is based mainly on observational studies and international guidelines. ESPEN and SCCM-ASPEN guidelines recommend withholding enteral nutrition until adequate hemodynamic stability has been achieved [1,5,20,45,54]. However, several studies and guidelines suggest that low-dose enteral nutrition may be cautiously initiated in patients receiving vasopressors when blood pressure is stable and vasopressor doses are stable or decreasing [1,5,45]. Multiple observational studies have reported that early enteral nutrition during vasopressor therapy was associated with reduced mortality, shorter duration of mechanical ventilation, and decreased intensive care unit length of stay [55-60]. Better enteral feeding tolerance has also been reported in patients receiving lower norepinephrine-equivalent doses. In contrast, elevated serum lactate levels, high-dose vasopressor requirements, tissue hypoperfusion, or suspected bowel ischemia may increase the

risk of enteral nutrition-related complications [45,54,61]. In addition, uncontrolled severe respiratory failure, active gastrointestinal bleeding, bowel ischemia, intestinal perforation, mechanical bowel obstruction, abdominal compartment syndrome, and severe gastrointestinal intolerance are recognized situations requiring withholding or discontinuation of enteral nutrition [1,5,20,45].

Overall, enteral nutrition should be initiated after adequate hemodynamic stability has been achieved in critically ill patients. Even in patients receiving vasopressors, cautious initiation of low-dose enteral nutrition may be considered when blood pressure is stable and vasopressor doses are stable or decreasing. However, enteral nutrition should be withheld or discontinued in cases of increasing vasopressor requirements, rising serum lactate levels, or suspected gastrointestinal hypoperfusion or ischemia (Supplement Tables 6, 7).

Enteral nutrition delivery and monitoring

KQ 5. How should EFI be assessed in critically ill adult patients receiving enteral nutrition?

R10. Assessment of EFI is suggested. EFI should be comprehensively assessed by observing gastrointestinal symptoms, such as vomiting or regurgitation, abdominal distension, diarrhea, abdominal pain, and gastrointestinal bleeding, with GRV measured selectively when clinically indicated. (Expert consensus, strong consensus: 92%)

R11. Routine measurement of GRV is not suggested. (Expert consensus, consensus: 84%)

EFI is a condition in which adequate nutritional delivery cannot be achieved because of impaired gastrointestinal function or gastrointestinal complications, and it may be associated with reduced nutritional intake and worse clinical outcomes [62-64]. Recent guidelines recommend comprehensive assessment of EFI based primarily on clinical symptoms, such as vomiting or regurgitation, abdominal distension, abdominal pain, diarrhea, and gastrointestinal bleeding, rather than relying solely on GRV measurement [1,4,5,65,66].

GRV has traditionally been used in intensive care unit settings to assess aspiration risk and EFI. However, GRV alone does not reliably predict aspiration or clinical outcomes, and omission of routine GRV monitoring has not been associated with increased ventilator-associated pneumonia, mortality, or intensive care unit length of stay [65,66]. Nevertheless, some studies reported increased vomiting events with non-monitoring strategies, suggesting that symptom-based monitoring remains important [66,67].

Selective GRV measurement may be considered in patients with recurrent vomiting or regurgitation, abdominal distension, abdominal pain, suspected aspiration, or gastrointestinal complications associated with hemodynamic deterioration. Observational studies and meta-analyses have suggested that enteral nutrition may be continued safely in the absence of symptoms even when GRV is within the range of 300–500 mL, and recent international guidelines generally consider GRV ≥500 mL over 4–6 hours to be clinically significant [1,4,5,68,69].

Overall, monitoring of enteral nutrition in critically ill adults should focus primarily on clinical symptoms related to EFI, and routine GRV measurement is not recommended. GRV may be used selectively as an adjunctive assessment tool in patients with suspected EFI or aspiration risk, and decisions regarding interruption of enteral nutrition should be based on comprehensive clinical assessment rather than GRV alone (Supplement Table 8).

KQ 6. In critically ill adult patients receiving enteral nutrition, does continuous feeding, compared with intermittent feeding, affect clinical outcomes?

R12. Continuous feeding may be considered the preferred approach. Intermittent feeding may also be considered in clinically stable patients or when continuous feeding is not feasible. (Low evidence, conditional for, strong consensus: 95%)

Enteral feeding methods are generally classified as continuous feeding and intermittent or bolus feeding. Continuous feeding provides nutrition at a constant rate over time and is commonly used in critically ill patients. A meta-analysis of seven RCTs demonstrated significantly lower intensive care unit mortality in the continuous feeding group than in the intermittent feeding group (relative risk [RR], 0.69; 95% confidence interval [CI], 0.48–0.99) (Fig. 2) [70-76]. Constipation tended to occur more frequently with continuous feeding, although the difference was not statistically significant, whereas other gastrointestinal complications, including vomiting and diarrhea, tended to occur less frequently in the continuous feeding group. In addition, several studies reported that continuous feeding was associated with improved achievement of target calorie and protein delivery, reduced glycemic variability, lower GRV, and improved gastrointestinal tolerance [74,76].

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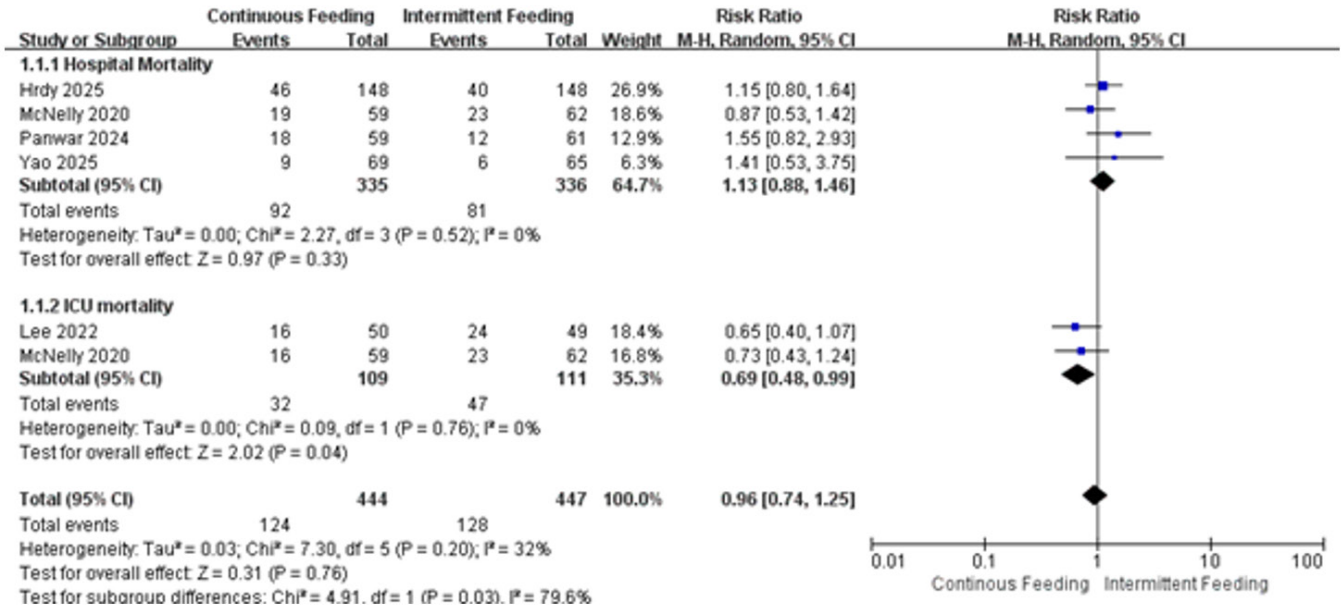

Fig. 2. Forest plots of mortality outcomes comparing continuous versus intermittent enteral feeding in critically ill adult patients. M-H, Mantel-Haenszel; CI, confidence interval; ICU, intensive care unit.

Results regarding aspiration and aspiration pneumonia have been inconsistent across studies. Some studies and meta-analyses reported no significant difference between feeding methods [77,78], whereas others suggested a potential increase in aspiration risk with intermittent or bolus feeding [79,80]. Recent ESPEN practice guidelines and SCCM-ASPEN guidelines recommend preferential consideration of continuous feeding in critically ill patients, particularly in those at high risk of aspiration or with poor tolerance of bolus feeding [1,5,20].

Overall, continuous feeding may provide advantages in feeding stability and gastrointestinal tolerance in critically ill adults and may be preferentially considered in patients at high risk of aspiration or EFI. However, the feeding strategy should be individualized according to the patient's clinical condition, institutional resources, and intensive care unit practice environment (Supplement Tables 9-11 and Supplement Figs. 1-4).

KQ 7. Does trophic feeding, compared with full feeding, improve clinical outcomes in adult critically ill patients?

R13. Trophic feeding may be considered during the early phase of intensive care unit admission when gastrointestinal function is uncertain or when advancement of enteral nutrition is challenging. (Low evidence, conditional for, strong consensus: 97%)

Trophic feeding is a strategy that provides a limited amount of nutrition to maintain intestinal mucosal integrity and prevent gastrointestinal atrophy; it is generally administered at approximately 10–20 kcal/hr or less than 500 kcal/day [1,20]. Recent international guidelines increasingly describe trophic feeding as an extreme form of hypocaloric feeding during the acute phase of critical illness [4,5,81].

A meta-analysis of three RCTs comparing trophic feeding and full feeding demonstrated no significant differences in mortality (RR, 1.03; 95% CI, 0.85–1.26), pneumonia (RR, 0.98; 95% CI, 0.68–1.43), or overall infection rates (RR, 1.10; 95% CI, 0.89–1.36) (Fig. 3) [82-84]. However, gastrointestinal intolerance, including vomiting, increased GRV, and constipation, tended to occur less frequently in the trophic feeding group.

ESPEN, SCCM-ASPEN, and Korean clinical practice guidelines recommend hypocaloric feeding strategies during the early acute phase of critical illness [4,5,18], and trophic feeding may be considered one form of this restricted-calorie approach. In particular, trophic feeding may serve as an initial strategy to maintain gastrointestinal function and improve feeding tolerance when advancement to full nutritional targets is difficult.

Although trophic feeding did not demonstrate clear benefits in mortality or infectious complications compared with full feeding, it showed potential advantages in reducing gastrointestinal intolerance. Therefore, trophic feeding may be selectively considered during the early acute phase in critically ill patients with uncertain gastrointestinal tolerance

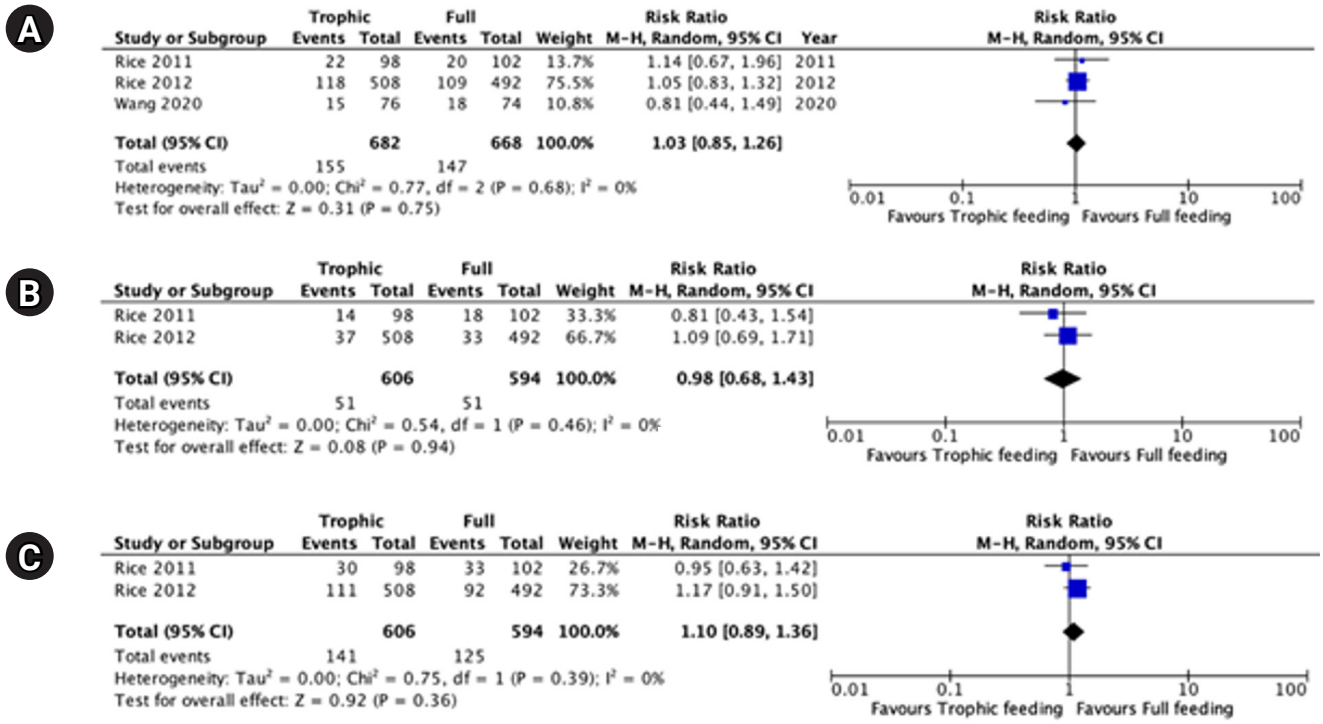

Fig. 3. Forest plots of synthesized outcomes comparing trophic versus full feeding in critically ill adult patients: (A) mortality, (B) pneumonia, and (C) any infection. M-H, Mantel-Haenszel; CI, confidence interval.

or difficulty achieving full nutritional targets, although the current level of evidence remains limited (Supplement Table 12-14 and Supplement Figs. 5-7).

KQ 8. How should aspiration risk be assessed and managed in critically ill adult patients receiving enteral nutrition?

R14. Assessment of aspiration risk should be considered in patients receiving enteral nutrition. (Low evidence, conditional for, strong consensus: 95%)

R15. Post-pyloric feeding should be considered rather than gastric feeding in patients at high risk of aspiration or with gastric feeding intolerance. (Moderate evidence, conditional for, strong consensus: 97%)

R16. The use of prokinetics is suggested in patients at high risk of aspiration or with EFI. (Expert consensus, strong consensus: 95%)

R17. Head-of-bed elevation at 30˚–45˚ and regular oral hygiene are suggested during enteral nutrition in mechanically ventilated patients. (Expert consensus, strong consensus: 100%)

Enteral nutrition in critically ill adults is commonly delivered through gastric or post-pyloric routes. Gastric feeding is the standard approach, but delayed gastric emptying and feeding intolerance may increase the risk of aspiration and pneumonia in high-risk patients [1,5]. SCCM-ASPEN guidelines emphasize the importance of aspiration risk assessment during enteral nutrition [1].

GRV monitoring has traditionally been used to assess aspiration risk [1,66,67]. Three RCTs were identified regarding GRV monitoring; however, one study was excluded from the pooled analysis because it enrolled patients with stroke and evaluated aspiration/vomiting rather than ventilator-associated pneumonia. Therefore, the meta-analysis included two RCTs and showed that routine GRV monitoring did not significantly reduce the incidence of ventilator-associated pneumonia (RR, 1.07; 95% CI, 0.72–1.59) (Fig. 4) [65,85,86]. Recent guidelines also suggest that GRV alone has limited value for aspiration risk assessment, and no standardized aspiration risk assessment tool has yet been established [87,88].

Post-pyloric feeding may be considered in patients at high risk of aspiration or with gastric feeding intolerance [1,5]. A meta-analysis of eight studies comparing gastric and post-pyloric enteral nutrition demonstrated that post-pyloric feeding significantly reduced ventilator-associated pneumonia (RR, 0.63; 95% CI, 0.45–0.86; P=0.004, I^2=0%) and duration of mechanical ventilation (mean difference [MD], –1.92 days; 95% CI, –3.33 to –0.51; P=0.008, I^2=74%) (Fig. 5) [89-96]. Post-py-

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loric feeding was also associated with reduced abdominal distension and EFI, although no significant differences were observed in overall pneumonia, mortality, or hospital length of stay. However, technical difficulty and patient characteristics should be considered when selecting the feeding route.

Prokinetics are recommended in patients with EFI [1,20]. Metoclopramide and erythromycin are the most commonly used agents and may improve delayed gastric emptying and feeding tolerance, although their effects on pneumonia prevention remain uncertain [1,5,20,97-99]. In Korea, metoclopramide is commonly available, whereas erythromycin is currently not available for clinical use. Itopride and DA-9701 may also be used as alternative agents, despite limited evidence in critically ill patients [100,101].

Head-of-bed elevation and oral hygiene are the most established nonpharmacologic interventions for aspiration prevention. Previous meta-analyses demonstrated that head-of-bed elevation at 30°–45° reduced ventilator-associated pneumonia [102,103], and oral care using chlorhexidine was also associated with reduced pneumonia risk [104].

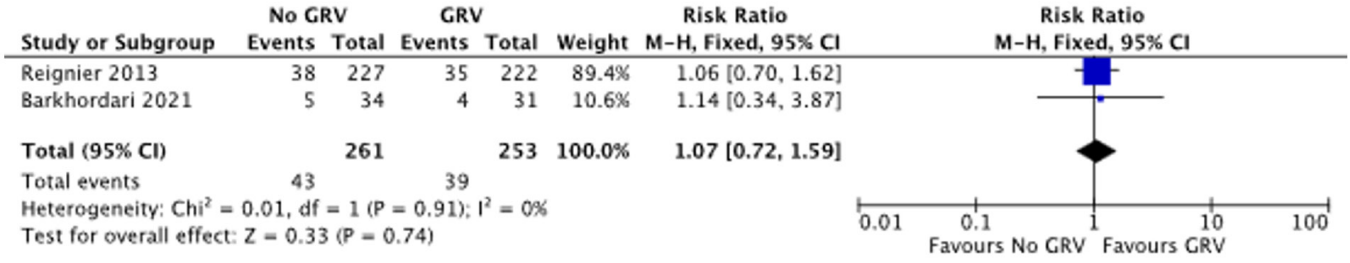

Fig. 4. Forest plot comparing the incidence of ventilator-associated pneumonia according to GRV monitoring in critically ill adult patients receiving enteral nutrition. GRV, gastric residual volume; M-H, Mantel-Haenszel; CI, confidence interval.

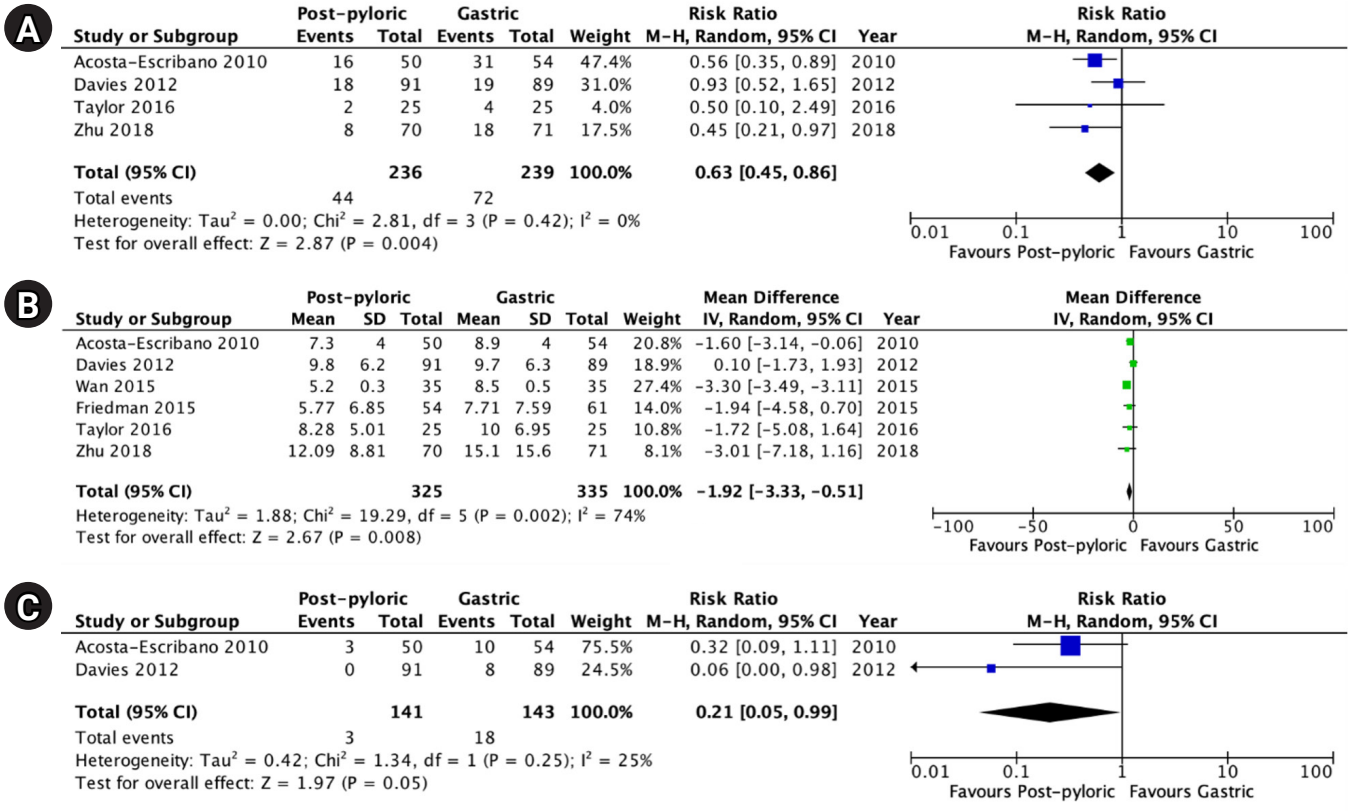

Fig. 5. Forest plots comparing post-pyloric versus gastric enteral nutrition in critically ill adult patients: (A) ventilator-associated pneumonia, (B) duration of mechanical ventilation, and (C) feeding intolerance. M-H, Mantel-Haenszel; CI, confidence interval; SD, standard deviation.

Overall, aspiration risk assessment is important in critically ill adults receiving enteral nutrition, although no single parameter reliably predicts aspiration risk. Routine GRV monitoring has limited clinical value, and post-pyloric feeding may be considered in high-risk patients. A multimodal strategy including prokinetics, head-of-bed elevation, and oral hygiene is recommended to reduce aspiration-related complications (Supplement Tables 15-20 and Supplement Figs. 8-12).

Energy requirements

KQ 9. What is the optimal method to determine energy requirements in critically ill adult patients?

R18. Indirect calorimetry (IC) is considered for determining energy requirements. (Low evidence, conditional for, strong consensus: 100%)

R19. When IC is unavailable, the use of weight-based formulas (25 kcal/kg/day), predictive equations, and carbon dioxide production (VCO_2)-based estimation methods (in mechanically ventilated patients) is suggested. (Expert consensus, strong consensus: 97%)

Energy requirements in critically ill patients change continuously according to disease severity, inflammatory response, and organ dysfunction; therefore, accurate assessment of energy expenditure is important. Common methods for estimating energy requirements include IC, predictive equations, weight-based formulas, and VCO_2-based estimation methods. ESPEN and SCCM-ASPEN guidelines recommend IC as the reference standard for determining energy requirements in critically ill patients [1,5,20].

A meta-analysis of RCTs comparing IC-guided energy provision with predictive equation- or weight-based approaches demonstrated no significant difference in estimated energy requirements (MD, 25.62 kcal/day; 95% CI, –156.47 to 207.71; P=0.78) or major clinical outcomes, including intensive care unit mortality, hospital mortality, infectious complications, and length of stay (Fig. 6) [24,105-113]. However, actual delivered energy and energy balance tended to be more appropriate in the IC-guided group. Overall heterogeneity among studies was substantial, and the certainty of evidence was low.

Observational studies have reported that predictive equations and weight-based formulas may either underestimate or overestimate energy expenditure depending on the patient population and disease phase [114-125]. In particular, greater inaccuracy has been reported in patients with sepsis, burns, trauma, and liver transplantation because of marked metabolic variability [116-121]. VCO_2-based estimation methods showed relatively small differences compared with IC and may be considered an alternative approach, although they cannot fully replace IC [126]. Weight-based formulas are easy to apply in routine practice, but their accuracy may be limited in patients with edema or obesity. In addition, recent studies suggested that individualized energy delivery strategies increased nutritional delivery without consistently improving major clinical outcomes [127].

IC remains the preferred method for determining energy requirements in critically ill adults because it provides the most accurate assessment of energy expenditure, although its impact on clinical outcomes remains uncertain. Repeated measurements may be helpful when feasible. When IC is unavailable, weight-based formulas, predictive equations, or VCO_2-based estimation methods may be selectively applied according to the patient's clinical condition (Supplement Tables 21-24 and Supplement Figs. 13-15).

Formulation of enteral nutrition

KQ 10. Does enteral fish oil supplementation improve clinical outcomes in critically ill adults?

R20. Routine enteral fish oil supplementation is not recommended. (Low evidence, conditional against, strong consensus: 100%)

R21. Enteral fish oil supplementation may be considered in perioperative patients or those at high risk for infection (e.g., patients undergoing cardiac surgery or those with abdominal sepsis). (Low evidence, conditional for, strong consensus: 91%)

Enteral fish oil supplementation containing eicosapentaenoic acid and docosahexaenoic acid may modulate inflammatory responses and promote resolution of inflammation and has been suggested to reduce infectious complications and shorten hospital stay [128-131]. However, whether these physiological effects consistently translate into improved clinical outcomes remains uncertain [131,132]. ESPEN and SCCM-ASPEN guidelines do not recommend routine enteral fish oil supplementation in critically ill adults [1,5].

A meta-analysis of seven RCTs demonstrated that enteral fish oil supplementation did not significantly reduce intensive

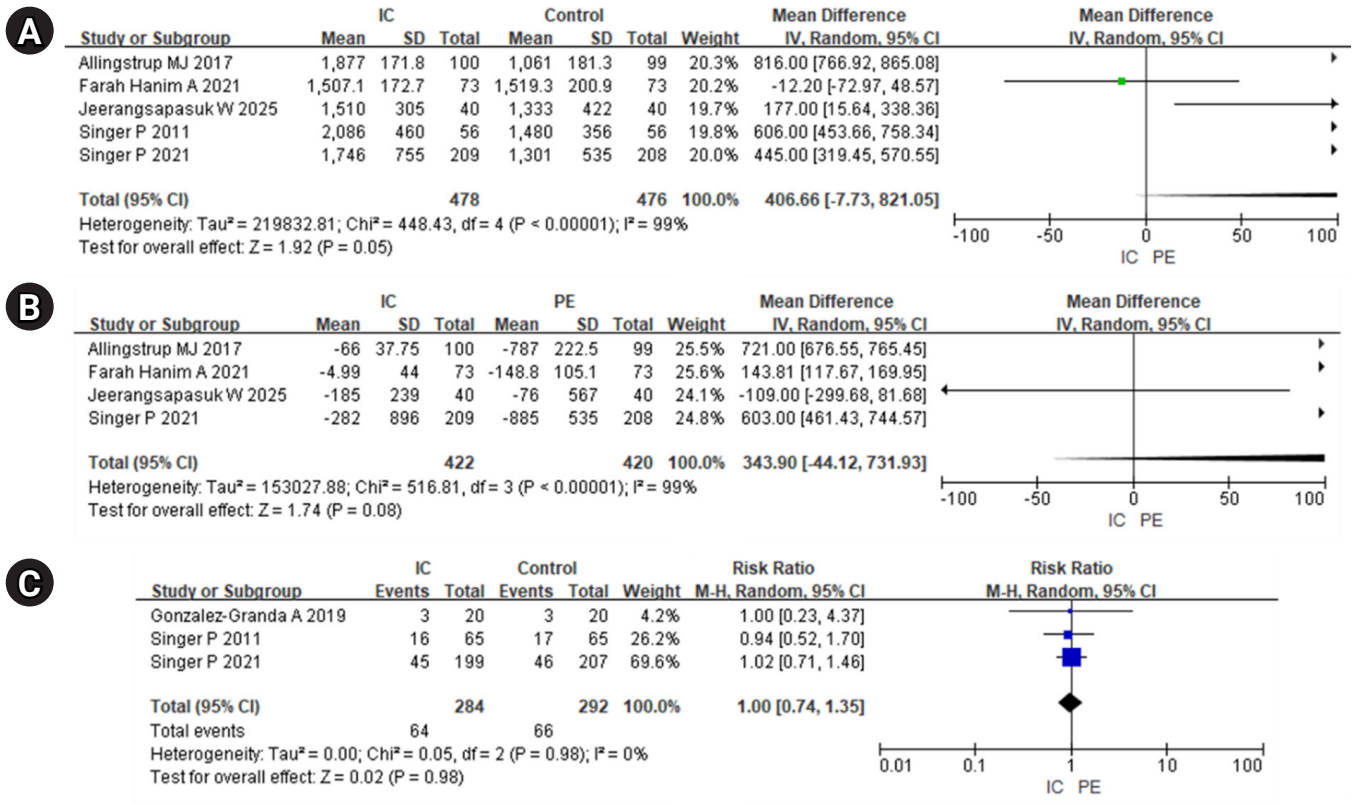

Fig. 6. Forest plots comparing IC-guided versus predictive equation-guided energy provision in critically ill adult patients: (A) daily energy delivery, (B) daily energy balance, and (C) intensive care unit mortality. IC, indirect calorimetry; SD, standard deviation; PE, predictive equation; IV, inverse variance; M-H, Mantel-Haenszel; CI, confidence interval.

care unit mortality (RR, 0.90; 95% CI, 0.59–1.40) or hospital mortality (RR, 0.95; 95% CI, 0.71–1.28) (Fig. 7) [133-139]. Intensive care unit length of stay was significantly shorter in the fish oil group; however, substantial heterogeneity among studies limits interpretation of this finding. Some studies also reported trends toward improvement in hospital length of stay, Sequential Organ Failure Assessment (SOFA) score, and incidence of septic shock, although statistical significance was not consistently demonstrated. Overall, the certainty of evidence was low to moderate because of heterogeneity in study populations, dosing regimens, and duration of supplementation.

Enteral fish oil supplementation has not demonstrated clear mortality benefits in critically ill adults, and current evidence does not support its routine use in the general intensive care unit population. However, selective use may be considered in specific patient populations, including perioperative patients and those at high risk of infectious complications, although further studies are needed (Supplement Tables 25-27, and Supplement Figs. 16-19).

KQ 11. Does additional immune-modulating enteral nutrition with arginine and glutamine affect clinical outcomes in critically ill adults?

R22. Routine enteral arginine supplementation is not recommended. Enteral arginine supplementation may be considered in patients with severe trauma or in postoperative critically ill patients. (Expert consensus, strong consensus: 97%)
R23. Routine enteral glutamine supplementation is not recommended. (Expert consensus, strong consensus: 95%)

Immune-modulating enteral nutrition containing specific nutrients, such as arginine, glutamine, and nucleotides, has been used to modulate immune function, regulate inflammatory responses, and maintain intestinal mucosal integrity [140,141]. However, whether these physiological effects consistently translate into improved clinical outcomes remains uncertain. ESPEN guidelines do not recommend routine use of arginine-containing immune-modulating formulas in critically ill adults, and SCCM-ASPEN guidelines also suggest limiting their use to selected populations, such as patients with severe trauma or surgical critical illness [1,5].

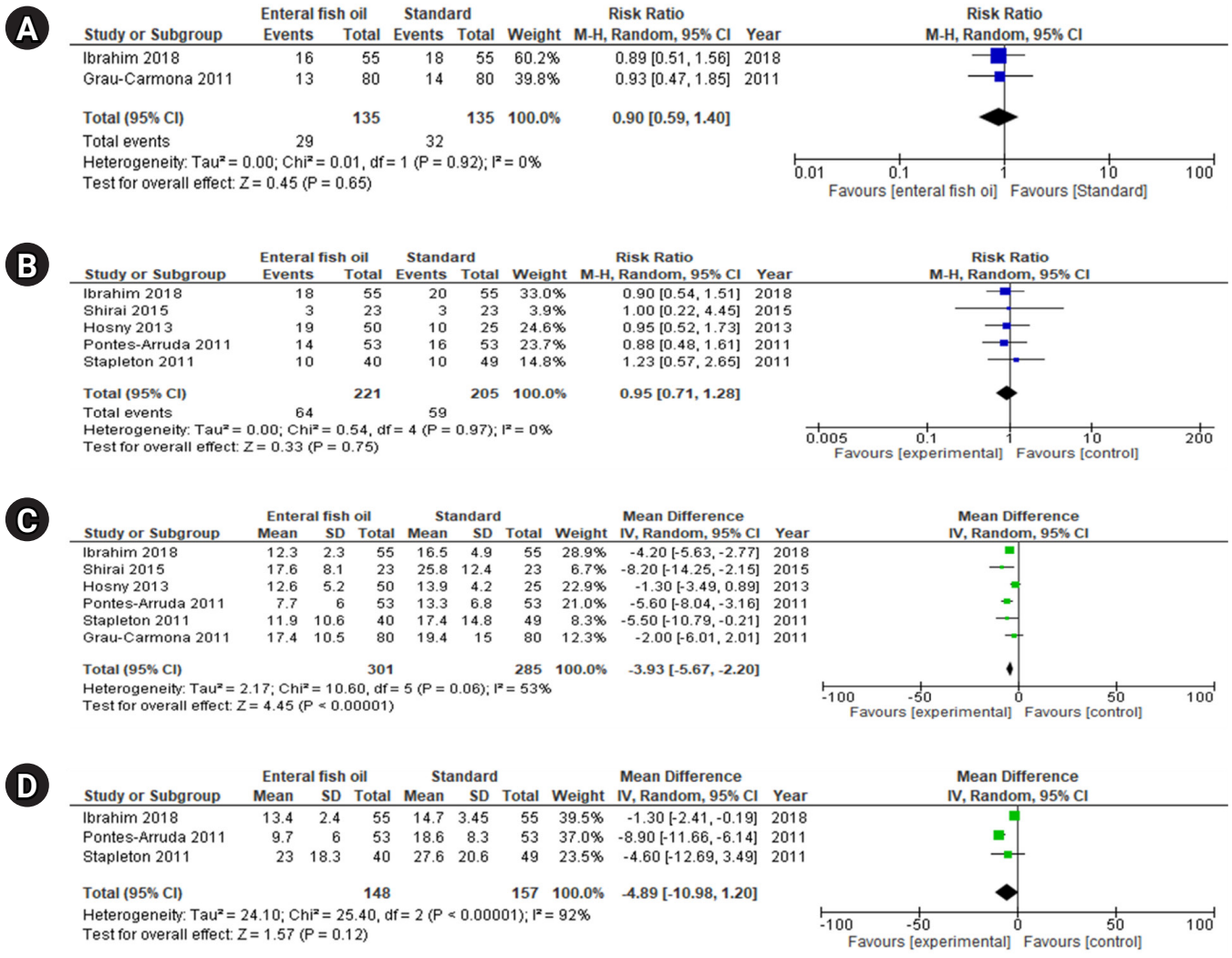

Fig. 7. Forest plots showing the effects of enteral fish oil supplementation in critically ill adult patients: (A) intensive care unit mortality, (B) hospital mortality, (C) intensive care unit length of stay, and (D) hospital length of stay. M-H, Mantel-Haenszel; CI, confidence interval; SD, standard deviation; IV, inverse variance.

Systematic reviews of arginine-containing enteral immunonutrition have reported improvements in immunological parameters and reductions in postoperative infectious complications and pneumonia [142]. However, most studies involved selected surgical populations, including patients undergoing gastric cancer surgery, and the independent effect of arginine alone remains difficult to determine. Therefore, current evidence supports only selective use in patients with severe trauma or postoperative critical illness rather than routine supplementation in the general intensive care unit population.

Meta-analyses of enteral glutamine supplementation demonstrated possible reductions in hospital length of stay, but no significant improvements in mortality or infectious complications were observed [143]. In addition, interpretation of the results is limited by substantial heterogeneity in study populations, dosing regimens, and duration of supplementation. Other studies suggested potential benefits in intestinal permeability and oxidative stress in selected patient groups, but consistent mortality benefits have not been demonstrated [143-147].

Nucleotides have mainly been studied as components of combined immune-modulating formulas, making their independent clinical effects difficult to evaluate. Clinical evidence regarding nucleotide supplementation in critically ill adults remains very limited [141,148-150].

Current evidence does not support routine supplementation with enteral arginine or glutamine in critically ill adults because clear benefits in mortality and infectious complications have not been demonstrated. Arginine supplementation may be selectively considered in specific surgical conditions, such as severe trauma or postoperative critical illness, where-

as routine use in the general intensive care unit population is not recommended. Likewise, routine enteral glutamine supplementation is not recommended because clinically meaningful benefits remain uncertain beyond possible reductions in hospital length of stay (Supplement Tables 28, 29).

KQ 12. In which situations can fiber-containing enteral formulas be used in critically ill adult patients?

R24. Routine use of fiber-containing enteral formulas is not suggested. (Expert consensus, strong consensus: 97%)
R25. In hemodynamically stable patients with preserved gastrointestinal function and persistent diarrhea, the use of fiber-containing enteral formulas is suggested. (Expert consensus, strong consensus: 100%)

Dietary fiber in enteral formulas may help maintain intestinal mucosal integrity and reduce EFI by modulating the gut microbiota and producing short-chain fatty acids [151-154]. Several clinical studies and meta-analyses have suggested that fiber supplementation may reduce the frequency and severity of diarrhea and improve feeding tolerance [154-157]. Soluble fiber has also been associated with potential benefits in glucose and lipid metabolism [152]. However, recommendations from international guidelines remain inconsistent. ESPEN and the Canadian Clinical Practice Guidelines concluded that current evidence is insufficient to support routine use of fiber-containing enteral formulas in critically ill patients [5,20,158]. In contrast, SCCM-ASPEN guidelines suggest the use of soluble fiber in hemodynamically stable patients with diarrhea during enteral nutrition [1]. Systematic reviews have also reported that soluble fiber appears safe and may reduce diarrhea in hemodynamically stable critically ill adults [159].

Insoluble fiber, however, may delay intestinal transit and increase intraluminal pressure, raising concerns about complications such as nonocclusive bowel ischemia in patients with hemodynamic instability or severe gastrointestinal dysmotility [160,161]. Most fiber-containing enteral formulas currently used in Korea contain a mixture of soluble and insoluble fiber, although direct comparative evidence by fiber type remains limited.

Current evidence does not support routine use of fiber-containing enteral formulas in all critically ill adults. However, in hemodynamically stable patients with preserved gastrointestinal function and persistent diarrhea after exclusion of non-nutritional causes, enteral formulas containing soluble fiber may be selectively considered (Supplement Tables 30, 31).

KQ 13. Does probiotic supplementation affect clinical outcomes in critically ill adults?

R26. Routine use of probiotics is not recommended. (Low evidence, conditional against, strong consensus: 100%)

Probiotics have been investigated as a strategy to modulate the gut microbiota, maintain intestinal barrier function, and reduce infectious complications in critically ill patients. A meta-analysis of 18 RCTs demonstrated that probiotic supplementation did not significantly reduce intensive care unit mortality, 28-/30-day mortality, or overall infection rates compared with control groups (Fig. 8) [162-179]. However, probiotic supplementation showed trends toward reductions in pneumonia, ventilator-associated pneumonia, and intensive care unit length of stay, although substantial heterogeneity was observed among studies. Constipation tended to decrease in the probiotic group, whereas no significant difference was observed in diarrhea incidence.

The included studies showed marked variability in probiotic strains, dosing regimens, administration routes, and treatment duration. In addition, study quality and design standardization were limited, resulting in overall low certainty of evidence. Accordingly, SCCM-ASPEN and Canadian Critical Care guidelines do not recommend routine use of probiotics in critically ill adults [1,180].

Probiotic supplementation may provide potential benefits in some infection-related outcomes; however, clear improvements in mortality or major clinical outcomes have not been consistently demonstrated. Given the substantial heterogeneity and potential risk of bias among studies, current evidence does not support routine use of probiotics in critically ill adults (Supplement Tables 32-34 and Supplement Figs. 20-23).

Parenteral nutrition

KQ 14. When should PN be initiated in critically ill adults when oral intake and enteral nutrition are not feasible?

R27. In patients unable to receive oral intake or enteral nutrition, initiation of PN within 3–7 days of intensive care unit admission should be considered. (Moderate evidence, conditional for, strong consensus: 92%)
R28. In patients with severe malnutrition, early initiation of PN is suggested. (Expert consensus, strong consensus: 97%)

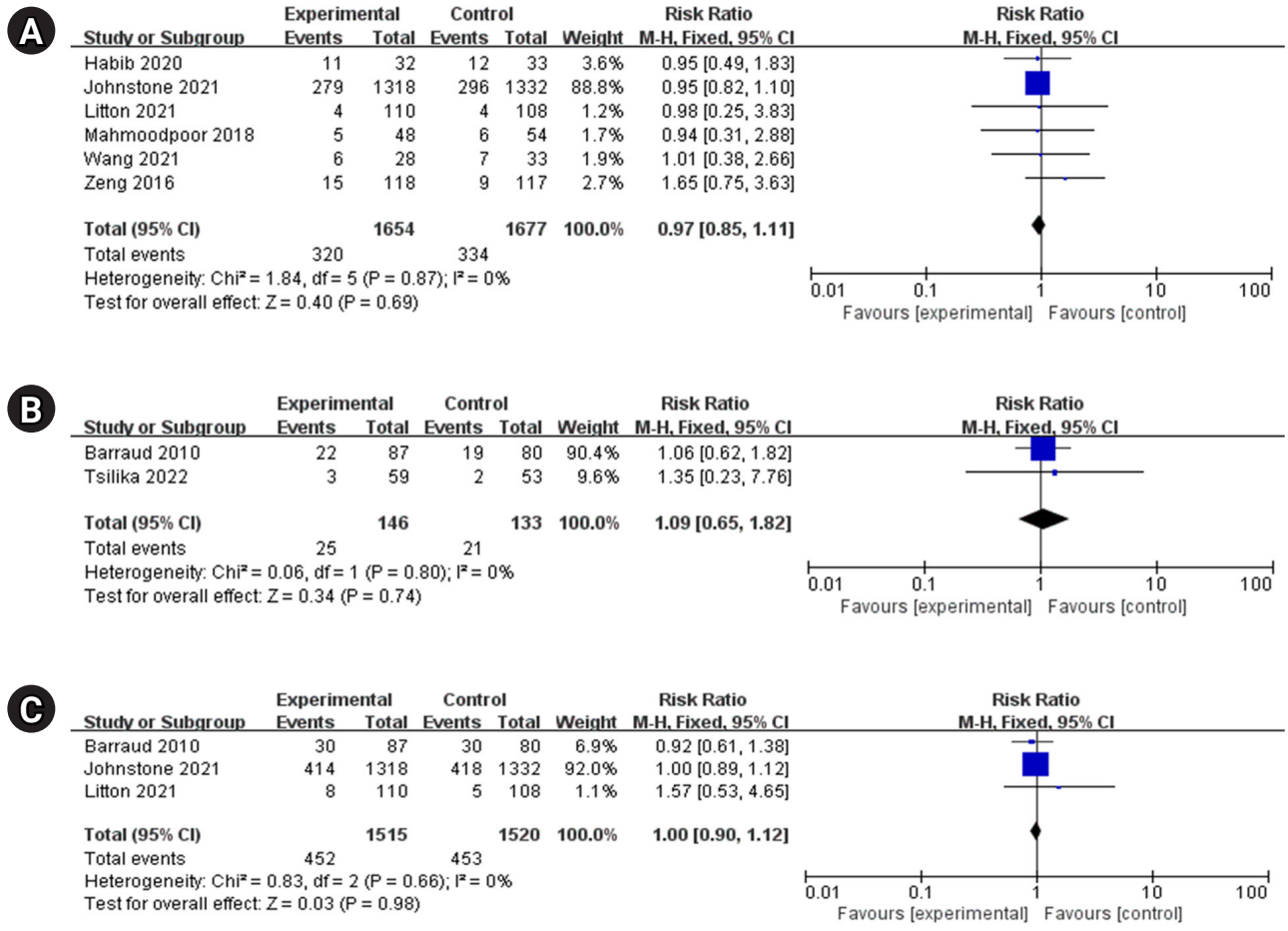

Fig. 8. Forest plots summarizing the effects of probiotic supplementation in critically ill adults: (A) intensive care unit mortality, (B) 28-/30-day mortality, and (C) incidence of infection. M-H, Mantel-Haenszel; CI, confidence interval.

PN is an alternative nutritional strategy for critically ill adults when oral intake and enteral nutrition are not feasible [5]. However, early PN during the acute phase of critical illness may be associated with overfeeding, hyperglycemia, and infectious complications; therefore, the timing of initiation requires careful consideration [1,3,181-183].

SCCM-ASPEN guidelines recommend considering early PN in patients with malnutrition or high nutritional risk when oral intake or enteral nutrition is not possible, whereas withholding PN during the first 7 days may be acceptable in well-nourished patients [4,5]. Subsequently, the CALORIES and NUTRIREA-2 trials demonstrated no significant differences in mortality or infectious complications between early enteral nutrition and PN strategies [184,185].

A meta-analysis of two RCTs comparing early and delayed PN, the EPaNIC trial and early PN trial, demonstrated no significant differences in intensive care unit mortality, hospital mortality, or long-term mortality between groups (Fig. 9) [50,186]. Early PN was associated with reduced hypoglycemia but increased infectious complications and longer duration of mechanical ventilation. These findings should be interpreted cautiously because calorie delivery and patient characteristics differed across studies.

In critically ill adults who cannot receive oral intake or enteral nutrition, initiation of PN within 3–7 days after intensive care unit admission may be considered in patients with adequate baseline nutritional status. In contrast, early PN may be selectively considered in patients with severe malnutrition or high nutritional risk to prevent further nutritional deterioration. PN should preferably be initiated at a low dose with careful monitoring of blood glucose and electrolytes, followed by gradual advancement according to clinical tolerance (Supplement Tables 35-37 and Supplement Figs. 24-26).

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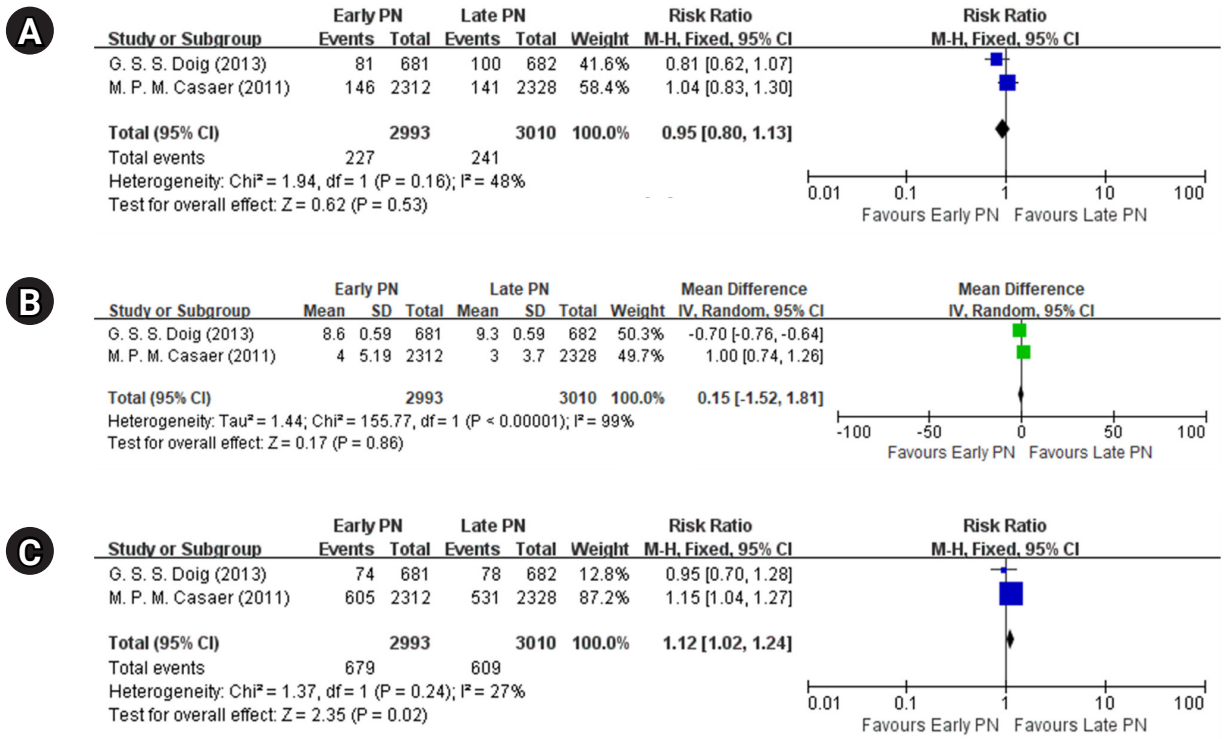

Fig. 9. Forest plots comparing early versus delayed PN in critically ill adult patients: (A) intensive care unit mortality, (B) intensive care unit length of stay, and (C) infectious complications. PN, parenteral nutrition; M-H, Mantel-Haenszel; CI, confidence interval; SD, standard deviation; IV, inverse variance.

KQ 15. In candidates for early PN, what is the appropriate target caloric intake?

R29. Hypocaloric PN (≤70% of estimated energy requirements or ≤20 kcal/kg/day) is suggested during the early phase of intensive care unit stay (within the first week), with subsequent gradual advancement according to the clinical course. (Expert consensus, strong consensus: 100%)

During the early phase of critical illness, acute stress responses and increased endogenous energy production may increase the risk of metabolic complications, such as hyperglycemia, hepatic steatosis, and infectious complications, when excessive caloric intake is provided [187]. Accordingly, hypocaloric feeding strategies have been proposed during the initial phase of PN to avoid overfeeding.

A meta-analysis involving critically ill patients, including surgical and trauma populations, demonstrated that hypocaloric PN strategies (15–20 kcal/kg/day) were associated with fewer infectious complications and shorter hospital stays [188]. In addition, several RCTs reviewed in the SCCM-ASPEN guidelines reported no significant difference in mortality between hypocaloric and normocaloric feeding strategies, although hypocaloric feeding was associated with reduced hyperglycemia [189-192].

ESPEN guidelines recommend hypocaloric nutrition during the first week of intensive care unit stay in patients unable to receive oral intake or enteral nutrition, generally targeting less than 70% of estimated energy requirements [5,20]. Similarly, SCCM-ASPEN guidelines recommend hypocaloric PN during the first week of intensive care unit stay, defined as ≤20 kcal/kg/day or less than 80% of estimated energy requirements [1].

In critically ill adults requiring early PN, initiation with hypocaloric feeding during the first 7 days of intensive care unit stay appears reasonable. Energy delivery may subsequently be advanced gradually toward target requirements according to the patient's clinical condition and metabolic stability. Careful monitoring for hyperglycemia, electrolyte imbalance, and refeeding syndrome is required during this period (Supplement Table 38).

Micronutrients

KQ 16. Does supplementation with micronutrients and antioxidants affect clinical outcomes in critically ill adult patients?

R30. Micronutrients and vitamins should be routinely provided to meet daily requirements; when PN is used, they

should be included at the recommended daily intake level. (Expert consensus, strong consensus: 100%)

R31. Additional supplementation with micronutrients and antioxidants above the recommended intake is not recommended. (Moderate evidence, conditional against, strong consensus: 92%)

R32. Routine high-dose vitamin C supplementation is not recommended. (Moderate evidence, conditional against, consensus: 78%)

R33. High-dose selenium supplementation is not recommended. (Low evidence, conditional against, strong consensus: 95%)

R34. Routine high-dose antioxidant supplementation, including vitamin D, thiamine, and N-acetylcysteine (NAC), is not recommended. (Low evidence, conditional against, strong consensus: 90%)

Micronutrients and vitamins play essential roles in metabolic regulation, antioxidant defense, and immune function, and deficiencies may contribute to organ dysfunction and increased complications in critically ill patients [193,194]. ESPEN guidelines and ASPEN expert consensus statements recommend routine provision of micronutrients and vitamins at the recommended daily intake level during PN in critically ill adults [5,20,194,195]. In contrast, routine supplementation above recommended daily requirements is not supported because evidence of clinical benefit is insufficient [1,5,20].

A meta-analysis including 64 RCTs demonstrated that micronutrient and antioxidant supplementation was associated with reduced 28-/30-day mortality, lower pneumonia incidence, and improved SOFA scores; however, no significant differences were observed in intensive care unit mortality or hospital mortality (Fig. 10) [196-259]. Considerable heterogeneity was present across most outcomes because of differences in patient populations, dosing regimens, duration of supplementation, and combination strategies.

Among individual micronutrients, high-dose vitamin C showed potential benefits in pneumonia reduction and shorter duration of mechanical ventilation in some studies, particularly in patients undergoing cardiovascular surgery, in whom possible reductions in 28-/30-day mortality were observed [196-220]. However, substantial heterogeneity and concerns about an increased need for renal replacement therapy have been reported, and current evidence remains insufficient to support routine use in the general intensive care unit population.

High-dose selenium, vitamin D, thiamine, NAC, and other antioxidant combinations demonstrated possible improvements in selected physiological or laboratory parameters, but consistent benefits in mortality or major clinical outcomes have not been demonstrated [221-259].

Adequate provision of micronutrients and vitamins at recommended daily intake levels remains important in critically ill adults. However, routine high-dose supplementation above recommended requirements is not supported because clinically meaningful benefits remain inconsistent and substantial heterogeneity exists among studies. Subgroup findings suggesting potential benefits of high-dose vitamin C in specific populations, particularly patients undergoing cardiovascular surgery, should be interpreted cautiously and require further validation (Supplement Tables 39-42 and Supplement Figs. 27-29).

Monitoring and metabolic complications

KQ 17. Which laboratory parameters should be monitored in critically ill adult patients receiving nutrition therapy?

R35. Blood glucose should be measured immediately after admission or initiation of nutritional therapy and at least every 4 hours during the first 48 hours. The suggested target blood glucose range is 140–180 mg/dL, and insulin therapy is suggested if blood glucose persistently exceeds 180 mg/dL, with institutional discretion for initiation up to 200 mg/dL. (Expert consensus, strong consensus: 97%)

R36. Blood electrolytes (phosphate, potassium, magnesium, sodium, chloride) should be measured at least once daily during the first week of nutritional therapy, with early phosphate measurement suggested within 6–12 hours of admission. (Expert consensus, strong consensus: 95%)

R37. Liver function tests should be measured twice weekly during the initial phase of nutritional therapy and at least once weekly during the stable phase thereafter. (Expert consensus, strong consensus: 100%)

R38. Serum triglyceride levels should be measured once or twice weekly during nutritional therapy. In particular, close monitoring is suggested in patients receiving lipid-containing PN or lipid-based medications. (Expert consensus, strong consensus: 95%)

R39. Prealbumin is suggested as a supplementary marker for assessing response to nutritional therapy, and weekly measurement together with C-reactive protein (CRP) is suggested. (Expert consensus, consensus: 87%)

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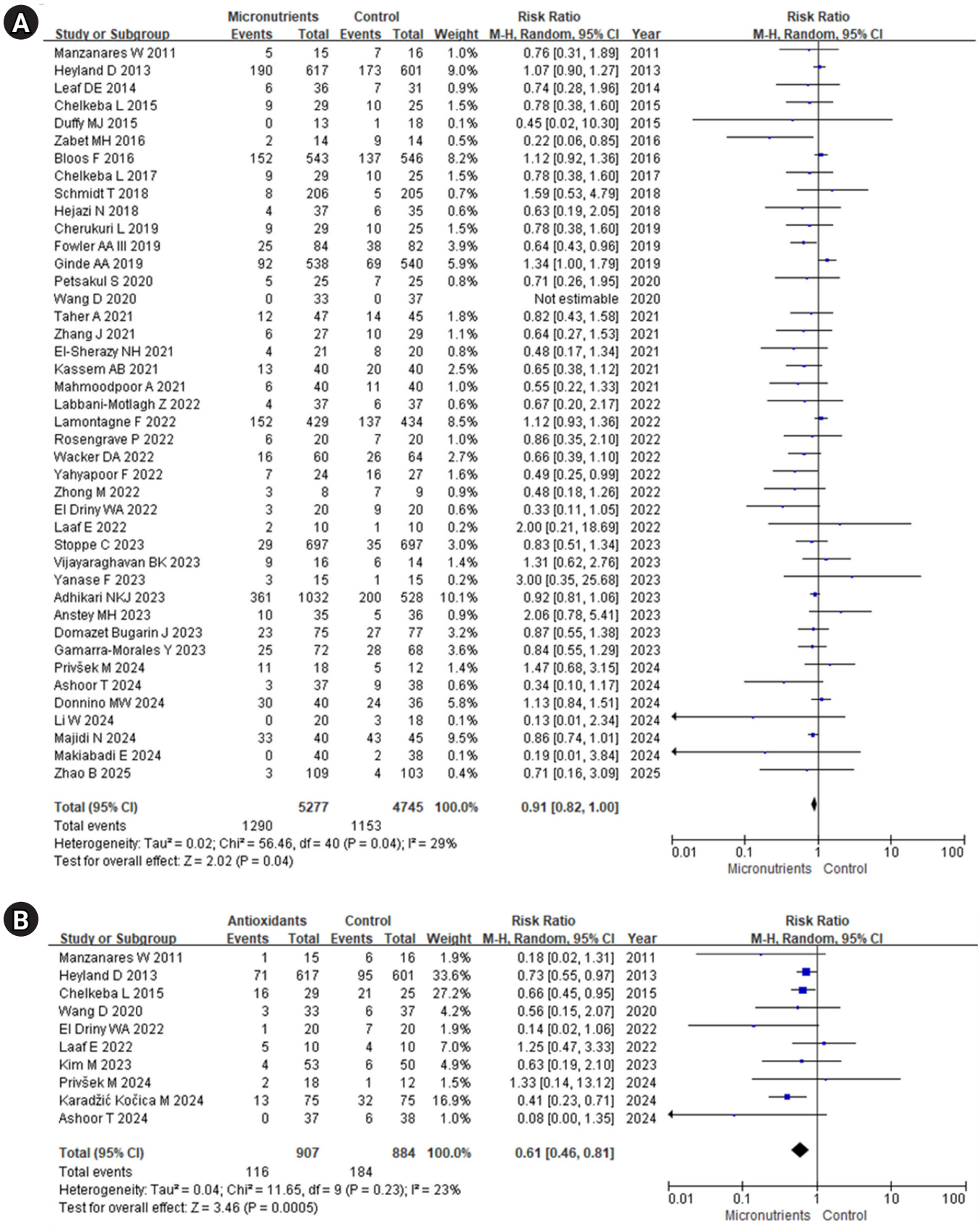

Fig. 10. Forest plots showing the effects of micronutrient and antioxidant supplementation in critically ill adults: (A) 28-/30-day mortality and (B) pneumonia. M-H, Mantel-Haenszel; CI, confidence interval.

R40. In patients at high risk of vitamin and trace element deficiencies, clinicians should assess whether thiamine, vitamin C, copper, selenium, zinc, and other essential micronutrients are being supplied adequately and monitor levels when necessary (e.g., prolonged continuous renal replacement therapy [CRRT] for >2 weeks, severe burns, malabsorption, malnutrition, chronic alcoholism, or significant fluid drainage). (Expert consensus, strong consensus: 95%)

R41. Measurement of nitrogen balance is suggested to assess protein adequacy, although its use is limited in dialysis patients. (Expert consensus, strong consensus: 91%)

Appropriate laboratory monitoring is important in critically ill adults receiving nutritional therapy because metabolic alterations and nutrition-related complications commonly occur during intensive care unit care [20,260]. Although direct comparative studies are limited, abnormal laboratory findings are closely associated with clinical course and prognosis, supporting the need for systematic monitoring of key laboratory parameters.

ESPEN guidelines recommend measuring blood glucose immediately after intensive care unit admission or initiation of nutritional therapy and at least every 4 hours during the first 48 hours [20,260]. The recommended target glucose range is 140–180 mg/dL, and persistent hyperglycemia (>180 mg/dL) has been associated with poor clinical outcomes and requires insulin therapy [20,260-262]. Conversely, hypoglycemia (<70 mg/dL) is also associated with increased mortality [20]. In Korean intensive care units, insulin initiation thresholds of approximately 200 mg/dL are also commonly used in practice. Therefore, this guideline recommends maintaining blood glucose within the target range of 140–180 mg/dL while considering insulin therapy when blood glucose persistently exceeds 180 mg/dL, with institutional discretion for initiation up to 200 mg/dL depending on local protocols and clinical judgment.

Electrolyte monitoring is particularly important for prevention and early detection of refeeding syndrome. Hypophosphatemia is a hallmark feature of refeeding syndrome and may contribute to cardiac failure, respiratory failure, and neurological complications. Accordingly, early phosphate measurement within 6–12 hours after intensive care unit admission or initiation of nutritional therapy is recommended, followed by at least daily monitoring during the first week [20,260,263]. Hypokalemia and hypomagnesemia may also occur during refeeding and often require frequent monitoring and replacement, particularly during the early phase of nutritional therapy. Measurement every 6 hours during the first 24 hours may be considered in high-risk patients, followed by at least daily monitoring during the first week [20,260,263]. Sodium and chloride should also be monitored because of their relationship with fluid balance and acid-base status [260].

Liver dysfunction during nutritional therapy may be associated with overfeeding, sepsis, shock, hypoxia, and medication use. Excessive energy delivery has been associated with cholestasis and elevated liver enzyme levels, particularly when energy intake exceeds approximately 26–28 kcal/kg/day [260,264]. Therefore, liver function tests, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin, are suggested twice weekly during the early phase of nutritional therapy and at least weekly thereafter during the stable phase [260,263,265].

Hypertriglyceridemia may develop in association with lipid-containing PN, prolonged propofol infusion, excessive carbohydrate administration, or sepsis. Serum triglyceride levels are therefore suggested to be monitored once or twice weekly, especially in patients receiving intravenous lipid emulsions or lipid-based medications [260,265]. Reduction or discontinuation of lipid administration may be considered when triglyceride levels exceed 400–500 mg/dL [266].

Prealbumin has a relatively short half-life and may reflect short-term changes in nutritional status; however, it is strongly influenced by acute inflammation and should therefore be interpreted together with CRP [260]. Several studies have demonstrated associations between low or decreasing prealbumin levels and increased disease severity, shock, and poor prognosis [267-271]. Recent studies also suggest that dynamic changes in prealbumin may serve as a useful supplementary marker for assessing response to nutritional therapy [272]. Nevertheless, routine use may be limited by cost and practical considerations.

Patients receiving prolonged CRRT (>2 weeks) are at increased risk of water-soluble vitamin and trace element losses. Reduced levels of vitamin C, selenium, zinc, and copper have been reported in these patients [273,274]. Similarly, patients with severe burns may experience substantial trace element losses through wound exudates, potentially impairing wound healing and immune function [275]. Therefore, patients with prolonged CRRT, severe burns, malabsorption, malnutrition, chronic alcoholism, or significant fluid losses should be assessed for adequate supply and potential deficiencies of thiamine, vitamin C, selenium, copper, and zinc when clinically indicated.

Nitrogen balance remains one representative method for assessing the adequacy of protein delivery. Negative nitrogen bal-

ance has been associated with muscle wasting and poor clinical outcomes, and improvement in nitrogen balance has been associated with improved survival in some studies [276-279]. However, interpretation of nitrogen balance is limited because accurate measurement requires 24-hour urinary urea nitrogen collection and may be influenced by renal function, dialysis, urine output, and inflammatory status. In particular, interpretation is limited in patients undergoing dialysis or CRRT because actual nitrogen losses may not be fully reflected [265].

Laboratory monitoring during nutritional therapy is essential for early detection of nutrition-related complications, such as refeeding syndrome, overfeeding, hyperglycemia, and micronutrient deficiencies. Repeated assessment of blood glucose, electrolytes, liver function, triglycerides, prealbumin, and micronutrient status according to the patient's clinical condition and phase of nutritional therapy is therefore important (Supplement Table 43).

KQ 18. What are strategies for assessing and preventing refeeding syndrome in critically ill adults?

R42. Structured screening for high risk of refeeding syndrome is suggested after intensive care unit admission. (Expert consensus, strong consensus: 97%)

R43. In patients at risk of refeeding syndrome, measurement of serum phosphate, potassium, and magnesium before and during the early phase of nutritional therapy, with supplementation when deficient and frequent reassessment, is suggested. (Expert consensus, strong consensus: 97%)

R44. In patients at risk of refeeding syndrome, initiation of nutrition with caloric restriction (100–150 g of glucose or 10–20 kcal/kg during the first 24 hours), followed by gradual advancement every 1–2 days, is suggested. (Expert consensus, strong consensus: 97%)

R45. In patients at risk of refeeding syndrome, administration of thiamine before initiation of nutritional therapy is suggested. (Expert consensus, strong consensus: 100%)

Refeeding syndrome is a metabolic complication that occurs when nutritional support is restarted after prolonged malnutrition or starvation. It is characterized by hypophosphatemia, hypokalemia, hypomagnesemia, thiamine deficiency, and fluid shifts [1,5,280-285]. These abnormalities usually develop within 72 hours after initiation of nutritional therapy and may result in severe complications, including arrhythmia, heart failure, respiratory failure, neurological dysfunction, and death. Refeeding syndrome may occur during both enteral nutrition and PN, and refeeding hypophosphatemia has been reported in 7%–62% of critically ill patients [284-287].

Patients with prolonged inadequate nutritional intake, significant recent weight loss, low body weight, baseline electrolyte abnormalities, severe illness, or major surgery are considered at high risk for refeeding syndrome [282,284,285]. ASPEN consensus recommendations provide structured criteria for patients at moderate and high risk and recommend systematic screening (Supplement Table 44) [280]. ESPEN and SCCM-ASPEN guidelines also emphasize early risk assessment and gradual nutritional advancement strategies [1,5,281-283,288].

During prolonged starvation, body stores of phosphate, potassium, magnesium, and thiamine become depleted while insulin secretion remains suppressed. After initiation of nutritional therapy, increased insulin secretion promotes rapid intracellular shifts of glucose and electrolytes, resulting in decreased serum concentrations [280,285,289-291]. Simultaneously, sodium and water retention may increase the risk of fluid overload and cardiovascular complications. Hypophosphatemia may impair myocardial and respiratory muscle function, whereas hypokalemia and hypomagnesemia are associated with life-threatening arrhythmias [280,285,289-291]. Thiamine deficiency may lead to lactic acidosis, heart failure (wet beriberi), and Wernicke–Korsakoff syndrome.

In high-risk patients, excessive caloric delivery during the initial phase of nutritional therapy may accelerate insulin-mediated electrolyte shifts and increase the risk of refeeding syndrome. Several studies have reported increased incidence of refeeding syndrome when initial caloric intake exceeded 20 kcal/kg/day, with higher mortality observed in patients with greater refeeding risk [284,291-294]. Therefore, ESPEN and SCCM-ASPEN guidelines recommend initiation of nutritional therapy with hypocaloric feeding (10–20 kcal/kg/day or 100–150 g/day of glucose), followed by gradual advancement according to clinical tolerance [1,5,280-283,292,293].

Electrolyte monitoring is a key component of prevention strategies. In high-risk patients, serum phosphate, potassium, and magnesium should be measured before initiation of nutritional therapy and monitored every 6–12 hours during at least the first 72 hours, followed by at least daily monitoring during the first week [1,260,280,288]. Aggressive supplementation and reassessment are required when deficiencies or rapid declines are detected.

Thiamine is an essential cofactor in glucose metabolism, and deficiency may result in lactic acidosis, heart failure, and Wernicke encephalopathy. Because thiamine requirements increase after initiation of nutritional therapy, international

guidelines recommend administration of 100–300 mg/day beginning at least 30 minutes before nutritional support in high-risk patients and continuing for several days [1,5,280-282,285,289,295]. Although RCTs have not consistently demonstrated improved major clinical outcomes with thiamine supplementation [296,297], prophylactic administration is generally recommended because of its favorable safety profile, low cost, and potential to prevent severe thiamine deficiency-related complications. Refeeding syndrome is a potentially fatal complication in critically ill adults, and early risk identification and preventive strategies are essential. Structured screening, close electrolyte monitoring and replacement, gradual advancement of nutritional therapy starting with hypocaloric feeding, and prophylactic thiamine administration are recommended in patients at risk of refeeding syndrome (Supplement Tables 44, 45).

Specific situation–acute respiratory failure

KQ 19. In patients with acute respiratory failure, including ARDS or acute lung injury (ALI), does enteral nutrition enriched with anti-inflammatory lipids affect clinical outcomes?

R46. Routine use of enteral formulas enriched with anti-inflammatory lipids, including omega-3 fatty acids and borage oil, is not recommended. (Moderate evidence, conditional against, strong consensus: 92%)

Enteral formulas enriched with anti-inflammatory lipids were developed to modulate inflammatory responses and attenuate lung injury through supplementation with eicosapentaenoic acid, docosahexaenoic acid, γ-linolenic acid (borage oil), and antioxidants. These formulations have been suggested to improve oxygenation and reduce organ dysfunction by decreasing inflammatory eicosanoid production, modulating neutrophil activation, and reducing alveolar-capillary membrane injury [129,298-300].

A meta-analysis of six RCTs evaluating anti-inflammatory lipid-enriched enteral nutrition in patients with ARDS or ALI showed no significant differences in 28-/60-day mortality (pooled RR, 1.23; 95% CI, 0.89–1.69; P=0.21), intensive care unit length of stay (MD, –0.90 days; 95% CI, –4.37 to 2.57; P=0.64), or ventilator-free days (MD, –0.70 days; 95% CI, –3.37 to 1.97; P=0.61) (Fig. 11) [135,139,301-304]. Some small studies reported improvements in SOFA score or Multiple Organ Dysfunction Score and reductions in new organ failure [303,304]. However, larger studies failed to demonstrate improvements in major clinical outcomes, and some even suggested potentially unfavorable effects [301]. Interpretation of the results is limited by heterogeneity in feeding protocols, formula composition, and patient populations.

Recent systematic reviews and meta-analyses have also shown that immune-modulating enteral formulas enriched with anti-inflammatory lipids do not significantly reduce mortality, and their effects on intensive care unit length of stay and duration of mechanical ventilation remain inconsistent [129,298-300]. Accordingly, both SCCM-ASPEN and ESPEN guidelines do not recommend routine use of these formulations in patients with ARDS or ALI [1,20,301,302,305,306].

Current evidence does not consistently support beneficial effects of anti-inflammatory lipid-enriched enteral formulas on major clinical outcomes in patients with ARDS or ALI, and some studies have reported potentially harmful outcomes. Therefore, routine replacement of standard enteral nutrition with these formulations is not recommended (Supplement Tables 46-49 and Supplement Figs. 30-32).

Specific situation–acute kidney injury

KQ 20. What is the optimal protein provision in critically ill adults with AKI?

R47. In patients with AKI (stage 1–3) who are not receiving renal replacement therapy, initial protein provision of 0.8–1.0 g/kg/day is suggested, with gradual advancement up to 1.2–1.3 g/kg/day according to the patient's catabolic state and nutritional status. (Expert consensus, strong consensus: 95%)

R48. In patients receiving CRRT, protein provision of 1.5–1.7 g/kg/day is suggested. (Expert consensus, strong consensus: 95%)

AKI occurs in approximately 40%–60% of critically ill patients and is associated with prolonged intensive care unit stay and increased mortality [307]. Critical illness induces systemic inflammation and hypercatabolism, leading to accelerated protein breakdown and negative nitrogen balance, which are often more pronounced in patients with AKI [1,20]. Therefore, preservation of lean body mass and minimization of nitrogen loss are considered important goals of nutritional therapy in critically ill patients with AKI.

However, recent evidence suggests that routine high-protein feeding during the acute phase may not provide clear clinical benefits in patients with AKI who are not receiving

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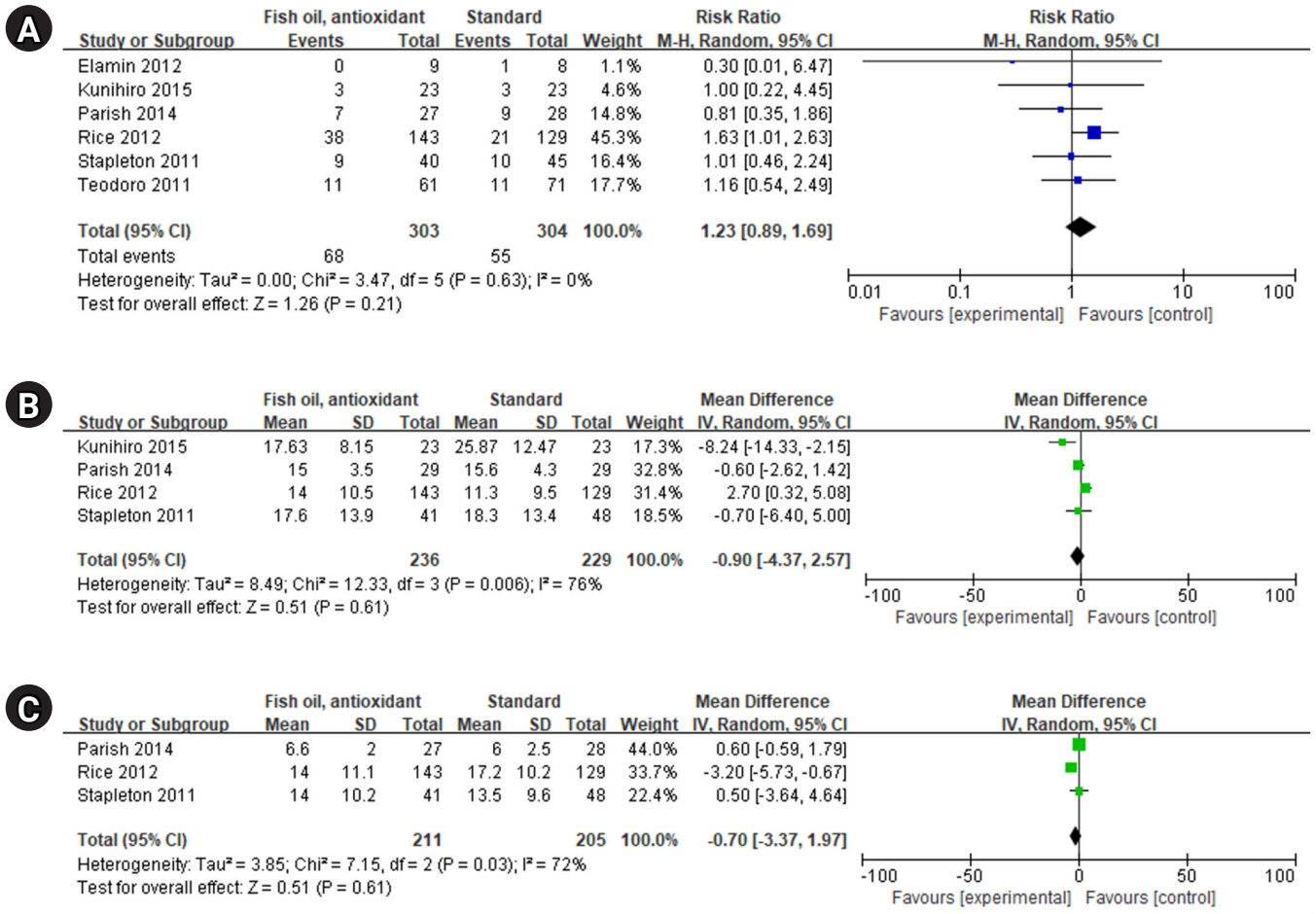

Fig. 11. Forest plots showing the effects of anti-inflammatory lipid-containing enteral nutrition formulations in patients with acute respiratory distress syndrome and acute lung injury: (A) 28-/60-day mortality, (B) intensive care unit length of stay, and (C) ventilator-free days. M-H, Mantel-Haenszel; CI, confidence interval; SD, standard deviation; IV, inverse variance.

renal replacement therapy [308,309]. Post hoc analyses of the EFFORT Protein trial reported that higher protein delivery (≥1.5–2.2 g/kg/day) in patients with nondialysis AKI was associated with increased 60-day mortality compared with standard protein provision (≤1.2 g/kg/day) [310-312]. Recent meta-analyses also demonstrated that high protein intake did not improve mortality, intensive care unit length of stay, or duration of mechanical ventilation and was associated with increased blood urea nitrogen levels [313,314]. In contrast, some studies suggested potential benefits in selected patients with stage III AKI or individualized protein strategies guided by nitrogen balance [106,315,316].

Current evidence suggests that routine high-protein feeding should not be universally applied during the acute phase of AKI in patients who are not receiving renal replacement therapy. An initial protein provision of approximately 0.8–1.0 g/kg/day, followed by gradual advancement up to 1.2–1.3 g/kg/day according to catabolic status, nutritional condition, and clinical course, appears to be a reasonable approach.

In contrast, patients receiving CRRT experience substantial amino acid and protein losses through the dialysis membrane, together with ongoing systemic catabolism, which increases the risk of negative nitrogen balance and muscle wasting [317-319]. Observational studies have suggested that higher protein intake may be associated with improved survival in patients receiving CRRT [320]. ESPEN guidelines recommend protein provision of at least 1.5 g/kg/day in patients receiving CRRT, with possible advancement up to 1.7 g/kg/day when clinically appropriate [20,307,310,311,313,314,321]. Individualization of protein delivery according to the patient's metabolic and clinical condition is also considered important [307,317-319,321].

Protein provision in critically ill adults with AKI should be individualized according to renal replacement status, catabolic burden, nutritional status, and clinical course. Moderate protein provision appears appropriate in patients with

non-CRRT AKI during the acute phase, whereas higher protein delivery is generally required in patients receiving CRRT because of increased protein losses and catabolism (Supplement Tables 50, 51).

Specific situation–liver failure

KQ 21. Does high protein provision affect clinical outcomes in critically ill adults with liver failure?

R49. High protein provision (1.2–1.5 g/kg/day) is suggested in patients with liver failure. (Expert consensus, strong consensus: 91%)

R50. In hyperacute liver failure, protein provision may be delayed for 24–48 hours, with gradual initiation suggested thereafter. (Expert consensus, strong consensus: 95%)

R51. Routine use of branched-chain amino acid (BCAA)-enriched protein supplementation is not recommended in patients with liver failure and hepatic encephalopathy. However, oral or enteral BCAA-enriched protein supplementation may be considered in those with suspected protein intolerance or recurrent hepatic encephalopathy. (Expert consensus, strong consensus: 93%)

Patients with liver failure commonly develop protein depletion and sarcopenia because of increased protein catabolism and reduced protein synthesis, both of which are associated with poor clinical outcomes [5,322-324]. In particular, patients with cirrhosis and chronic liver failure frequently experience negative nitrogen balance and progressive muscle loss, whereas unnecessary protein restriction may further aggravate catabolism and malnutrition [325-328]. Current international guidelines do not recommend routine protein restriction in patients with liver failure. ESPEN guidelines recommend protein provision of approximately 1.2–1.5 g/kg/day in patients with liver failure and cirrhosis [5,322-324].

Some studies have suggested that higher protein intake or BCAA supplementation may improve nutritional parameters, such as muscle mass, handgrip strength, and serum albumin levels [329-332]. However, consistent improvements in mortality or long-term clinical outcomes have not been demonstrated. In addition, regular meal patterns and late-evening snacks may reduce overnight protein catabolism and nitrogen loss, whereas increased protein intake combined with exercise may help preserve muscle mass in patients with sarcopenia or sarcopenic obesity [322,333].

In hyperacute liver failure, elevated serum ammonia levels (>150 μmol/L) are associated with cerebral edema and increased intracranial pressure. Because patients are often metabolically unstable during the early phase, a stepwise nutritional approach may be required [334-339]. Accordingly, temporary delay or restriction of protein provision during the initial 24–48 hours, followed by gradual reintroduction, has been proposed. After protein reintroduction, close monitoring of ammonia levels and neurological status is necessary.

Routine protein restriction is also not recommended in patients with hepatic encephalopathy. RCTs have shown that normal-protein diets do not worsen hepatic encephalopathy [328], whereas protein restriction may aggravate catabolism and malnutrition. However, some patients may demonstrate protein intolerance, and in such cases, plant-based protein or BCAA-enriched protein supplementation at approximately 0.25 g/kg/day may be considered [322,338,340]. Systematic reviews and meta-analyses have shown that BCAA supplementation may improve symptoms of hepatic encephalopathy, although consistent benefits in mortality or long-term outcomes have not been demonstrated [341-344].

Long-term oral BCAA supplementation has been associated with improved event-free survival and quality of life in patients with advanced cirrhosis [345,346]. However, clear clinical benefits of intravenous BCAA administration in acute hepatic encephalopathy have not been established [339,343,344]. Therefore, BCAA supplementation may be selectively considered in patients with suspected protein intolerance or recurrent hepatic encephalopathy. In patients with obesity-associated nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, protein provision of approximately 1.0–1.2 g/kg/day based on adjusted body weight may be considered, whereas higher protein intake may be required in those with malnutrition or sarcopenia [5,338].

Sufficient protein provision (1.2–1.5 g/kg/day) is generally preferred over routine protein restriction in critically ill adults with liver failure. However, temporary restriction followed by gradual advancement may be appropriate during the early unstable phase of hyperacute liver failure. Routine protein restriction is also not recommended in patients with hepatic encephalopathy, although selective use of BCAA-enriched protein supplementation may be considered in patients with suspected protein intolerance or recurrent hepatic encephalopathy (Supplement Table 52).

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Specific situation–trauma

KQ 22. Does early enteral nutrition, compared with delayed enteral nutrition, improve clinical outcomes in adult trauma patients?

R52. Early enteral nutrition is suggested in patients with acute traumatic brain injury and acute spinal cord injury once hemodynamic stability has been achieved and gastrointestinal function is adequate. (Very low evidence, conditional for, strong consensus: 100%)

R53. Early enteral nutrition is suggested in patients with acute spinal cord injury once hemodynamic stability has been achieved and gastrointestinal function is adequate. (Expert consensus, strong consensus: 100%)

R54. Early enteral nutrition is suggested in patients with abdominal trauma who are hemodynamically stable and have confirmed or restored gastrointestinal continuity. (Expert consensus, strong consensus: 97%)

Trauma patients develop a marked catabolic response and increased metabolic demands immediately after injury, leading to rapid protein breakdown and negative nitrogen balance. These metabolic alterations are associated with muscle wasting, impaired immune function, and increased infectious complications, and delayed nutritional support may contribute to worse clinical outcomes. Therefore, initiation of enteral nutrition after hemodynamic stabilization has been advocated. In patients with traumatic brain injury, energy and protein requirements increase early after injury, and persistent nutritional deficits may be associated with infection, organ dysfunction, and delayed neurological recovery [347]. International guidelines, including the American College of Surgeons Trauma Quality Programs (ACS TQP) 2023 guidelines, ESPEN 2019/2023 guidelines, SCCM-ASPEN 2016 guidelines, and ESICM 2017 guidelines, recommend initiation of early enteral nutrition within 24–72 hours after hemodynamic stabilization [1,5,20,45,347,348]. A meta-analysis of two RCTs demonstrated that early enteral nutrition did not significantly reduce mortality, pneumonia, or hospital length of stay compared with delayed feeding (Fig. 12) [349,350]. However, early enteral nutrition was shown to be feasible and potentially beneficial without significant safety concerns. Because the number of studies and sample sizes were limited, the certainty of evidence was considered very low.

In patients with acute spinal cord injury, increased nitrogen loss and rapid muscle wasting occur early after injury, resulting in prolonged negative nitrogen balance [351-353]. Historically, nutritional support was often delayed because of concerns about ileus and EFI. However, recent studies and international guidelines recommend initiation of enteral nutrition as early as feasible, generally within 48 hours after hemodynamic stabilization [1,5,20,45,351,352]. Although direct randomized evidence remains limited, early enteral nutrition is considered clinically reasonable for maintaining gastrointestinal integrity and preventing nutritional deterioration.

In patients with abdominal trauma, disruption of gut barrier integrity and bacterial translocation may occur after injury or surgery, while profound catabolism develops simultaneously [5,354]. Therefore, early enteral nutrition has been advocated when gastrointestinal continuity is preserved or surgically restored and when contraindications, such as bowel ischemia, uncontrolled bleeding, or mechanical obstruction, are absent [5,45,355,356]. ESICM, ESPEN, SCCM-ASPEN, and recent trauma nutrition guidelines recommend initiation of enteral nutrition within 24–48 hours, and up to 72 hours, after hemodynamic stabilization [1,5,20,45,355,356]. Some studies have suggested potential benefits in reducing infections and preserving gastrointestinal function. The European Society for Trauma and Emergency Surgery Recommendations on Acute Care Surgery and Trauma Intensive Care guideline additionally suggested initiation of low-volume trickle feeding as early as feasible once gastrointestinal continuity has been surgically restored [355].

Although direct evidence demonstrating a survival benefit

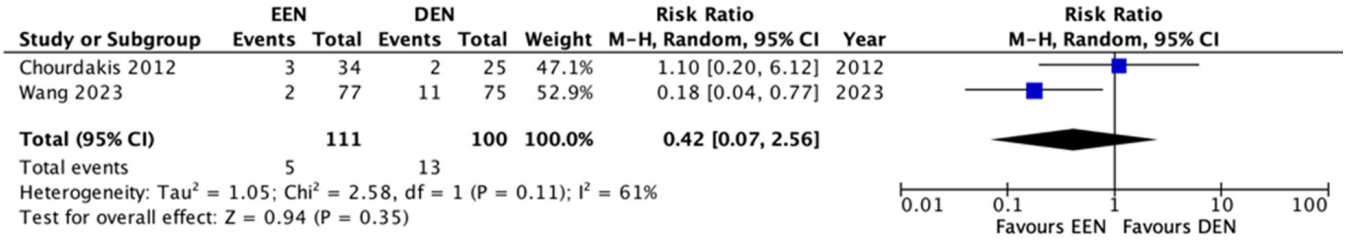

Fig. 12. Forest plot comparing mortality between EEN and DEN in patients with traumatic brain injury. EEN, early enteral nutrition; DEN, delayed enteral nutrition; M-H, Mantel-Haenszel; CI, confidence interval.

of early enteral nutrition in trauma patients remains limited, international guidelines consistently recommend initiation of enteral nutrition as early as possible after hemodynamic stabilization. In particular, in patients with traumatic brain injury, acute spinal cord injury, and abdominal trauma, early enteral nutrition may help reduce cumulative energy and protein deficits and preserve gastrointestinal function. Therefore, its application should be individualized according to the patient's hemodynamic status and gastrointestinal function (Supplement Tables 53-55, and Supplement Figs. 33-35).

Specific situation—sepsis

KQ 23. In critically ill adults with sepsis, does early enteral nutrition, compared with delayed enteral nutrition, improve clinical outcomes?

R55. Early enteral nutrition is suggested in patients with sepsis once hemodynamic stability has been achieved, with gradual advancement according to clinical status. (Expert consensus, strong consensus: 100%)

In patients with sepsis, systemic inflammation and tissue hypoperfusion may lead to intestinal mucosal injury, gut microbiota dysbiosis, and bacterial translocation, all of which may contribute to multiple organ dysfunction and poor clinical outcomes [1,45,357]. Enteral nutrition may help attenuate these pathophysiological processes by preserving intestinal mucosal integrity, maintaining gut-associated immune function, and preventing mucosal atrophy [1]. Accordingly, international guidelines recommend initiation of enteral nutrition as early as possible after hemodynamic stabilization.

Several studies have suggested that early enteral nutrition initiated within 24–48 hours after intensive care unit admission or sepsis diagnosis may be associated with shorter duration of mechanical ventilation, reduced intensive care unit length of stay, and shorter hospital stay compared with delayed enteral nutrition [358-361]. In addition, studies in patients with surgical sepsis have reported improvements in immunological parameters associated with early enteral nutrition [362]. However, the effect on mortality has been inconsistent across studies, and interpretation is limited by heterogeneity in patient populations and feeding strategies.

In patients with septic shock or hemodynamic instability, concerns remain about the risk of bowel ischemia due to impaired splanchnic perfusion [363-365]. In particular, aggressive early feeding may increase the risk of gastrointestinal complications [57,364]. Nevertheless, recent studies have demonstrated that trophic enteral nutrition initiated after stabilization of blood pressure and tissue perfusion, even in patients receiving vasopressors, was not associated with increased rates of severe bowel ischemia or intestinal necrosis and may be associated with shorter duration of mechanical ventilation and intensive care unit stay [57,366].

Although the current evidence remains limited and heterogeneous, early enteral nutrition appears feasible and relatively safe in patients with sepsis and may provide potential benefits, including reduced intensive care unit stay and shorter duration of mechanical ventilation. Therefore, initiation of enteral nutrition as early as possible after hemodynamic stabilization, generally within 24–48 hours, with low-dose initiation and gradual advancement according to gastrointestinal tolerance and clinical condition, is considered a reasonable strategy (Supplement Tables 56, 57).

Specific situation—obesity

KQ 24. What is the optimal nutritional therapy for critically ill adults with obesity?

R56. Early initiation of enteral nutrition is suggested once hemodynamic stability has been achieved. (Expert consensus, strong consensus: 100%)

R57. IC is suggested as the preferred method for measuring energy requirements. (Expert consensus, strong consensus: 95%)

R58. When IC is unavailable, hypocaloric nutrition of 20–25 kcal/kg/day based on adjusted body weight is suggested during the acute phase, with gradual advancement toward measured energy expenditure during the recovery phase. (Expert consensus, strong consensus: 95%)

R59. Protein provision of ≥1.3 g/kg/day based on adjusted body weight is suggested. (Expert consensus, strong consensus: 95%)

Nutritional therapy in critically ill adults with obesity should aim to minimize loss of lean body mass while avoiding overfeeding. In critically ill patients with obesity, energy calculation based on actual body weight may lead to overfeeding, whereas protein provision is often insufficient. Therefore, a hypocaloric, high-protein strategy has been proposed as the preferred nutritional approach [5,367-378].

There is no evidence supporting delayed enteral nutrition solely because of obesity. Early enteral nutrition after hemody-

namic stabilization is considered appropriate. Observational studies have suggested that initiation of enteral nutrition within 24–48 hours after intensive care unit admission may be associated with shorter duration of mechanical ventilation and reduced intensive care unit length of stay, although mortality benefits have not been consistently demonstrated [369,371,375,376]. International guidelines also recommend early enteral nutrition after hemodynamic stabilization [1,5].

IC is considered the most accurate method for determining energy requirements in critically ill patients with obesity. Predictive equations may substantially overestimate or underestimate actual energy expenditure in this population [379,380]. When IC is unavailable, initiation of hypocaloric feeding using 20–25 kcal/kg/day based on adjusted body weight (= ideal body weight + 0.25 × [actual body weight – ideal body weight]) has been proposed to avoid overfeeding during the acute phase [1,5,380-383]. Gradual advancement according to the clinical course, recovery phase, and changes in energy expenditure is considered reasonable.

Adequate protein provision is a key component of nutritional therapy to reduce muscle wasting and intensive care unit-acquired weakness. ESPEN guidelines recommend protein provision of approximately 1.3 g/kg/day based on adjusted body weight [5,367,368,372-374,377,378,384]. Several studies have suggested that high-protein feeding based on ideal or adjusted body weight may improve nitrogen balance and help preserve lean body mass [1,377,378]. However, very high protein provision has not consistently demonstrated improvements in major clinical outcomes and may be associated with potential harm in some patient populations, indicating the need for individualized approaches [372,373].

In critically ill adults with obesity, early enteral nutrition after hemodynamic stabilization and assessment of energy requirements using IC are recommended whenever feasible. When IC is unavailable, initiation of hypocaloric feeding based on adjusted body weight together with a high-protein strategy targeting ≥1.3 g/kg/day is considered a reasonable approach (Supplement Tables 58, 59).

Discussion

Nutritional therapy is an essential component of critical care management. Accordingly, several international societies and research groups, including the ESPEN, ESICM, SCCM-ASPEN, ASPEN, and the Canadian Critical Care Nutrition group, have published evidence-based clinical practice guidelines and systematic reviews on nutritional therapy in critically ill patients [1,4,5,20,45,385]. However, these guidelines differ in the timing and route of nutritional therapy, energy and protein targets, and disease-specific nutritional strategies. In addition, some recommendations are difficult to apply directly in Korean intensive care units because of differences in medical resources, nutritional support systems, medication availability, and clinical practice patterns. Accordingly, KSPEN developed evidence-based clinical practice guidelines for nutritional therapy in critically ill adults that reflect Korean clinical practice. In 2024, KSPEN published a preliminary Part I guideline addressing seven key clinical questions [18]. The current guideline expands on the previous version and provides a comprehensive guideline covering broader aspects of nutritional therapy in critically ill adults.

One strength of the present guideline is that it incorporated relatively recent evidence by primarily including studies published after 2010. Whenever possible, recommendations were based on RCTs, systematic reviews, and meta-analyses. For clinical topics with insufficient RCT evidence or substantial heterogeneity among studies, recommendations were developed using narrative evidence synthesis and expert consensus. This approach allowed broad clinical coverage while maintaining evidence-based recommendation development. The present guideline also sought to reflect Korean intensive care unit practice patterns and domestic clinical environments. Although efforts were made to include Korean studies and domestic clinical data whenever available, high-quality Korean evidence remains limited. Most available domestic studies were observational or retrospective, and large-scale, well-controlled RCTs involving Korean critically ill patients were scarce. Therefore, many recommendations were still based largely on international evidence and did not substantially differ from existing ESPEN or ASPEN guidelines.

Nevertheless, several recommendations were adapted to address practical issues specific to Korea. For example, although IC is recommended as the preferred method for energy assessment, its routine use remains limited because of restricted equipment availability and operational barriers in many Korean intensive care units [5,105]. In addition, because intravenous erythromycin is currently unavailable in Korea, recommendations regarding prokinetic agents were adapted to reflect domestically available medications, such as metoclopramide, itopride, and DA-9701. Differences in intensive care unit staffing, nutrition support team availability, enteral formula accessibility, and institutional resources were also considered during recommendation development. Therefore, some recommendations differ from international guide-

lines in practical implementation and clinical applicability. Another important strength of the present guideline is its emphasis on individualized nutritional therapy according to hemodynamic status, metabolic phase, nutritional risk, organ dysfunction, and disease-specific conditions rather than uniform application of aggressive nutritional strategies. This approach is consistent with emerging evidence suggesting that excessive early caloric delivery may not improve clinical outcomes and may potentially increase metabolic complications during the acute phase of critical illness [185,186].

Limitations

Several limitations should be acknowledged. First, because the guideline addressed a broad range of clinical questions, the certainty of evidence varied considerably across recommendations. In several areas, including immune-modulating nutrition, micronutrient supplementation, probiotics, and disease-specific nutritional therapy, evidence heterogeneity and limited high-quality studies resulted in low or very low certainty of evidence. Consequently, many recommendations were presented as conditional recommendations or expert consensus statements rather than strong evidence-based recommendations. Second, because of the relative lack of Korean-specific evidence on nutritional therapy in critically ill adults, adaptation of international evidence was unavoidable in several sections. Differences in healthcare systems, intensive care unit resources, patient characteristics, and nutritional practices may influence the direct applicability of international evidence to Korean clinical practice. Additional multicenter studies involving Korean critically ill patients are needed to establish higher-quality domestic evidence. Third, because these guidelines addressed a broad range of nutritional issues in critically ill adults, different methodological approaches were used according to evidence availability and quality. Some key clinical questions were supported by formal systematic reviews and meta-analyses, whereas others relied primarily on narrative evidence synthesis and expert consensus. Nevertheless, efforts were made to ensure transparency and methodological rigor through structured literature review, multidisciplinary participation, application of GRADE methodology, and independent external review.

Despite these limitations, the present guideline has several strengths. First, it represents a multidisciplinary effort involving physicians, pharmacists, nurses, dietitians, and methodology experts. Second, the guideline incorporates both evidence synthesis and practical applicability in Korean intensive care units. Third, detailed supplementary materials, including search strategies, evidence summaries, risk of bias assessments, and meta-analyses, were provided to enhance transparency and reproducibility. Fourth, the recommendations cover a wide spectrum of nutritional issues encountered in daily intensive care unit practice and may facilitate standardized nutritional management in critically ill adults. Implementation of some recommendations, including IC-guided nutritional assessment and post-pyloric feeding, may be limited by institutional resources, staffing, and equipment availability. Therefore, flexibility and adaptation according to local intensive care unit resources may be necessary. Because evidence regarding critical care nutrition continues to evolve, periodic revision and updating of these guidelines will be necessary. Additional Korean multicenter clinical studies and implementation research are also needed to improve the quality of evidence and evaluate the clinical impact of guideline adherence in Korean intensive care units.

Conclusion

These guidelines provide practical, evidence-based recommendations for nutritional therapy in critically ill adults while reflecting current international evidence and Korean clinical practice. The guideline may contribute to improved standardization, consistency, and quality of nutritional support in critically ill patients in Korea and may serve as a foundation for future research and implementation of evidence-based critical care nutrition practices.

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Conflict of interest

Yun Tae Jung has served as an Editorial Board Member of the *Annals of Clinical Nutrition and Metabolism*. However, he was not involved in the peer review process or decision-making regarding publication. Otherwise, no other potential conflict of interest relevant to this article was reported.

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Data availability

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.15747/ACNM.26.0059

Supplement Table 1. Literature search strategy for KQ1: candidates for nutritional therapy in critically ill adult patients

Supplement Table 2. Summary of included studies evaluating candidates for nutritional therapy in critically ill adult patients (KQ1)

Supplement Table 3. Literature search strategy for KQ2: screening and assessment of malnutrition and nutritional risk in critically ill adult patients

Supplement Table 4. Literature search strategy for KQ3:

timing of nutritional therapy initiation in critically ill adult patients

Supplement Table 5. Summary of included studies comparing the timing of nutritional therapy initiation in critically ill adult patients (KQ3)

Supplement Table 6. Literature search strategy for KQ4: delayed initiation or discontinuation of enteral nutrition in critically ill adult patients

Supplement Table 7. Summary of included studies evaluating enteral nutrition in critically ill adult patients receiving vasopressors (KQ4)

Supplement Table 8. Literature search strategy for KQ5: assessment of enteral feeding intolerance in critically ill adult patients receiving enteral nutrition

Supplement Table 9. Literature search strategy for KQ6: continuous versus intermittent enteral feeding in critically ill adult patients

Supplement Table 10. Summary of randomized controlled trials comparing continuous versus intermittent enteral feeding in critically ill adult patients (KQ6)

Supplement Table 11. Summary of clinical outcomes comparing continuous versus intermittent enteral feeding in critically ill adult patients (KQ6)

Supplement Table 12. Literature search strategy for KQ7: trophic versus full feeding in critically ill adult patients

Supplement Table 13. Summary of randomized controlled trials comparing trophic versus full feeding in critically ill adult patients (KQ7)

Supplement Table 14. Summary of clinical outcomes comparing trophic versus full feeding in critically ill adult patients (KQ7)

Supplement Table 15. Literature search strategy for KQ8: aspiration risk assessment and management in critically ill adult patients receiving enteral nutrition

Supplement Table 16. Summary of randomized controlled trials evaluating gastric residual volume-based monitoring in critically ill adult patients receiving enteral nutrition (KQ8)

Supplement Table 17. Summary of clinical outcomes from randomized controlled trials evaluating gastric residual volume-based monitoring in critically ill adult patients receiving enteral nutrition (KQ8)

Supplement Table 18. Summary of randomized controlled trials comparing post-pyloric versus gastric enteral nutrition in critically ill adult patients (KQ8)

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Supplement Table 20. Summary of studies evaluating gastric residual volume-based monitoring, aspiration risk assessment, and non-feeding route-based preventive strategies in critically ill adult patients receiving enteral nutrition (KQ8)

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Supplement Table 25. Literature search strategy for KQ10: enteral fish oil supplementation in critically ill adult patients

Supplement Table 26. Summary of randomized controlled trials evaluating enteral fish oil supplementation in critically ill adult patients (KQ10)

Supplement Table 27. Summary of clinical outcomes from randomized controlled trials evaluating enteral fish oil supplementation in critically ill adult patients (KQ10)

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Supplement Table 29. Summary of studies evaluating immune-modulating enteral nutrition in critically ill adults (KQ11)

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Supplement Table 38. Literature search strategy for KQ15: target caloric intake during early parenteral nutrition in critically ill adult patients

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Supplement Table 56. Literature search strategy for KQ23: early versus delayed enteral nutrition in critically ill adult patients with sepsis

Supplement Table 57. Characteristics of studies evaluating early versus delayed enteral nutrition in critically ill adult patients with sepsis (KQ23)

Supplement Table 58. Literature search strategy for KQ24: nutritional therapy in critically ill adults with obesity

Supplement Table 59. Summary of studies evaluating nutritional therapy in critically ill adults with obesity (KQ24)

Supplement Fig. 1. PRISMA flow diagram of studies evaluating continuous versus intermittent enteral feeding in critically ill adult patients (KQ6)

Supplement Fig. 2. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials evaluating continuous versus intermittent enteral feeding in critically ill adult patients (KQ6)

Supplement Fig. 3. GRADE Summary of Findings generated using GRADEpro GDT for continuous versus intermittent enteral feeding in critically ill adult patients (KQ6)

Supplement Fig. 4. Forest plots comparing continuous versus intermittent enteral feeding in critically ill adult patients (KQ6)

Supplement Fig. 5. PRISMA flow diagram of studies included in the meta-analysis for KQ7

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Supplement Fig. 7. GRADE Summary of Findings generated using GRADEpro GDT for trophic versus full feeding in critically ill adult patients (KQ7)

Supplement Fig. 8. PRISMA flow diagram of studies included in the meta-analysis evaluating gastric residual volume-based monitoring (KQ8)

Supplement Fig. 9. PRISMA flow diagram of studies includ-

ed in the meta-analysis comparing post-pyloric versus gastric enteral nutrition (KQ8)

Supplement Fig. 10. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials evaluating gastric residual volume-based monitoring in critically ill adult patients receiving enteral nutrition (KQ8)

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Supplement Fig. 13. PRISMA 2020 flow diagram of studies included in the meta-analysis evaluating energy requirement assessment methods in critically ill adult patients (KQ9)

Supplement Fig. 14. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials evaluating indirect calorimetry-guided versus predictive equation-guided energy provision in critically ill adult patients (KQ9)

Supplement Fig. 15. GRADE Summary of Findings generated using GRADEpro GDT for indirect calorimetry-guided versus predictive equation-guided energy provision in critically ill adult patients (KQ9)

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Supplement Fig. 17. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials evaluating enteral fish oil supplementation in critically ill adult patients (KQ10)

Supplement Fig. 18. Forest plots showing additional clinical outcomes of enteral fish oil supplementation in critically ill adult patients (KQ10)

Supplement Fig. 19. GRADE Summary of Findings generated using GRADEpro GDT for enteral fish oil supplementation in critically ill adult patients (KQ10)

Supplement Fig. 20. PRISMA flow diagram of studies included in the meta-analysis evaluating probiotics supplementation in critically ill adults (KQ13)

Supplement Fig. 21. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials evaluating probiotics supplementation in critically ill adults (KQ13)

Supplement Fig. 22. GRADE Summary of Findings generated using GRADEpro GDT for probiotics supplementation in critically ill adults (KQ13)

Supplement Fig. 23. Forest plots summarizing additional clinical outcomes of probiotics supplementation in critically ill adults (KQ13).

Supplement Fig. 24. Forest plots summarizing additional clinical outcomes of probiotics supplementation in critically ill adults (KQ13)

Supplement Fig. 25. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials comparing early versus delayed parenteral nutrition in critically ill adult patients (KQ14)

Supplement Fig. 26. GRADE Summary of Findings generated using GRADEpro GDT for early versus delayed parenteral nutrition in critically ill adult patients (KQ14)

Supplement Fig. 27. PRISMA 2020 flow diagram of studies included in the meta-analysis evaluating micronutrient and antioxidant supplementation in critically ill adults (KQ16)

Supplement Fig. 28. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials evaluating micronutrient and antioxidant supplementation in critically ill adults (KQ16)

Supplement Fig. 29. GRADE Summary of Findings generated using GRADEpro GDT for micronutrient and antioxidant supplementation in critically ill adults (KQ16)

Supplement Fig. 30. PRISMA 2020 flow diagram of studies included in the meta-analysis evaluating anti-inflammatory lipid-containing enteral nutrition formulations in patients with ARDS and ALI (KQ19)

Supplement Fig. 31. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials evaluating anti-inflammatory lipid-containing enteral nutrition formulations in patients with ARDS and ALI (KQ19)

Supplement Fig. 32. GRADE Summary of Findings generated using GRADEpro GDT for anti-inflammatory lipid-containing enteral nutrition formulations in patients with ARDS and ALI (KQ19)

Supplement Fig. 33. PRISMA 2020 flow diagram of studies included in the systematic review and meta-analysis evaluating early versus delayed enteral nutrition in patients with traumatic brain injury (KQ22)

Supplement Fig. 34. Risk of bias assessment using the Cochrane Risk of Bias 1.0 tool for randomized controlled trials comparing early versus delayed enteral nutrition in patients with traumatic brain injury (KQ22)

Supplement Fig. 35. GRADE Summary of Findings generated using GRADEpro GDT for early versus delayed enteral nutrition in patients with traumatic brain injury (KQ22)

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Review Article

Mechanistic insights, clinical significance, and management strategies for postgastrectomy hypoglycemia in gastric cancer patients in the era of continuous glucose monitoring: a narrative review

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Abstract

Purpose: Postgastrectomy hypoglycemia (PGH) is increasingly recognized as a potential metabolic complication after gastrectomy for gastric cancer. This narrative review summarizes its clinical relevance, underlying mechanisms, and management strategies in the era of continuous glucose monitoring.

Current concept: Traditionally considered part of the spectrum of late dumping syndrome, PGH arises from rapid nutrient transit, which leads to postprandial hyperglycemia followed by exaggerated insulin secretion and subsequent hypoglycemia. Emerging evidence suggests that glycemic disturbances after gastrectomy extend beyond symptomatic postprandial events to include asymptomatic and nocturnal hypoglycemia, as well as marked glycemic variability. Proposed mechanisms include postprandial hyperinsulinemia mediated by incretin hormones, particularly glucagon-like peptide-1, peptide YY, and glucose-dependent insulinotropic polypeptide. These disturbances may contribute to fatigue, impaired concentration, nutritional deterioration, and increased vulnerability to adverse events. Dietary modification, including frequent small meals emphasizing low–glycemic-index carbohydrates with adequate protein and fiber, remains the cornerstone of management. Pharmacologic interventions may be considered in refractory cases, although evidence specific to PGH remains limited and is often extrapolated from related conditions.

Conclusion: PGH after gastrectomy for gastric cancer is an underrecognized but clinically meaningful metabolic disturbance. Greater awareness and individualized management are essential to mitigate long-term nutritional and functional consequences. Further research is needed to clarify its mechanisms and establish evidence-based management strategies.

Keywords: Continuous glucose monitoring; Dumping syndrome; Gastrectomy; Hypoglycemia; Stomach neoplasms

Introduction

Background

Gastric cancer remains one of the most common malignancies worldwide and a leading cause of cancer-related mortality [1]. Gastrectomy, usually performed with regional lymphadenectomy, remains the primary curative treatment for resectable disease. However, it inevitably causes profound anatomical and physiological changes, including loss of gastric reservoir capacity, impaired mechanical digestion, and accelerated gastric emptying [2].

Among the metabolic disturbances resulting from post-gastrectomy anatomical and physiological changes, postgastrectomy hypoglycemia (PGH) has emerged as a

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clinically significant but often underrecognized complication in gastric cancer patients. In this review, PGH refers to objectively documented hypoglycemia occurring after gastrectomy. Although it most commonly develops in the postprandial period, continuous glucose monitoring (CGM) has shown that hypoglycemia may also occur in asymptomatic or nocturnal settings, thereby expanding the recognized clinical spectrum.

In contrast, late dumping syndrome (LDS) is a symptom-based entity characterized by postprandial autonomic (adrenergic) and hypoglycemic manifestations triggered by rapid nutrient transit. It typically occurs 1–3 hours after meals because of accelerated glucose absorption and exaggerated insulin secretion [3-5]. LDS is a common postoperative complication after gastrectomy for malignant or benign disease, as well as after esophageal and bariatric (metabolic) surgery [6,7].

Although PGH and LDS share overlapping pathophysiological mechanisms, PGH is defined by objectively measured glucose decline regardless of symptom presence, whereas LDS is defined primarily by its clinical symptom constellation.

Accordingly, conventional dietary recommendations after gastrectomy have focused on mitigating abrupt postprandial hyperglycemia and subsequent hypoglycemia. These strategies include eating slowly, consuming smaller and more frequent meals, avoiding concomitant fluid intake, limiting simple sugars, and emphasizing protein, complex carbohydrates, and fiber [2].

The advent of CGM has broadened our understanding of PGH and suggests that post-gastrectomy glucose fluctuations may be more complex and clinically meaningful than previously appreciated. In gastric cancer patients, several studies have reported pronounced glycemic variability and persistent nocturnal hypoglycemia, as well as possible associations with postoperative malnutrition [2,6-8]. Importantly, PGH may also lead to severe, life-altering consequences, including hypoglycemia-related accidents, disability, and restrictions in daily and social functioning [9].

Despite these clinical implications, optimal approaches to prevention and management, particularly nutritional management, remain inadequately defined. This underscores the need for a comprehensive review of PGH in gastric cancer patients in the CGM era, including its clinical significance, underlying mechanisms, diagnostic advances, and management strategies, with the ultimate aim of improving patient outcomes and quality of life.

Objectives

This review aims to clarify the clinical significance of PGH in patients undergoing gastrectomy for gastric cancer, including its often unrecognized nocturnal manifestations and potential persistence beyond the early postoperative period. By synthesizing current evidence, this review discusses its underlying mechanisms and available management strategies. CGM has broadened our understanding of the glycemic phenotype and may help identify patients at risk.

Methods

Ethics statement

This was a literature-based study. Therefore, neither institutional review board approval nor informed consent was required.

Search strategy

This narrative review did not follow a formal systematic review protocol; however, efforts were made to enhance transparency in the literature selection process. A targeted PubMed search was conducted to identify relevant studies published through September 2025. Representative search terms included “postgastrectomy hypoglycemia,” “hypoglycemia after gastrectomy,” “continuous glucose monitoring,” “dumping syndrome,” and “gastric cancer.” The primary focus was on studies involving patients who underwent gastrectomy for gastric cancer. Clinical review articles, prospective and retrospective studies, and relevant case reports addressing hypoglycemia in this population were included. Titles and abstracts were screened for relevance, followed by full-text review when appropriate. Reference lists of selected articles were also reviewed manually to identify additional relevant studies.

Studies focusing exclusively on bariatric surgery populations were generally excluded; however, selected studies were considered when they provided mechanistic or therapeutic insights relevant to PGH. In total, seven key studies specifically addressing hypoglycemia in gastric cancer patients after gastrectomy were identified and informed the main discussion of this review. Additional literature on post-bariatric hypoglycemia (PBH) and dumping syndrome was also considered to provide a broader context for the pathophysiology and management strategies. For clarity, in this review, the term PGH refers exclusively to hypoglycemia occurring in patients with gastric cancer.

Current understanding of PGH

CGM as a theranostic tool in PGH

Before CGM was considered for its theranostic utility in PGH, the diagnosis of postprandial hypoglycemia relied primarily on detailed clinical history combined with biochemical confirmation of a plasma glucose level below 55 mg/dL [10]. Provocative testing, including the oral glucose tolerance test and mixed-meal tolerance test, was sometimes used [11], although these methods had limitations, including the risk of inducing severe hypoglycemia and the potential for false-positive results [12].

CGM provides a more comprehensive assessment by continuously recording interstitial glucose levels and capturing both postprandial excursions and nocturnal episodes over a 24-hour period. This approach enables clinicians to detect patterns that might otherwise go unrecognized, thereby offering deeper insight into the glycemic profile of post-gastrectomy patients [2]. In the cited study, CGM was performed using a sensor attached to the posterior aspect of the upper arm. The device continuously measured glucose concentrations in the subcutaneous interstitial fluid at 15-minute intervals for up to 14 days. Data stored in the sensor were transmitted wirelessly to the reader and subsequently analyzed using the manufacturer's dedicated software [13].

Supporting this clinical utility, Ri et al. [14] demonstrated that CGM-based assessment enabled detection of asymptomatic hypoglycemia and clinically significant glycemic excursions, including postprandial spikes, in patients who had undergone gastrectomy for gastric cancer.

Clinical implications and pathophysiology of PGH

PGH has emerged as an increasingly recognized complication, largely because of its association with marked glycemic variability and frequent nocturnal hypoglycemia [2]. CGM studies by Kubota et al. [2,6] in gastric cancer patients showed that glycemic variability was more pronounced after gastrectomy than after local resection and worsened further at 1 year postoperatively compared with 1 month. They also reported that total gastrectomy was associated with more severe fluctuations and more prolonged nocturnal hypoglycemia than distal gastrectomy, reflecting the greater loss of gastric reservoir function.

These disturbances have consequences beyond transient discomfort. Glycemic variability and recurrent hypoglycemia may impair quality of life and are increasingly recognized as important in clinical studies, with growing evidence linking them to adverse long-term outcomes [2,15,16]. Several studies support this. For example, Nusca et al. [15] identified glycemic variability as an independent predictor of cardiovascular events in both diabetic and nondiabetic cohorts. Similarly, other studies have linked recurrent glucose fluctuations and hypoglycemia to cardiovascular disease, arrhythmias, cognitive decline, and dementia [8,17-20]. Evidence further indicates that blood glucose fluctuations may also contribute to sarcopenia, suggesting that their adverse effects extend beyond cardiovascular and neurological outcomes [21,22]. Although these studies involved different patient populations, the documented risks associated with glycemic variability and hypoglycemia suggest that patients with PGH may likewise be vulnerable to similar long-term complications, highlighting the importance of careful monitoring and management.

Particular concern arises from nocturnal hypoglycemia. Nishibeppu et al. [8] demonstrated that, in predominantly nondiabetic older adults with gastric cancer, hypoglycemia persisted for up to 1 year after gastrectomy, with nocturnal episodes being especially pronounced. Prolonged nocturnal hypoglycemia was more common in malnourished patients, underscoring its association with nutritional status.

Although evidence remains limited, the pathophysiology of PGH is thought to be multifactorial and may involve delayed metabolic consequences of the rapid nutrient transit characteristic of early dumping, along with additional alterations in hormonal, autonomic, and metabolic regulation. As described above, PGH is conceptualized here as a glucose-defined metabolic disturbance rather than a symptom-based syndrome such as LDS.

Early dumping is thought to occur when hyperosmolar nutrients enter the small intestine rapidly, potentially exceeding its absorptive capacity [23]. The resulting osmotic shift draws fluid from the vascular compartment into the intestinal lumen, leading to relative hypovolemia and cardiovascular manifestations such as tachycardia, hypotension, and, in severe cases, syncope [23]. In addition to these osmotic effects, an exaggerated release of gastrointestinal hormones, including vasoactive peptides (e.g., neurotensin and vasoactive intestinal peptide), incretins (e.g., glucagon-like peptide-1 [GLP-1], peptide YY, and glucose-dependent insulinotropic polypeptide), and glucose modulators such as insulin, may further contribute to gastrointestinal and cardiovascular responses [23]. These early manifestations typically develop within 30 minutes after food intake and may be followed by postprandial hyperglycemia and an exaggerated insulin response, which in turn may predispose susceptible individuals to subsequent PGH [6].

GLP-1 is a key mediator of postprandial glucose regulation. After gastrectomy, rapid nutrient transit to the small intestine

provokes an exaggerated incretin response, particularly involving GLP-1, leading to insulin secretion that is disproportionately high relative to the glycemic load [24]. As reviewed by Sheehan and Patti [9], excessive GLP-1 secretion and postprandial hyperinsulinemia are thought to play a central role in PGH. This may be further exacerbated by inadequate suppression of pancreatic β-cell insulin secretion and reduced insulin clearance during hypoglycemic episodes.

Although the precise mechanisms of PGH remain incompletely understood, emerging evidence suggests that its manifestations may extend beyond purely postprandial processes. For example, CGM studies have described substantial glycemic variability and episodes of nocturnal hypoglycemia, implying that additional physiological disturbances may contribute to PGH.

One proposed contributor is altered autonomic counter-regulation after upper gastrointestinal surgery [9]. Under normal circumstances, hypoglycemia triggers catecholamine release, cortisol secretion, and sympathetic activation. However, Sheehan and Patti [9] observed that these responses appear to be attenuated postoperatively, which could delay recovery from hypoglycemia and reduce symptom perception. Possible impairments in pancreatic α-cell function, insufficient glucagon release, and reduced hepatic glycogen reserves may further weaken counter-regulatory defenses.

Repeated hypoglycemia may further weaken autonomic defenses, a phenomenon known as hypoglycemia-associated autonomic failure, which is particularly pronounced during sleep [8,25]. Although the relevance of hypoglycemia-associated autonomic failure to post-gastrectomy physiology has not been clearly established, these observations raise the possibility that recurrent hypoglycemia itself may exacerbate autonomic vulnerability.

Nutritional and body-composition changes after gastrectomy, such as reduced hepatic glycogen stores, sarcopenia-related decreases in gluconeogenic capacity, and malnutrition after total gastrectomy, have also been proposed as factors that may predispose patients to prolonged or nocturnal hypoglycemia [6]. Recent studies suggest that postprandial hyperglycemia may stimulate macrophages to secrete IL-1β, which may enhance insulin secretion and reduce the hypothalamic threshold for noradrenergic activation [9].

Finally, although PGH and PBH arise in different surgical populations, insights from PBH are often informative because both conditions involve altered gastrointestinal anatomy and nutrient handling. PBH studies suggest that adaptive changes in intestinal glucose absorption may contribute to glycemic instability. In particular, a small observational study in Roux-en-Y gastric bypass patients [26] and a gastrectomy-related case report [27] suggest that increased intestinal glucose transport, potentially via enhanced sodium-glucose cotransporter-1 (SGLT-1) expression, could accelerate carbohydrate absorption and thereby amplify glycemic fluctuations, although direct evidence in PGH remains limited.

Taken together, these findings suggest that PGH is a multifactorial condition influenced by altered autonomic responses, inflammatory and metabolic adaptations, nutritional status, and potential changes in intestinal glucose absorption. This broader perspective underscores the importance of careful monitoring and individualized metabolic support, particularly for patients with significant glycemic variability or nocturnal hypoglycemia. Table 1 summarizes the proposed pathophysiological mechanisms underlying PGH.

Table 1. Pathophysiological mechanisms and features potentially associated with postgastrectomy hypoglycemia

Pathophysiological aspect	Key processes	Study design	Reference
Exaggerated incretin response (GLP-1, GIP, PYY)	Accelerated nutrient transit → particularly excessive GLP-1 secretion → disproportionate insulin secretion relative to glycemic load → hyperinsulinemic hypoglycemia	Clinical review, mechanistic review	[6,9,23]
Blunted autonomic counter-regulation after upper gastrointestinal surgery	Postoperative attenuation of catecholamine, cortisol, and sympathetic responses to hypoglycemia → may reduce symptom perception	Clinical review	[8,9]
Metabolic impairments	Hepatic glycogen depletion, sarcopenia, reduced gluconeogenesis, and malnutrition after total gastrectomy → increased vulnerability to nocturnal and prolonged hypoglycemia	Prospective study, retrospective study, cross-sectional observational study, review article	[6]
Inflammatory modulation	IL-1β secretion by macrophages in response to hyperglycemia → increased insulin release and reduced hypothalamic noradrenergic threshold → enhanced susceptibility to hypoglycemia	Clinical review	[9]
Intestinal adaptation (SGLT-1 upregulation)	Increased glucose absorption in the small intestine after gastrectomy due to mucosal adaptation → exacerbated glycemic variability	Prospective study, case report on PBH	[26,27]

GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; PYY, peptide YY; IL, interleukin; SGLT-1, sodium-glucose cotransporter-1; PBH, post-bariatric hypoglycemia.
Note: Because postgastrectomy hypoglycemia-specific mechanistic studies are limited, some of the pathways listed above are drawn from studies of gastrointestinal surgery, including post-bariatric procedures and late dumping syndrome.

Nutritional and therapeutic management of PGH

Nutritional interventions

Dietary modification is the cornerstone of PGH management. Patients are advised to consume smaller, more frequent meals and to limit high-carbohydrate foods in order to reduce rapid glycemic fluctuations. Adherence to dietary recommendations is encouraged even in the absence of overt hypoglycemia, as it may help stabilize glucose levels and prevent later complications [8].

Evidence specific to PGH remains limited but suggests a potential benefit of glycemic modulation strategies. A small pilot study using CGM in four patients who developed symptomatic postprandial hypoglycemia after esophageal or gastric cancer surgery suggested that a low–glycemic-index diet might reduce symptoms, although detailed dietary protocols were not reported [28]. In another PGH-specific study, Kubota et al. [29] demonstrated that a low-carbohydrate, high–monounsaturated fatty acid formula improved nocturnal hypoglycemia after gastrectomy, although daytime glycemic variability remained largely unchanged.

Because controlled dietary trials specifically targeting PGH are scarce, additional guidance is drawn largely from the PBH and broader dumping syndrome literature. Nutritional strategies in these populations focus on reducing postprandial glucose spikes by limiting high–glycemic-index foods, avoiding simple sugars, and encouraging smaller, more frequent meals [30]. Individualized carbohydrate restriction is central to therapy and is often operationalized through structured meal distribution, such as six daily meals containing up to 30 g of carbohydrate each [31,32]. Quantitative macronutrient recommendations are similarly derived from bariatric surgery guidelines rather than PGH-specific trials. Bariatric surgery guidelines suggest approximately 30 g of protein per meal [33,34]. Daily protein intake of 60–80 g [35] or 1.5–2.1 g/kg of ideal body weight [36] has also been recommended. Evidence from PBH and dumping syndrome studies also suggests that selected dietary fats may provide caloric support without directly stimulating insulin secretion [37] and that soluble fiber supplementation may attenuate postprandial glucose excursions [38]. Similarly, a single study evaluating the effects of glucomannan on glucose tolerance and absorption in 10 children with dumping symptoms after various types of gastric surgery reported that glucomannan significantly improved glucose tolerance, although it had no overall effect on glucose absorption [39].

Importantly, although these studies provide useful guidance, the underlying pathophysiology and patient populations differ substantially between bariatric surgery, performed primarily for metabolic indications, and gastrectomy for gastric cancer, performed for oncologic resection. These differences should be carefully considered in clinical application. A summary of nutritional interventions potentially applicable to PGH is presented in Table 2.

Pharmacological interventions

When dietary modification alone is insufficient, pharmacological therapy may be considered. However, evidence from studies of patients who do not respond to nutritional therapy remains limited [23]. Because PGH-specific studies are scarce, most of the following recommendations are derived from research on LDS after various gastrointestinal operations, including bariatric procedures. Therefore, these recommendations should be applied cautiously in the man-

Table 2. Dietary interventions potentially applicable to postgastrectomy hypoglycemia

Strategy	Intervention/limitation	Study design	Reference
Dietary modification	Smaller, more frequent meals and low–glycemic-index/low-carbohydrate foods to reduce postprandial glycemic excursions. Pilot studies and PBH analogies suggest improvement in symptoms and glucose variability, but effectiveness varies and depends on patient adherence.	Prospective interventional study (pilot study), randomized crossover trial, prospective cohort study, prospective cohort (case series), prospective cohort study	[28-30]
Protein and fat intake adjustment	A total daily protein intake of 60–80 g, and 1.5–2.1 g/kg of ideal body weight; adequate dietary fat may slow carbohydrate absorption without stimulating insulin secretion. Careful meal planning is required.	Clinical practice guideline, expert opinion, guideline, narrative review, case series (small cohort study)	[35-37]
Soluble fiber supplementation	Pectin, glucomannan, and guar gum may be effective, particularly in pediatric patients, by slowing intestinal transit and delaying glucose absorption. Long-term use may be limited by palatability, availability, and preparation challenges.	Both interventional studies (small clinical trials)	[38,39]

PBH, post-bariatric hypoglycemia.
Note: Most strategies listed here are adapted from studies of late dumping syndrome and postprandial hypoglycemia after gastrointestinal surgery, including post-bariatric procedures, because postgastrectomy hypoglycemia-specific evidence remains limited.

agement of patients with PGH.

α-Glucosidase inhibitors are among the most extensively studied pharmacological agents for LDS [40,41]. These agents delay carbohydrate digestion by competitively and reversibly inhibiting pancreatic α-amylase and intestinal α-glucosidases, thereby attenuating postprandial glucose excursions. Acarbose, a representative α-glucosidase inhibitor, is typically administered at doses of 25–100 mg before meals and has demonstrated efficacy in reducing postprandial hyperglycemia and glycemic variability [42]. Owing to its favorable safety profile and broad availability, it is generally considered a first-line pharmacologic option, with supporting evidence derived largely from PBH studies [42,43]. Similarly, voglibose, another α-glucosidase inhibitor, has shown potential benefit in PGH. In a case series of three patients who underwent gastrectomy, Son et al. [44] reported improvements in time in range and reductions in glycemic variability after voglibose administration. However, Kubota et al. [6] observed that, in gastric cancer patients after gastrectomy, suppression of postprandial hyperglycemia with α-glucosidase inhibitors did not necessarily prevent nocturnal hypoglycemia, suggesting that additional pathophysiological mechanisms may contribute to glucose instability in this population.

Diazoxide, a potassium channel activator that inhibits insulin release, has been reported to improve hypoglycemia in LDS at doses of 100–150 mg three times daily, although evidence is limited to case reports and retrospective series [45-47]. Its use is generally reserved for refractory cases [23].

Somatostatin analogues delay gastric emptying, slow small-bowel transit, inhibit gastrointestinal hormone release, reduce insulin secretion, and attenuate postprandial vasodilation, thereby improving both early dumping syndrome and LDS [23]. Short-acting formulations, such as subcutaneous octreotide administered at doses of 50–100 μg three times daily, have demonstrated efficacy, although the need for multiple daily injections may limit long-term adherence [5].

Calcium channel blockers inhibit voltage-dependent calcium channels in pancreatic β-cells, thereby reducing insulin secretion. Recent evidence suggests that, in patients who underwent Roux-en-Y gastric bypass, these agents may modestly decrease postprandial hypoglycemic episodes. However, because this evidence is derived primarily from bariatric surgery populations, and because of additional concerns such as dizziness, hypotension, edema, and weight gain, their applicability to post-gastrectomy patients remains uncertain [48].

SGLT-1/SGLT-2 inhibitors have been explored as potential therapeutic agents in PBH [27,49]. Martinussen et al. [49] reported that canagliflozin 600 mg reduced postprandial glucose, insulin, and GLP-1 excursions in PBH, suggesting that intestinal glucose absorption through SGLT-1 may contribute to exaggerated incretin responses. Clinical evidence in PGH is currently limited [27]. A summary of pharmacological interventions potentially applicable to PGH is presented in Table 3. In clinical practice, screening, CGM application, nutritional intervention, and criteria for pharmacologic escalation should be considered comprehensively (Fig. 1).

Table 3. Pharmacological interventions potentially applicable to postgastrectomy hypoglycemia

Agent	Mechanism	Evidence/limitation	Study design	Reference
α-Glucosidase inhibitors (e.g., acarbose)	Inhibit pancreatic α-amylase and intestinal α-glucosidases, thereby delaying glucose absorption	Reduce postprandial glucose excursions; considered a first-line pharmacologic option in LDS; may not prevent nocturnal hypoglycemia	Case report, narrative review, prospective interventional study	[42-44]
Diazoxide	Activates potassium channels → inhibits insulin release	Suggests efficacy in LDS; generally reserved for refractory cases	Review article, case report, multicenter observational cohort	[45-47]
Somatostatin analogues (e.g., octreotide)	Delay gastric emptying, slow small-bowel transit, inhibit gastrointestinal hormone release, and reduce insulin secretion	Effective for early dumping syndrome and LDS; administered as short-acting subcutaneous injections three times daily; multiple daily injections may limit adherence	Consensus statement, review article	[5,23]
SGLT-1/SGLT-2 inhibitors (e.g., canagliflozin)	Reduce intestinal glucose absorption through SGLT-1 → lower postprandial glucose and incretin responses	Preliminary PBH study showed reductions in glucose, insulin, and GLP-1 excursions; clinical evidence remains limited, and further investigation is needed	Case report, interventional clinical study/mechanistic trial	[27,49]

LDS, late dumping syndrome; SGLT-1/SGLT-2, sodium-glucose cotransporter 1 and 2; PBH, post-bariatric hypoglycemia; GLP-1, glucagon-like peptide-1.
Note: Most approaches described here are adapted from evidence in LDS and PBH, as postgastrectomy hypoglycemia-specific trials are scarce.

Clinical approach to PGH

1. Screening and diagnosis
   - Consider PGH in post-gastrectomy patients with postprandial dizziness, fatigue, palpitations, or nocturnal symptoms
   - Consider screening in high-risk individuals (e.g., those with total gastrectomy, older age, malnutrition), even in the absence of overt symptoms
   - Confirm a plasma glucose level <55 mg/dL during symptomatic episodes when feasible [10]
2. Indications for CGM
   - Recurrent, unexplained, or nocturnal hypoglycemia
   - Suspected asymptomatic hypoglycemia
   - Assessment of high-risk patients for glycemic variability and guidance of dietary adjustment [2,13]
3. First-line management: nutritional interventions
   - Small, frequent meals (approximately 5–6 meals/day)
   - Restrict simple sugars and high–glycemic-index carbohydrates [8,28,30]
   - Individualized carbohydrate distribution
   - Adequate protein intake (60–80 g/day; 1.5–2.1 g/kg of ideal body weight) and inclusion of healthy fats [35–37]
   - Consideration of soluble fiber supplementation (e.g., pectin, guar gum, glucomannan) when tolerated [38,39]
   - Emphasis on dietary adherence, including in asymptomatic patients
4. Criteria for escalation to pharmacologic therapy
   - Persistent or severe symptomatic hypoglycemia despite optimized dietary modification
   - Recurrent or prolonged nocturnal hypoglycemia documented on CGM
   - Significant impact on quality of life or nutritional status

4.1. Pharmacologic options (evidence largely extrapolated from LDS/PBH literature):
   - α-Glucosidase inhibitors (e.g., acarbose) [42-44]
   - Diazoxide (refractory cases) [45-47]
   - Somatostatin analogues (e.g., octreotide) [5,23]

5. Follow-up and monitoring
   - Periodic CGM to assess response and glycemic variability [2,13,25]
   - Monitoring of weight, nutritional status, and sarcopenia risk [6,8]
   - Multidisciplinary care (dietitian, endocrinologist, surgical team) [23]

Fig. 1. Practical clinical approach to postgastrectomy hypoglycemia (PGH) in gastric cancer patients. CGM, continuous glucose monitoring; LDS, late dumping syndrome.

Discussion

Future perspectives and recommendations

The use of CGM has led to increasing recognition of PGH; however, its underlying mechanisms, diagnosis, and management remain incompletely defined. Although PGH, driven primarily by exaggerated incretin responses, may explain many cases, nocturnal hypoglycemia likely involves additional mechanisms, including impaired counter-regulation, glycogen depletion, and malnutrition. Future studies should aim to clarify this mechanistic heterogeneity and establish standardized diagnostic criteria, potentially incorporating CGM-derived metrics.

Nutritional modification remains the first-line therapy, although its long-term efficacy and adherence remain uncertain. Controlled trials are needed to refine optimal dietary strategies, and pharmacological options, such as α-glucosidase inhibitors, diazoxide, and somatostatin analogues used in LDS, should be evaluated further in larger cohorts [5,23]. Moreover, novel approaches targeting incretin signaling, as well as glucose transport pathways studied in PBH, warrant further investigation in the context of PGH.

Given the persistence of PGH and its potential association with malnutrition, sarcopenia, and cardiovascular risk, long-term multidisciplinary follow-up may be beneficial. Personalized management strategies guided by CGM data and comprehensive nutritional assessment may improve clinical outcomes and quality of life in gastrectomy survivors.

Limitations

A key limitation of this review is that the current evidence base for PGH in gastric cancer patients remains limited in both scope and methodological rigor. The available literature consists predominantly of small, single-center observational cohorts and case reports, with very few PGH-specific interventional or randomized trials. Consequently, the strength of evidence supporting diagnostic and therapeutic strategies remains modest.

Furthermore, several aspects of the management discussion are informed by data extrapolated from related but distinct populations, including patients with PBH or dumping syndrome. Although these studies provide valuable mechanistic and therapeutic insights, differences in surgical indications, metabolic context, and nutritional status limit their direct applicability to gastric cancer patients after gastrectomy. Accordingly, such evidence should be regarded as indirect and hypothesis-generating.

As a narrative review without a formal systematic methodology, this manuscript aims to synthesize and contextualize existing knowledge rather than establish definitive clinical guidelines. Therefore, the therapeutic recommendations presented herein should be interpreted cautiously and individualized in clinical practice pending further validation.

Future multicenter prospective studies specifically targeting PGH in gastric cancer patients are needed to strengthen the evidence base and support more robust, evidence-based clinical recommendations.

Conclusion

PGH in gastric cancer survivors is an underrecognized yet clinically important metabolic complication characterized by marked glycemic variability, asymptomatic episodes, and nocturnal hypoglycemia, with potential nutritional and functional consequences. CGM has broadened our understanding of its clinical phenotype and may facilitate individualized assessment and management. Dietary modification remains the cornerstone of treatment, whereas pharmacologic inter-

ventions may be considered selectively in patients with persistent or severe symptoms.

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Authors' contribution

All work was performed by Cheong Ah Oh.

Conflict of interest

The author of this manuscript has no conflicts of interest to disclose.

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Data availability

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Supplementary materials

None.

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Review Article

Nutritional insights in endodontics: a review of micronutrients in root canal therapy

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Abstract

Purpose: Micronutrients play critical and multifaceted roles in the biological processes governing endodontic healing. This review aimed to evaluate the therapeutic roles of essential micronutrients, including vitamin D, vitamin C, calcium, zinc, magnesium, and selenium, in modulating immune responses, promoting tissue repair, and enhancing bone regeneration during endodontic healing.

Current concept: The findings indicate that vitamin D supports odontoblast differentiation, immune regulation, and modulation of inflammatory pathways, whereas vitamin C enhances collagen synthesis, antioxidant protection, and pulp regeneration. Calcium and phosphorus are vital for hydroxyapatite formation and dentin mineralization, whereas zinc contributes to immune balance, enzymatic activation, and wound repair. Magnesium exhibits anti-inflammatory and bone-supportive properties, and selenium provides antioxidant and antimicrobial defense. Clinical studies have associated micronutrient deficiencies with delayed healing, increased infection risk, and reduced treatment success. Emerging innovations, such as bioactive sealants that release therapeutic minerals and diagnostic tools for nutrient profiling, highlight new directions in personalized endodontic care.

Conclusion: Integrating micronutrient assessment and targeted supplementation strategies into clinical endodontic practice may optimize healing responses, minimize inflammation, and improve long-term treatment outcomes.

Keywords: Antioxidants; Bone regeneration; Dental pulp; Dietary supplements; Micronutrients

Introduction

Background

Inflammatory oral diseases, such as gingivitis and periapical periodontitis, represent major public health concerns worldwide because of their high prevalence and socioeconomic burden [1]. These conditions are characterized by chronic infiltration of immune cells, including polymorphonuclear leukocytes, monocytes, lymphocytes, plasma cells, and mast cells, into affected tissues, leading to cascades of inflammatory and degenerative changes. Gingivitis, for example, is a common periodontal disease characterized by gingival inflammation and clinical signs such as bleeding, edema, redness, and ulceration [2]. Similarly, inflammatory periapical disease typically arises from pulp necrosis induced by dental caries and reflects the body's localized immune response to contain infection within the periapical tissues [3]. Fig. 1 illustrates deep dental caries resulting in periapical inflammation.

Healing in these conditions is multifaceted and involves both repair and regeneration. It begins with an inflammatory phase that serves as both a defense mechanism and a

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trigger for tissue recovery. The trajectory of healing depends on several factors, including the regenerative capacity of affected cells, the extent of tissue damage, and the proliferative potential of the surrounding stromal tissue. In connective tissues, healing occurs primarily through repair, in which granulation tissue formation and fibroblast infiltration lead to scar formation. In contrast, non-connective tissues, such as glandular organs, muscles, and peripheral nerves, undergo regeneration through proliferation of surviving functional cells, thereby restoring structural and physiological integrity. Regeneration involves the replacement of lost cells with phenotypically and functionally similar cells, allowing restoration of the original tissue architecture. Repair, by contrast, compensates for tissue loss through the formation of fibrous connective tissue, which may lack the functional characteristics of the original tissue [4]. Fig. 2 depicts the roles of micronutrients (vitamins A, B_6, B_9, B_{12}, C, D, and E) and minerals (Zn, Fe, Cu, Se, and Mg) in root canal treatment, including support of infection control, inflammation modulation, tissue repair, and bone regeneration.

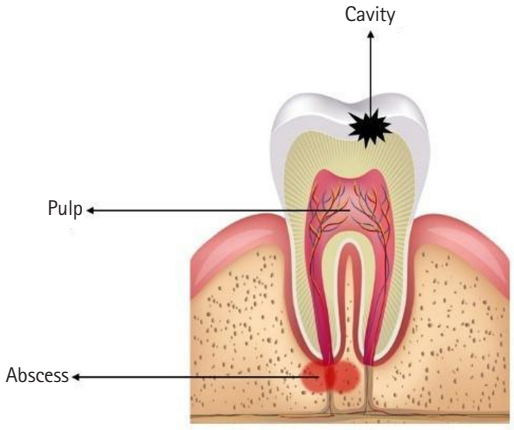

Fig. 1. Periapical inflammation caused by deep dental caries leading to pulp necrosis and abscess formation.

A critical aspect of successful healing is neutralization of the antigens or pathogens that initiate the inflammatory response. In endodontic infections, pulpal necrosis results in loss of vascular supply, creating an environment conducive to bacterial colonization and proliferation. The host responds with a robust inflammatory reaction in the periapical region, leading to bone resorption that facilitates immune cell infiltration. These immune cells then organize into a biological barrier that aims to sequester infection and prevent systemic spread [5].

Modern endodontic practice has been strengthened by technological advances such as dental operating microscopes, digital radiography, and electronic apex locators, which have improved diagnostic and treatment precision. These developments have enabled clinicians to disinfect the root canal system more effectively, thereby helping to prevent or reverse apical periodontitis and restore the health of

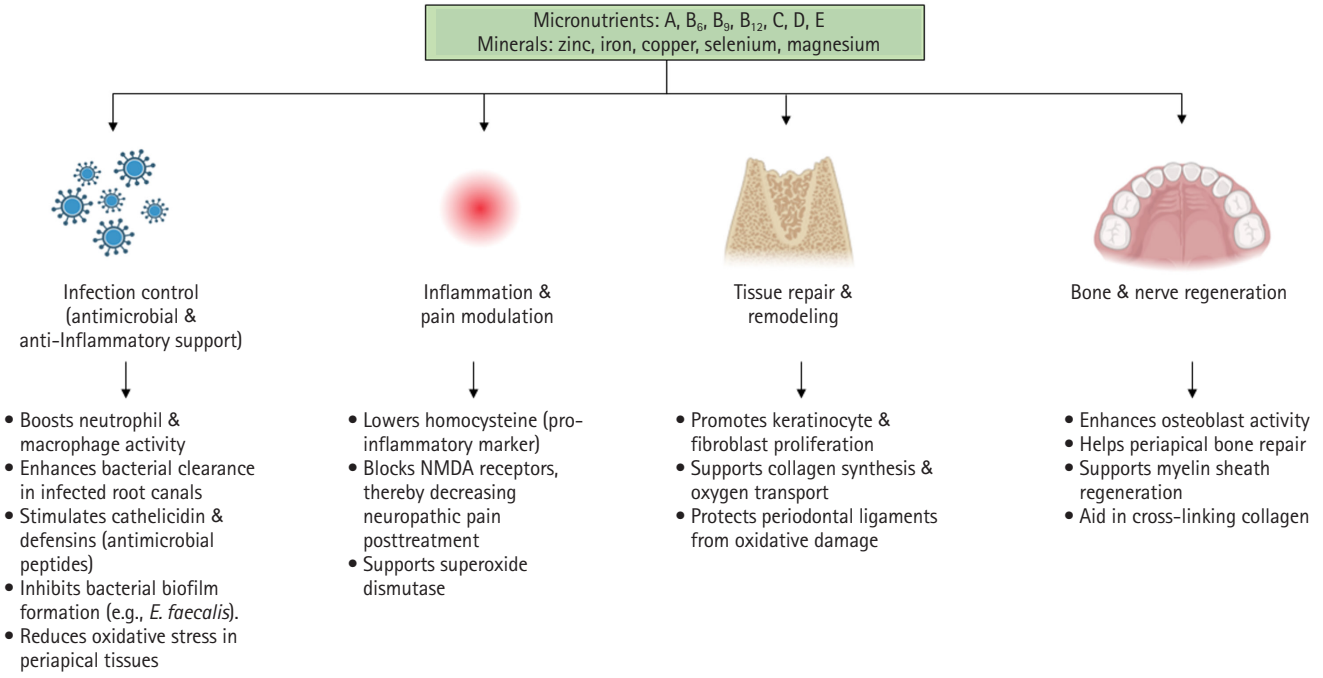

Fig. 2. Key micronutrients and minerals in root canal healing: boosting immunity, reducing inflammation, and aiding tissue repair. NMDA, N-methyl-D-aspartate; *E. faecalis, Enterococcus faecalis*.

periradicular tissues. The success of endodontic treatment is typically evaluated through a combination of clinical assessment and radiographic evidence of healing [6]. While the mechanical and chemical aspects of endodontic therapy are well established, growing evidence also highlights the importance of a patient's systemic nutritional status in influencing healing outcomes.

Micronutrients, including essential vitamins and minerals, play pivotal roles in modulating immune responses, supporting tissue repair, and promoting bone regeneration, all of which are critical to the success of root canal therapy [6,7]. Key micronutrients such as vitamin D, vitamin C, calcium, magnesium, and zinc have demonstrated beneficial effects on host defense mechanisms and periapical tissue regeneration [8,9]. Vitamin D, for example, enhances innate immune function, stimulates production of antimicrobial peptides, and regulates calcium and phosphate metabolism, thereby facilitating bone healing and reducing post-treatment inflammation. Vitamin C is essential for collagen synthesis and functions as a potent antioxidant, whereas calcium and magnesium contribute to bone mineralization. Zinc also plays a central role in immune cell function, enzymatic activity, and wound healing.

This growing body of evidence supports the view that endodontic therapy should not be considered solely a localized mechanical or chemical intervention. Rather, it should be viewed as part of a comprehensive, patient-centered healing strategy. Procedures such as root canal debridement, disinfection, and obturation are essential for removing infection and preventing recurrence; however, the patient's overall health, particularly nutritional status, may significantly influence both the success and pace of healing. Micronutrients participate in biological processes that underpin healing, including immune modulation, angiogenesis, collagen production, antioxidant defense, and osteoblastic activity. For instance, vitamin D contributes not only to bone health but also to the regulation of innate and adaptive immune responses. Similarly, vitamin C supports tissue strength through collagen synthesis, whereas zinc and magnesium are essential for immune function and enzymatic activity. Deficiencies in these nutrients may impair healing, prolong inflammation, or contribute to treatment failure. Therefore, optimizing micronutrient intake through a balanced diet, supplementation, or therapeutic monitoring should be considered an important adjunct to endodontic care, particularly in patients with chronic conditions, poor dietary habits, or compromised immunity [10]. This integrative approach may accelerate tissue regeneration and reduce the risk of postoperative complications such as persistent periapical lesions or reinfection.

Objectives

The present review focuses on the role of micronutrients in oral inflammatory conditions, including periodontal diseases, inflammatory lesions of the oral mucosa, and pulpal and periapical lesions.

Methods

Ethics statement

This was a literature-based study. Institutional Review Board approval and informed consent were not required because the research did not involve human participants.

Study design

This review was designed as a narrative, literature-based synthesis examining the roles of selected micronutrients—vitamin D, vitamin C, calcium, zinc, magnesium, selenium, and related minerals—in pulpal and periapical healing, endodontic infection control, and root canal treatment outcomes. The scope also included mechanistic and translational evidence from periodontal and oral inflammatory diseases in which the underlying pathways overlapped with endodontic healing, such as immune modulation, antioxidant defense, and bone metabolism.

Inclusion criteria

The inclusion criteria were as follows: (1) peer-reviewed original research, clinical trials, cohort studies, case series, or reviews published in English between January 1996 and October 2025; (2) studies directly addressing the effects of the selected micronutrients on endodontic outcomes or mechanistically related oral inflammatory processes; and (3) human, animal, or in vitro studies with clear relevance to pulpal or periapical pathology, immune response, or tissue repair.

Exclusion criteria

The exclusion criteria were as follows: (1) studies lacking primary data or mechanistic insight, such as purely descriptive commentaries; (2) studies focused solely on non-overlapping conditions, such as systemic diseases without endodontic relevance; (3) non-English publications; and (4) duplicate or retracted articles. Articles were selected on the basis of title and abstract relevance to the search terms, followed by full-text review to determine eligibility.

Search strategy

Electronic searches were conducted in PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar to identify relevant literature published between January

1996 and October 2025. The search strategy combined Medical Subject Headings and free-text terms, including "micronutrients," "vitamin D," "vitamin C," "calcium," "zinc," "magnesium," "selenium," "antioxidants," "endodontics," "root canal therapy," "periapical lesion," "pulpal healing," "periapical healing," "oral inflammatory diseases," and "nutritional supplements," using the Boolean operators "AND" and "OR" to refine sensitivity and specificity. Reference lists of key articles and of narrative and systematic reviews on micronutrients and oral health were also hand-searched to identify potentially missed or in-press studies.

Results

Role in pulpal and periapical tissue healing

Micronutrient sufficiency, particularly of vitamin D, calcium, and zinc, is a fundamental biological prerequisite for successful healing and regeneration of dental pulp and periapical tissues following injury or infection. These micronutrients exert specific regulatory functions within the complex cascades of inflammation modulation, cellular repair, and extracellular matrix synthesis that characterize reparative processes. Inadequate levels demonstrably impair healing trajectories, whereas optimal availability promotes tissue restoration and functional recovery [11].

Within the pulp, healing requires coordinated processes, including odontoblastic differentiation for reparative dentinogenesis, collagen and matrix synthesis, and angiogenesis. Vitamin D directs the differentiation of dental pulp stem cells into functional odontoblast-like lineages, thereby facilitating the formation of mineralized reparative dentin bridges that are essential for pulp protection after exposure. It also promotes mineralization processes [12]. Calcium serves dual roles: it acts as an intracellular signaling mediator that activates pathways central to reparative dentinogenesis, and it serves as a direct mineral substrate supplied both systemically and locally through therapeutic agents such as calcium hydroxide during pulp capping procedures [13]. Zinc supports cellular proliferation through its role in DNA synthesis, thereby enabling replacement of necrotic or damaged pulp cells. It also contributes to extracellular matrix formation through collagen synthesis and exhibits immunomodulatory activity by functioning as an antioxidant that mitigates excessive inflammatory responses.

Periapical healing involves the resolution of inflammatory osteolytic lesions and the regeneration of bone and connective tissue at the root apex. This process depends on the elimination of the infectious and inflammatory source, modulation of immune responses, and stimulation of osteogenesis and angiogenesis. Vitamin D contributes by downregulating excessive pro-inflammatory signaling and enhancing production of anti-inflammatory cytokines such as interleukin-10 [14], thereby limiting persistent lesions and pathological bone resorption. Calcium provides the mineral substrate required for osteoblastic activity and new bone formation following infection control. Zinc supports immune cell function, which is essential for pathogen clearance and progression through the sequential stages of soft- and hard-tissue repair [15].

The clinical implications of micronutrient status are substantial. Success in vital pulp therapy depends in part on nutrient-supported odontoblast differentiation and mineralization. The rate and completeness of periapical bone and soft-tissue regeneration following root canal treatment are influenced by circulating micronutrient levels. In addition, the efficacy of emerging regenerative endodontic procedures, which rely on stem cells and bioactive signaling, is optimized by adequate levels of vitamin D, calcium, and zinc because these nutrients regulate cellular behavior, inflammatory balance, and tissue synthesis [16]. Accordingly, assessment of micronutrient status may represent a strategic approach to enhancing postoperative healing, reducing complication risk, accelerating regeneration, and improving overall patient outcomes [17]. Fig. 3 depicts the interactions among vitamin D, zinc, and calcium in bone and immune function.

Antioxidant and anti-inflammatory properties

Micronutrients enhance pulpal and periapical healing through antioxidant and anti-inflammatory mechanisms. Vitamin D exhibits anti-inflammatory effects by suppressing pro-inflammatory cytokines such as interleukin-6 and tumor

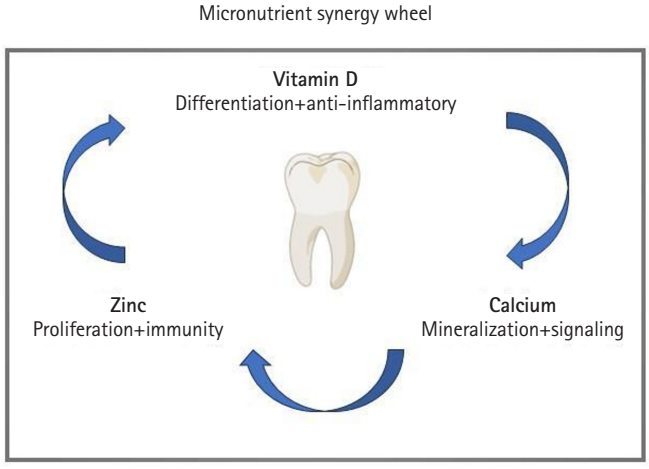

Fig. 3. Roles of vitamin D, calcium, and zinc in pulpal tissue healing.

necrosis factor-alpha and by upregulating anti-inflammatory mediators, thereby creating a favorable environment for tissue repair [18]. It also promotes human dental pulp stem cell proliferation and odontogenic differentiation through activation of extracellular signal-regulated kinases. Calcium, particularly in the form of calcium hydroxide, demonstrates anti-inflammatory activity by neutralizing bacterial toxins and denaturing pro-inflammatory cytokines, thereby reducing inflammatory burden and supporting repair [19]. Zinc acts as a cofactor for antioxidant enzymes such as superoxide dismutase, facilitating neutralization of reactive oxygen species. It also regulates immune cell function, and its incorporation into endodontic materials enhances biological performance by protecting against matrix metalloproteinase-mediated collagen degradation [20]. Magnesium exerts anti-inflammatory effects by reducing neutrophil activity and stabilizing cellular membranes, thereby decreasing free radical formation [21]. Magnesium deficiency is associated with periodontal disease, whereas supplementation or magnesium-based therapies improve outcomes by modulating immune responses and promoting bone regeneration [22]. Vitamin C (ascorbic acid), a major extracellular antioxidant essential for collagen biosynthesis and wound healing [23], promotes human dental pulp stem cell proliferation and differentiation; optimal concentrations (0.1–0.5 mM) increase expression of proliferation markers such as OCT4, NANOG, and SOX2, and supplementation has been reported to restore pulpal blood flow and enhance repair in diabetic conditions [24]. Selenium exhibits strong antioxidant activity, exceeding that of vitamins E, C, and A; compounds such as Selenase reduce nitrosative stress and enhance antioxidant enzyme activity [25]. Its antimicrobial properties and potential to enhance antibiotic efficacy further support infection control. Synergistic combinations, such as selenium with green tea and alpha-tocopherol, may yield enhanced effects by targeting multiple oxidative and inflammatory pathways. Clinically, adequate micronutrient status is associated with improved outcomes, whereas deficiencies are associated with increased complication risk. Accordingly, nutritional assessment, adjunctive antioxidant supplementation, whether systemic or local, and micronutrient-enriched materials represent promising strategies for reducing inflammation and optimizing healing in endodontic and periodontal therapies [26].

Influence on immune response and infection control

Micronutrients exert immunomodulatory and antimicrobial functions that are critical for host defense and infection resolution during pulpal and periapical healing, directly influencing the success of endodontic treatment. Vitamin D demonstrates multifaceted immunoregulatory activity by enhancing both innate and adaptive immune responses in oral tissues. One key mechanism involves induction of antimicrobial peptides, particularly cathelicidin (LL-37), in oral epithelial cells, thereby providing broad-spectrum activity against pathogens implicated in pulpal and periapical infections [27]. In addition, vitamin D upregulates tight-junction proteins, strengthening epithelial barrier integrity at sites such as the root apex and pulp chamber and thereby limiting bacterial invasion. It also modulates inflammation by downregulating pro-inflammatory cytokines, including interleukin-6, interleukin-8, and tumor necrosis factor-alpha, thereby reducing excessive tissue damage and supporting a balanced immune response [28].

Calcium functions as a critical signaling ion and structural component in immune defense and tissue repair. It is required for activation, chemotaxis, and functional activity of immune effector cells, particularly neutrophils and macrophages, during early responses to root canal infections, thereby facilitating microbial clearance [29]. Beyond its immunological roles, calcium supports biomineralization processes that form physical barriers, such as reparative dentin and periapical bone, thereby limiting residual microbial spread and preventing reinfection [30]. Calcium deficiency disrupts these processes, impairing immune cell function and antimicrobial activity within infected pulpal and periapical tissues.

Zinc functions as an essential enzymatic cofactor and structural component of proteins required for immune competence. It regulates proliferation, differentiation, and cytotoxic activity of immune cells, including neutrophils, natural killer cells, and macrophages, thereby enhancing pathogen clearance [31]. Zinc also contributes to redox homeostasis by supporting antioxidant enzymes and preserving immune cell function within oxidative stress-prone environments such as infected dental tissues [32]. In addition, zinc maintains epithelial and mucosal barrier integrity, providing a first line of defense against pathogen entry. Zinc deficiency is associated with impaired barrier function, dysregulated inflammation, reduced microbial killing, delayed healing, and increased susceptibility to persistent or recurrent endodontic infections [33].

Collectively, adequate levels of micronutrients, particularly vitamin D, calcium, and zinc, support a multilayered antimicrobial defense system by enhancing endogenous peptide activity, promoting phagocytic clearance, reinforcing structural barriers, and facilitating tissue repair following root canal therapy [19]. Conversely, deficiencies in these micronutrients create conditions that favor microbial prolifera-

tion, weaken immune responses, prolong inflammation, and increase complication risk, thereby compromising pulpal and periapical healing [34]. These findings underscore the importance of micronutrient status as a determinant of infection resolution and regenerative outcomes in endodontic care.

Practical implications in root canal therapy for post-treatment healing and recovery

A balanced diet is essential for supplying the nutrients required for root canal therapy and subsequent tissue repair. Accordingly, both clinicians and patients should be more aware of the influence of nutrition on treatment success. Table 1 [35–44] summarizes the key findings regarding micronutrients in root canal therapy, and Fig. 4 illustrates their proposed applications. Certain micronutrients may promote healing and improve host responses to infection associated with root canal treatment. Micronutrients such as vitamins A, C, D, and K; essential minerals including calcium, magnesium, phosphorus, and zinc; and antioxidants may support recovery [45]. Therefore, incorporating these nutrients into the diet may contribute to improved treatment outcomes.

Calcium hydroxide, available as Pulpdent (Pulpdent Corporation) and Dycal (Dentsply Sirona), is widely used for apexification in immature teeth. When applied as an intracanal medicament with 5.25% sodium hypochlorite (e.g., Clorox), it promotes apical closure, with a high success rate reported at 3 months. Selenium-based sealants such as SeLECT-Defense, developed by Element-34 Technologies, inhibit bacterial biofilm formation. When paired with gutta-percha (e.g., Dentsply Sirona GP points), these materials reportedly maintain antibacterial activity for up to 90 days [46-48]. Experimentally zinc oxide nanoparticle sealers have demonstrated reduced microleakage compared with traditional sealers. Combined with 2% chlorhexidine (e.g., Consepsis, Ultradent), they may further enhance antibacterial efficacy in infected canals [42]. Probiotic and vitamin D supplementation have been investigated as supportive therapy for periodontal healing. Probiotic formulations containing *Limosilactobacillus reuteri* such as BioGaia ProDentis have

Table 1. Therapeutic roles of micronutrients in modern root canal treatment

Micronutrient	Application in root canal therapy	Key findings	Reference
Calcium hydroxide	Used for apexification in immature teeth with open apices to induce apical closure.	Effective in inducing apical barrier formation; combined with mineral trioxide aggregate, it showed improved results.	[35]
Omega-3 fatty acids	Investigated for reducing postoperative complications, with indirect relevance to endodontics.	Associated with reduced postoperative infections, shorter hospital stay, and lower mortality. Their anti-inflammatory properties may benefit endodontic outcomes.	[36]
Selenium	Incorporated into dental sealants (SeLECT-Defense) to inhibit bacterial biofilm formation.	Completely inhibited Streptococcus mutans and Streptococcus salivarius biofilms and demonstrated a durable antibacterial effect.	[37]
Silver nanoparticles	Used as root canal irrigants because of their antimicrobial properties.	Effective against Enterococcus faecalis; efficacy depended on particle size and contact time. They were less effective than NaOCl but showed potential.	[38]
Vitamin C	Studied for antioxidant and anti-inflammatory effects in periodontal therapy.	Topical application reduced gingival inflammation and improved wound healing; vitamin C may also support periodontal and endodontic healing.	[39]
Vitamin E	Investigated for antioxidant properties in periodontal therapy.	Reduced oxidative stress and improved periodontal health; vitamin E may enhance healing in endodontic cases with inflammation.	[40]
Vitamin D	Linked to immune regulation; deficiency may exacerbate periodontitis.	Vitamin D deficiency was associated with increased periodontal inflammation, and supplementation improved outcomes.	[41]
Zinc oxide nanoparticles	Used as root canal sealers (nano-ZOE) to improve sealing ability.	Nano-ZOE sealers showed significantly less microleakage than conventional sealers (AH26 and micro-ZOE).	[42]
Magnesium	Incorporated into dental materials to enhance mechanical properties, such as enamel remineralization.	Increased enamel hardness by approximately 20% through Mg-doped apatite formation, with potential applications in regenerative dentistry.	[43]
Silicon	Doped into calcium phosphate cements (Si-CPC) for controlled antibiotic release.	At 80%, Si-CPC enabled zero-order vancomycin release, and nanoporosity (37 nm) improved sustained delivery.	[44]

ZOE, zinc oxide–eugenol; Si-CPC, silicon-doped calcium phosphate cement.

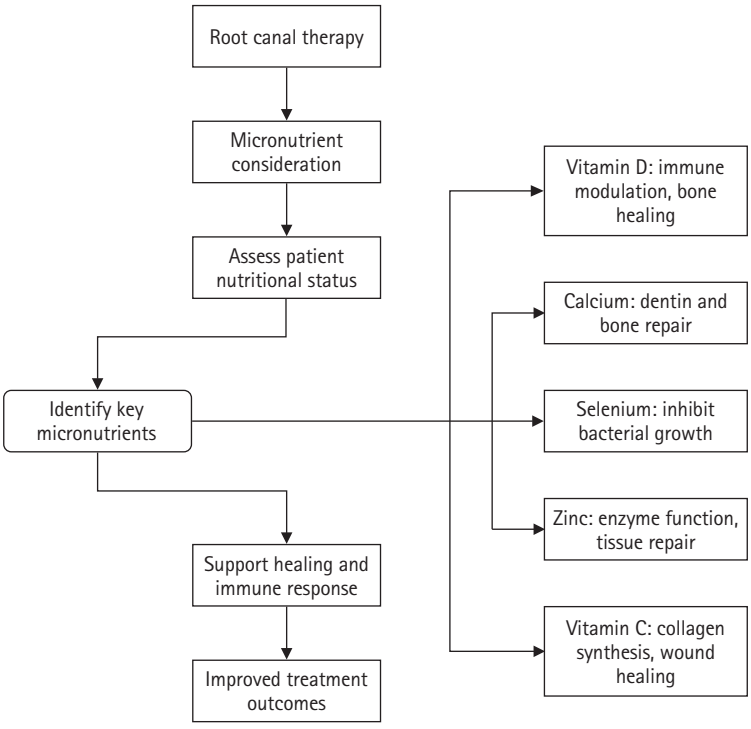

Fig. 4. Roles of micronutrients in root canal treatment.

demonstrated beneficial effects on periodontal parameters in clinical studies. When used alongside bioceramic sealers such as EndoSequence BC Sealer (Brasseler), they have been associated with improved bone density outcomes [41]. Omega-3 fatty acid products such as Omegaven (Fresenius Kabi) may reduce postoperative inflammation in perforation repair [49]. When combined with mineral trioxide aggregate, they have been reported to lower complication rates by 80%. Topical vitamin C gels such as PerioGard (with ascorbic acid, Colgate) reduced gingival inflammation by 75% when used with ethylenediaminetetraacetic acid (e.g., SmearClear, SybronEndo) and bioceramic obturation [39]. Vitamin E antioxidant gels have been reported to accelerate periapical healing by 70% in retreatment cases when used with AH Plus sealer (Dentsply Sirona) [40].

Cross-sectional and cohort studies have shown that patients with micronutrient deficiencies have higher complication rates after root canal therapy and may also experience delayed wound healing, increased infection risk, and impaired mineralization of dental tissues. Fig. 5 depicts the endodontic risks associated with micronutrient deficiencies. Supplementation trials have reported improvements in healing and reductions in inflammatory markers among patients who received vitamin C, vitamin E, and zinc during post-endodontic recovery [19]. Patients with insufficient vitamin C levels were reported to have a 42% increased risk of enamel or dentin fractures. Because vitamin C is essential for collagen synthesis and wound healing, deficiency may impair tissue repair. Vitamin D deficiency has been associated with a 35% higher risk of periapical infections because of its role in immune regulation and calcium metabolism. In periapical tissues, inadequate vitamin D status may impair healing and promote persistent inflammation. Insufficient calcium has been linked to a 30% higher incidence of inadequate dentin mineralization, thereby weakening dental structures and delaying healing after therapy. Calcium is the principal mineral required for the mineralization of hard dental tissues. Inadequate phosphorus status was associated with a 28% increase in delayed tissue repair, which may manifest as prolonged postoperative recovery. Zinc deficiency increased the risk of infection and gingival inflammation by 33%. Zinc is essential for immune function, anti-inflammatory responses, and enzymatic repair processes. Magnesium deficiency has been associated with a 25% longer wound-healing time, most likely because of its role in inflammatory regulation and enzyme activity [28]. Recent literature suggests that deficiencies in these nutrients, especially vitamin D, calcium, vitamin C, and zinc, may slow tissue repair and increase susceptibility to persistent infection and other complications after root canal therapy. Although most long-term studies and meta-analyses have focused on technical and procedural variables, there is increasing recognition that optimal nutritional status, par-

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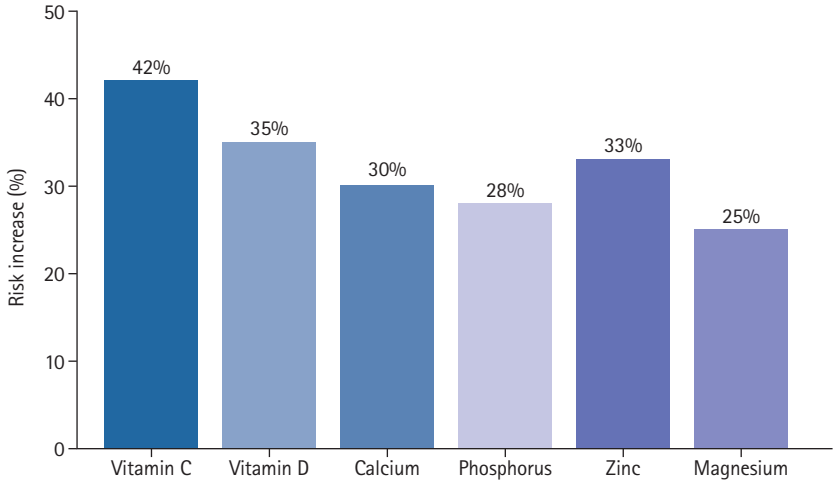

Fig. 5. Micronutrient deficiencies and endodontic risk.

ticularly with respect to these micronutrients, may improve both early healing and long-term outcomes in patients undergoing root canal treatment.

Antioxidant efficacy is relevant to endodontics because oxidative stress may increase after root canal treatment as reactive oxygen species are generated [25]. The therapeutic use of antioxidants is therefore biologically plausible in this setting as a means of supporting healing. Antioxidants act by quenching free radicals through electron donation, inactivating them before they damage tissues, or protecting normal cells from oxidative injury. Dietary components rich in antioxidants include vitamin C, vitamin E, tannic acid, and quercetin. Increased salivary antioxidant levels may contribute to improved periodontal health. Radical scavengers such as vitamins C, E, and A inhibit radical chain reactions [49]. Another antioxidant mechanism involves the prevention of radical formation. Some antioxidants also chelate metal ions, thereby inhibiting metal-dependent radical generation. Many compounds act through multiple antioxidant mechanisms, including lipoic acid and melatonin. Antioxidants are widely discussed in the literature and vary considerably in structure and function. Natural sources of antioxidant molecules include honey, polyphenols, flavonoids, and phytochemicals.

Discussion

Current high-level reviews and meta-analyses in endodontics primarily address technical factors affecting root canal outcomes, such as root filling quality or pre-existing dental lesions, rather than patient micronutrient status [11]. As a result, high-quality aggregated evidence directly linking specific micronutrients, including vitamin D, vitamin C, calcium, zinc, phosphorus, and magnesium, to endodontic healing success or failure remains limited. This evidence gap constrains the ability to draw strong conclusions regarding the extent to which these nutrients influence long-term root canal outcomes. Methods used to assess micronutrient status also vary substantially across studies. Some studies use dietary recall, others measure serum levels, and others report supplementation without biochemical confirmation. This heterogeneity makes it difficult to compare findings across studies or develop standardized recommendations for micronutrient intake or supplementation in endodontic practice [27]. The available studies also span diverse populations with respect to age, health status, and geography and use different protocols for micronutrient measurement and supplementation, further limiting the generalizability of nutritional recommendations for endodontic patients. Future studies should prioritize multicenter randomized controlled trials specifically designed to determine whether correction of deficiencies in key micronutrients, such as vitamin D, vitamin C, calcium, zinc, magnesium, and phosphorus, improves healing and reduces complications after root canal therapy. These trials should include adequate sample sizes and longer follow-up to evaluate long-term effects. Studies should also examine the practicality, cost-effectiveness, and patient outcomes associated with routine nutritional risk screening in dental clinics. Rather than investigating individual nutrients in isolation, future research should also evaluate the combined or interactive effects of multiple micronutrients on healing and resistance to endodontic complications.

Conclusion

The interplay between micronutrients and endodontic

health underscores the importance of nutrition in optimizing root canal therapy outcomes. Adequate levels of vitamins, minerals, and antioxidants support essential biological processes, including tissue repair, immune defense, and inflammation control, all of which contribute to successful healing. Deficiencies in key micronutrients, by contrast, may impair dentin formation, prolong recovery, and increase susceptibility to infection. Although current evidence suggests potential benefits of micronutrient supplementation in endodontic care, further clinical research is needed to establish precise dietary recommendations for patients undergoing root canal treatment. Integrating nutritional assessment into endodontic practice may enhance treatment efficacy, improve patient outcomes, and support a more holistic approach to oral health care. Future interdisciplinary studies integrating dentistry and nutritional science will be essential for developing evidence-based strategies to harness the therapeutic potential of micronutrients in endodontics. Ultimately, recognizing nutrition as a modifiable factor in root canal therapy may inform improved clinical protocols and long-term oral health outcomes.

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Conceptualization: AK, NS. Investigation: AK, VG. Methodology: NS, SR. Supervision: NS, SR. Visualization: VG, AK. Writing–original draft: AK, NS. Writing–review & editing: NS, VG. All authors read and approved the final manuscript.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Supplementary materials

None.

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Original Article

Postoperative nausea and vomiting after emergent abdominal surgery in trauma patients in Korea: a multicenter retrospective observational study

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Abstract

Purpose: The present study aimed to assess the incidence and risk factors of postoperative nausea and vomiting (PONV) after emergency abdominal surgery in trauma patients.
Methods: This retrospective observational study included trauma patients who underwent emergency abdominal surgery at two trauma centers between January 2024 and May 2025. Medical records were reviewed according to the occurrence of PONV.
Results: A total of 114 patients were included in the analysis, of whom 35 patients (30.7%) developed PONV. Patients with a history of PONV had a higher incidence of PONV than those without such a history (80% vs. 28.4%; P=0.030). The lymphocyte percentage was lower in the PONV group (27.8% vs. 20.0%; P=0.023). In binary logistic regression analysis, previous PONV (B=2.469, P=0.033; odds ratio [OR], 11.807; 95% confidence interval [CI], 1.224–113.897) and lymphocyte percentage (B=–0.034, P=0.021; OR, 0.967; 95% CI, 0.939–0.995) were significant risk factors. PONV severity was also associated with a higher segmented neutrophil percentage, a higher neutrophil-to-lymphocyte ratio, and a lower lymphocyte percentage.
Conclusion: The incidence of PONV was 30.7%. Previous PONV and a lower lymphocyte percentage were identified as risk factors for PONV after emergency abdominal surgery in trauma patients. Further studies are needed to develop strategies for reducing PONV in this population.

Keywords: Abdominal injuries; Incidence; Postoperative nausea and vomiting; Risk factors

Introduction

Background

Since Henrik Kehlet introduced the concept of Enhanced Recovery After Surgery (ERAS), ERAS has been widely adopted across surgical specialties [1]. ERAS protocols aim to improve patient outcomes by standardizing several areas of perioperative care and typically include preoperative, intraoperative, and postoperative components delivered through a multidisciplinary team approach. Reduction of postoperative nausea and vomiting (PONV) is a common component of ERAS protocols in both elective and emergency surgery [2-5].

PONV is a common postoperative complication. Its incidence has been reported to range from 10% to 50% and to

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increase to as high as 80% in high-risk populations [6-8]. To prevent and control PONV, current recommendations include minimizing nitrous oxide and volatile anesthetics, reducing opioid use, and administering 5-HT3 receptor antagonists, corticosteroids, antihistamines, and other antiemetic agents [9]. However, opioid analgesics are commonly used for analgosedation in patients in the intensive care unit and may be required for pain control in severely injured patients [10]. Therefore, trauma patients may be vulnerable to PONV, and efforts to reduce PONV in this population are needed. However, evidence in this area remains limited.

Objectives

This study aimed to describe the basic characteristics of PONV in trauma patients. A retrospective observational study using medical records was conducted to assess the incidence and risk factors of PONV after abdominal surgery in trauma patients.

Methods

Study design and setting

Trauma patients who underwent emergency abdominal surgery at two trauma centers between January 2024 and May 2025 were included. For this analysis, emergency abdominal surgery was defined as any surgery involving the region from the diaphragm to the pelvis, including procedures for injuries to the abdominal wall, intraperitoneal organs, and retroperitoneal organs such as the pancreas, kidneys, and major vessels.

Ethics statement

The Catholic University of Korea Uijeongbu St. Mary's Hospital Institutional Review Board approved this study (No. UC25RIDI0062), and the requirement for informed consent was waived because only deidentified data were used and no intervention was performed. All methods were conducted in accordance with relevant guidelines and regulations.

Participants

Patients who received prolonged mechanical ventilation for more than 48 hours, had psychiatric disorders or intellectual disability, died within 48 hours, or were younger than 18 years were considered unable to report PONV accurately and were excluded from the statistical analysis.

Definition and assessment of PONV

The research team investigated and recorded PONV occurring on the first postoperative day. Any nausea or vomiting that occurred on the first day after surgery was defined as PONV-positive and used for categorical analysis. PONV severity was assessed using a visual analog scale from 0 to 10 and a simplified scoring system: 0, none; 1, nausea without vomiting; 2, 1–2 vomiting episodes; and 3, 3 or more vomiting episodes. Patients with missing data were also excluded from the analysis.

Data collection

Other clinical information, including medical history, injury severity, operative findings and related procedures, in-hospital mortality, and other morbidities, was reviewed. Initial vital signs and laboratory findings upon arrival at the trauma center were analyzed.

Statistical analysis

Patients were divided according to the occurrence of PONV, and their characteristics were compared. The independent *t*-test was used for continuous variables, and the Pearson chi-square test and the Fisher exact test were used for categorical variables. Binary logistic regression was performed to identify risk factors and calculate odds ratios (ORs). Parameters correlated with PONV severity were identified using Spearman correlation analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp.). A P-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 155 trauma patients who underwent abdominal surgery at two trauma centers were identified during the study period. After application of the inclusion and exclusion criteria, 114 patients were included in the final statistical analysis; this process is summarized in the flowchart in Fig. 1. Six patients who underwent emergency abdominal surgery for diaphragmatic or flank hernias were initially included based on suspected acute traumatic pathology. However, operative findings demonstrated severe adhesions, suggesting a chronic etiology rather than acute trauma. Therefore, these cases were excluded from the final analysis because they were not considered to represent trauma-related surgical conditions. Overall, 35 patients (30.7%) developed PONV. By institution, the incidence of PONV was 5.6% (1/18) at one hospital and 35.4% (34/96) at the other hospital. Baseline characteristics were comparable between the two institutions, with no significant differences in age or sex distribution. Baseline characteristics and medical history are shown in Table 1. Patients with a history of PONV had a higher

incidence of PONV than those without such a history (80.0% vs. 28.4%; P=0.030). Initial patient condition, laboratory findings, and injury severity are summarized in Table 2. The lymphocyte percentage was lower in the PONV group (27.8% vs. 20.0%; P=0.023).

Risk factor analysis

In binary logistic regression analysis, previous PONV (B=2.469, P=0.033; OR, 11.807; 95% confidence interval [CI], 1.224–113.897) and lymphocyte percentage (B=–0.034, P=0.021; OR, 0.967; 95% CI, 0.939–0.995) were significant risk factors. No statistically significant parameters were identified in the operation-related variables or clinical outcomes, which are summarized in Tables 3 and 4.

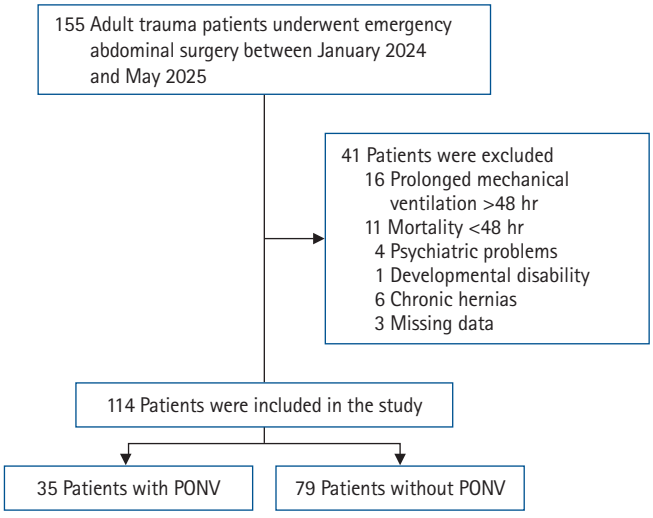

Fig. 1. Flowchart of inclusion and exclusion in the study. PONV, postoperative nausea and vomiting.

Correlation analysis

Table 5 shows the results of the Spearman correlation analysis. Segmented neutrophil percentage and neutrophil-to-lymphocyte ratio (NLR) demonstrated significant positive correlations with PONV severity, whereas lymphocyte percentage was negatively correlated with PONV severity, suggesting that initial inflammation was related to PONV severity. These correlations are presented with scatterplots and trendlines in Fig. 2.

Discussion

Main findings

The objective of this study was to determine the incidence and risk factors of PONV after abdominal surgery in trauma patients. The incidence of PONV was approximately 30%, and the identified risk factors were a history of PONV and a lower lymphocyte percentage. PONV severity was correlated with the initial severity of inflammation. Because this topic has rarely been investigated, these findings may provide a useful basis for further research.

Table 1. Baseline characteristics and past history

Variable		Postoperative nausea and vomiting		P-value
		Negative (n=79)	Positive (n=35)	
Age (yr), mean±SD		55.5±17.9	55.0±16.1	0.879
Sex	Male	50 (71.4)	20 (28.6)	0.534
	Female	29 (65.9)	15 (34.1)	
Previous postoperative nausea and vomiting[a]	No	78 (71.6)	31 (28.4)	0.030
	Yes	1 (20.0)	4 (80.0)	
Current smoker	No	31 (70.5)	13 (29.5)	0.832
	Yes	48 (68.6)	22 (31.4)	
Hypertension	No	56 (70.0)	24 (30.0)	0.803
	Yes	23 (67.6)	11 (32.4)	
Diabetes	No	62 (69.7)	27 (30.3)	0.873
	Yes	17 (68.0)	8 (32.0)	
Liver cirrhosis	No	78 (69.0)	35 (31.0)	>0.999
	Yes	1 (100.0)	0	
Chronic kidney disease	No	79 (69.3)	35 (30.7)	NA
	Yes	0	0	

Values are presented as number (%) unless otherwise indicated.
SD, standard deviation; NA, not available.
[a]Result of logistic regression analysis: previous postoperative nausea and vomiting (B=2.469, P=0.033, odds ratio [95% confidence interval]=11.807 [1.224–113.897]).

Table 2. Parameters reflecting initial condition and injury severity

Variable	Postoperative nausea and vomiting		P-value
	Negative (n=79)	Positive (n=35)	
Glasgow Coma Score	14.0±2.8	14.4±2.2	0.432
Systolic blood pressure (mmHg)	110.3±32.8	105.8±29.1	0.483
Pulse rate (beats/min)	88.9±24.1	82.3±15.5	0.086
Initial intubation			
No	53 (71.6)	21 (28.4)	
Yes	26 (65.0)	14 (35.0)	
Initial vasopressor			0.052
No	33 (80.5)	8 (19.5)	
Yes	46 (63.0)	27 (37.0)	
Hemoglobin (g/dL)	12.8±2.3	12.6±2.3	0.536
White blood cell count (/μL)	12,481±5,259	13,130±7,247	0.591
Segmented neutrophils (%)	66.4±20.7	73.9±14.3	0.056
Lymphocyte (%)[a]	27.8±17.7	20.0±13.8	0.023
NLR	5.8±10.5	6.2±4.7	0.800
Platelet (/μL)	243,329±76,227	233,486±84,039	0.539
Blood urea nitrogen (mg/dL)	16.4±11.9	16.0±5.5	0.816
Creatinine (mg/dL)	1.0±0.6	1.0±0.3	0.680
Albumin (g/dL)	4.0±0.6	3.9±0.6	0.352
INR	1.1±0.1	1.0±0.1	0.509
Head and neck	0.7±1.2	0.7±1.0	0.960
Face	0.2±0.5	0.1±0.4	0.372
Chest	1.4±1.5	1.7±1.6	0.302
Abdomen	2.7±1.1	2.8±1.1	0.552
Extremity	1.1±1.7	1.2±1.5	0.892
External	0.6±0.6	0.5±0.6	0.942
Injury severity score	17.7±12.5	19.4±11.7	0.497
Major trauma			0.380
No	34 (73.9)	12 (26.1)	
Yes	45 (66.2)	23 (33.8)	

Values are presented as mean±SD or number (%). Abbreviated Injury Scores for Head and Neck, Face, Chest, Abdomen, Extremity, and External are presented.
NLR, neutrophil-lymphocyte ratio; INR, international normalized ratio; SD, standard deviation.
[a]Result of logistic regression analysis: Lymphocyte percent (B=–0.034, P=0.021, odds ratio [95% confidence interval]=0.967 [0.939–0.995]).

Table 3. Operation-related information

Variable		Postoperative nausea and vomiting		P-value
		Negative (n=79)	Positive (n=35)	
Surgery type	Laparoscopic	27 (75.0)	9 (25.0)	0.370
	Open/conversion	52 (66.7)	26 (33.3)	
Damage control surgery	No	54 (65.1)	29 (34.9)	0.108
	Yes	25 (80.6)	6 (19.4)	
Combined operation other than abdomen	No	67 (69.1)	30 (30.9)	>0.999
	Yes	12 (70.6)	5 (29.4)	
Intraabdominal adhesion	No	75 (70.1)	32 (29.9)	0.674
	Yes	4 (57.1)	3 (42.9)	
Transfusion within POD 1	No	52 (69.3)	23 (30.7)	0.991
	Yes	27 (69.2)	12 (30.8)	
Opioid administration within POD 1	No	2 (100.0)	0	>0.999
	Yes	77 (68.8)	35 (31.3)	

Values are presented as number (%).
POD, postoperative day.

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Table 4. Clinical outcomes

Variable		Postoperative nausea and vomiting		P-value
		Negative (n=79)	Positive (n=35)	
Superficial surgical site infection	No	74 (68.5)	34 (31.5)	0.665
	Yes	5 (83.3)	1 (16.7)	
Deep surgical site infection	No	79 (69.3)	35 (30.7)	NA
	Yes	0	0	
Organ space infection	No	78 (69.0)	35 (31.0)	>0.999
	Yes	1 (100.0)	0	
Delirium	No	74 (67.9)	35 (32.1)	0.321
	Yes	5 (100.0)	0	
In-hospital mortality	No	73 (67.6)	35 (32.4)	0.175
	Yes	6 (100.0)	0	

Values are presented as number (%).
NA, not available.

Table 5. Parameters correlated to the severity of postoperative nausea and vomiting

	Segmented neutrophils (%)		Lymphocyte (%)		NLR	
	r	P-value	r	P-value	r	P-value
VAS	0.226	0.016	–0.214	0.022	0.214	0.022
Simplified score	0.213	0.023	–0.205	0.029	0.204	0.030

NLR, neutrophil-lymphocyte ratio; r, correlation coefficient; VAS, visual analog score.

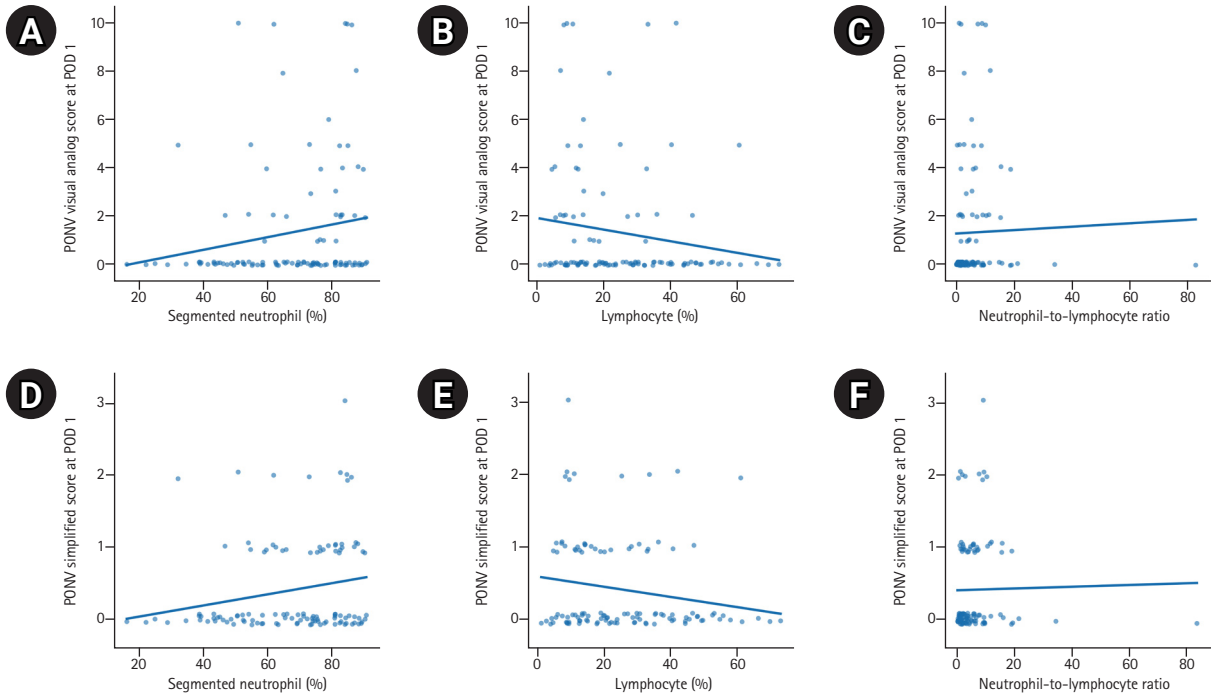

Fig. 2. Correlations between PONV severity and inflammatory markers. PONV, postoperative nausea and vomiting; POD, postoperative day.

The overall incidence of PONV after abdominal surgery in trauma patients was similar to that reported in previous studies [7,8]. Opioids, which are well-known risk factors for PONV, were administered to almost all patients (98.2%). In addition, 5-HT3 receptor antagonists, which can be used for both prophylaxis and treatment of PONV, were used in 102 patients (89.5%). However, because this was a retrospective observational study, the type of perioperative medication, in-

dication, timing of administration, and duration of treatment were determined by the clinical judgment of each surgeon and anesthesiologist and were not standardized. These variables may have acted as confounding factors for PONV, and the inability to control for them is a limitation of this study. Additionally, 5-HT3 receptor antagonists, other perioperative antiemetics, and anesthetic methods were not included in the statistical analysis. Further well-controlled studies of PONV management are required.

Limitations

The relatively small number of enrolled patients should be considered when interpreting the results of this study. Initial vital signs, injury severity, operative methods, and PONV incidence differed between the two participating institutions. However, one institution performed fewer than 20 surgeries during a study period of more than 1 year, which limited statistical analysis. Previous PONV, a known risk factor for PONV, was also identified as a risk factor in this study. However, other known risk factors, such as current smoking, were not statistically significant. Multicenter studies can strengthen statistical power by collecting cases with diverse characteristics. In particular, multicenter studies may be useful for investigating uncommon clinical scenarios, such as trauma patients undergoing emergency abdominal surgery. Nevertheless, the number of cases in this study was relatively small. Further analyses in larger populations are needed to validate these risk factors.

Another significant risk factor was a lower lymphocyte percentage. Along with segmented neutrophil percentage and NLR, lymphocyte percentage was correlated with PONV severity. NLR, in particular, is an indicator of systemic inflammation and has been reported as a risk factor for PONV. Yildiz Altun et al. [11] reported that NLR was a risk factor for PONV in patients after septorhinoplasty. Arpaci et al. [12] used NLR to guide metoclopramide administration. Dexamethasone has also been reported to reduce the incidence of PONV [13,14]. Further analyses of dexamethasone and other anti-inflammatory drugs for PONV management in trauma patients are warranted.

Conclusion

This study assessed the incidence and risk factors of PONV after abdominal surgery in trauma patients. The incidence of PONV was 30.7%. Previous PONV and a lower lymphocyte percentage were associated with PONV. Further research is needed to improve the understanding of PONV and patient outcomes in this population.

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Conceptualization: MK, HK, JA. Data curation: DHK, HP, MK, DSL, THH, HJC. Formal analysis: MK. Funding acquisition: DHK, MK. Investigation: DHK, HK, JA, MK. Methodology: HP, MK. Resources: DHK, MC. Supervision: MK. Validation: DL, HTH, HJC. Writing–original draft: DHK, HP, MK. Writing–review & editing: HK, JA, MC, DSL, THH, MK, HJC. All authors read and approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest regarding the publication of this article.

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Data availability

The raw data supporting the conclusions presented in this article will be made available by the authors upon request.

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Supplementary materials

None.

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Original Article

Association between vitamin D deficiency and psychological distress in Korean adults: a population-based cross-sectional study

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Abstract

Purpose: Vitamin D deficiency is prevalent in Korea, but evidence on its association with psychological distress remains limited. This study examined the association between vitamin D levels and psychological distress, depression, and anxiety among Korean adults.
Methods: This cross-sectional study included 4,712 adults aged ≥19 years from the 2022 Korea National Health and Nutrition Examination Survey (KNHANES). Participants were classified as vitamin D-deficient (<20 ng/mL) or non-deficient (≥20 ng/mL) groups. Psychological distress, depression, and anxiety were assessed using the Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7. Multivariable logistic regression was used to estimate adjusted odds ratios for these outcomes according to vitamin D status.
Results: The weighted prevalence of vitamin D deficiency was 45.6%. Unadjusted analyses showed higher prevalences of psychological distress (11.2% vs. 8.5%; P=0.004) and anxiety (9.2% vs. 6.5%; P=0.005) in the deficient group, especially among women and adults aged 19–64 years. After adjustment, the associations were attenuated and not statistically significant in the total population. In age-stratified models, vitamin D deficiency remained significantly associated with psychological distress in adults aged 19–64 years and ≥65 years and with anxiety in adults aged 19–64 years.
Conclusion: Although psychological distress was more prevalent in the vitamin D-deficient group before adjustment, the association was not statistically significant after covariate adjustment in the total population. Subgroup analyses showed higher unadjusted prevalences of psychological distress and anxiety among women with vitamin D deficiency. Adjusted models showed significant associations with psychological distress in both age groups. These findings suggest potential subgroup-specific associations, warranting longitudinal studies to confirm causality.

Keywords: Anxiety; Depression; Psychological distress; Vitamin D

Introduction

Background

Psychological distress, including depression and anxiety, is a widespread public health problem globally [1]. It imposes a substantial socioeconomic burden, reduces quality of life, and is associated with increased risks of mortality and suicide [2,3]. Recent data show a marked increase in the global burden of mental disorders, with depression and anxiety as the leading contributors [4]. This rising prevalence poses a challenge for clinical care because psychological comorbidities can complicate management and prognosis. Korea follows this global pattern; in the 2021 Survey of Mental Health, one in four Korean adults reported experiencing a mental

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disorder at least once during their lifetime [5].

The association between micronutrients and mental health has received considerable attention, and vitamin D has been a particular focus. In addition to its role in bone metabolism, vitamin D functions as a neurosteroid: vitamin D receptor (VDR) is widely distributed in brain regions involved in emotion regulation, and vitamin D contributes to the synthesis of neurotransmitters such as serotonin [6]. Vitamin D deficiency remains a common public health problem and is especially pronounced in Korea. An analysis of the 2008–2014 Korea National Health and Nutrition Examination Survey (KNHANES) found that adult vitamin D deficiency (<50 nmol/L) was present in 65.7% of men and 76.7% of women, a prevalence markedly higher than that reported in Western countries [7]. This high prevalence in Korea may reflect the combined effects of predominantly indoor lifestyles, inadequate sun exposure, widespread sunscreen use, and insufficient dietary vitamin D intake [8].

However, few studies have evaluated the association between vitamin D deficiency and standardized mental health measures in large Korean populations. Although the KNHANES includes validated screening tools, including the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), research using these measures to assess psychological distress, defined to encompass both depression and anxiety, remains limited [9].

Objectives

This study aimed to investigate the association between vitamin D deficiency and psychological distress in Korean adults using nationally representative data.

Methods

Ethics statement

The primary KNHANES protocol was approved by the Institutional Review Board (IRB) of the Korea Disease Control and Prevention Agency (IRB No. 2018-01-03-4C-A). The present study was exempted from review by the IRB of Sookmyung Women's University (IRB No. SMWU-2509-HR-076) because it used publicly available, anonymized data.

Study design and participants

This cross-sectional study used data from the 2022 KNHANES. KNHANES is a nationwide, population-based survey that uses a complex, stratified, multistage probability sampling design to assess the health and nutritional status of the Korean population. The 2022 survey measured serum vitamin D concentrations, including 25-hydroxyvitamin D2 [25(OH)D2] and 25-hydroxyvitamin D3 [25(OH)D3], and administered the PHQ-9 and GAD-7 to adults aged ≥19 years.

Among all 2022 KNHANES participants, adults aged ≥19 years were initially selected. Participants were included in the final analysis only if they had complete data on serum vitamin D concentrations, PHQ-9 scores, and GAD-7 scores. Participants with missing data for more than one key variable were counted only once in the overall exclusion count. Therefore, the sum of the variable-specific missing counts shown in Fig. 1 exceeds the total number of excluded individuals (n=610), reflecting overlapping missingness for vitamin D, PHQ-9, and GAD-7. The final analytic sample included 4,712 participants. To examine demographic differences, analyses were stratified by sex and age group (19–64 years and ≥65 years).

Assessment of vitamin D status

In the 2022 KNHANES, serum 25(OH)D2, 25(OH)D3, and 3-epi-25(OH)D3 concentrations were measured at GC Labs using liquid chromatography–tandem mass spectrometry, in accordance with the KNHANES IX (2022–2023) laboratory protocol [9]. Serum vitamin D level was defined as the sum of 25(OH)D2 and 25(OH)D3 concentrations. For samples with 25(OH)D2 levels below the limit of detection (<0.30 ng/mL), the value was treated as 0, and total vitamin D level was calculated from the 25(OH)D3 concentration. Participants were classified according to the Endocrine Society clinical practice guideline as vitamin D-deficient (<20 ng/mL) or non-deficient (≥20 ng/mL) [10].

Assessment of mental health outcomes

Mental health outcomes were assessed using the PHQ-9 for depression and the GAD-7 for anxiety. Both instruments were administered as part of the 2022 KNHANES [9] and assessed symptoms during the preceding 2 weeks, with each item scored on a 0–3-point scale. The PHQ-9 includes 9 items (total score range, 0–27), with scores ≥10 indicating clinically significant depressive symptoms [11]. The GAD-7 includes 7 items (total score range, 0–21), with scores ≥8 widely accepted as the clinical cutoff for anxiety [12]. Psychological distress was defined as meeting the criterion for either depression (PHQ-9 ≥10) or anxiety (GAD-7 ≥8). The primary outcomes were the prevalence of psychological distress, depression, and anxiety. Secondary outcomes were symptom severity scores, measured as mean PHQ-9 and GAD-7 scores.

Covariates

To adjust for potential confounding of mental health outcomes, sociodemographic characteristics, lifestyle factors, and

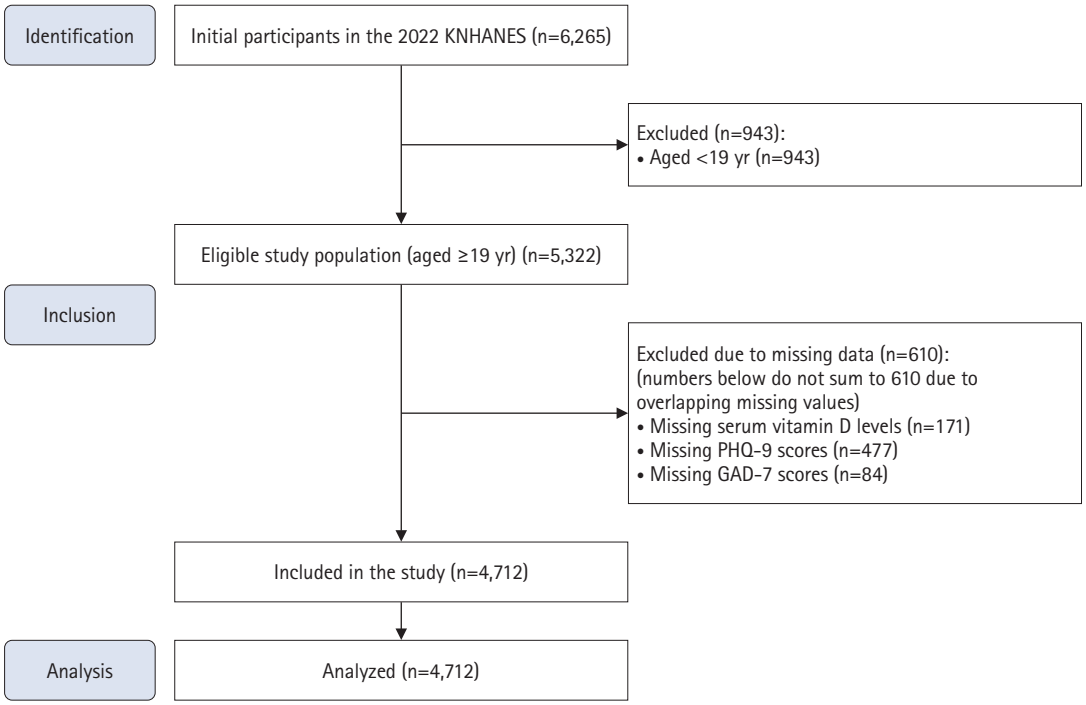

Fig. 1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow diagram showing participant selection and the final analytic sample. KNHANES, Korea National Health and Nutrition Examination Survey; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7.

health status were included as covariates. Sociodemographic variables included sex (male or female), age (19–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years), and residential area (urban or rural). Lifestyle variables included sleep duration (≤5, 6–8, or ≥9 hours), current alcohol consumption (yes or no), and current smoking status (yes or no). According to official KNHANES definitions, current alcohol consumption was defined as drinking alcohol at least once per month during the past year, and current smoking was defined as having smoked ≥100 cigarettes during one's lifetime and currently smoking. Health status was assessed by comorbidity status; participants were classified as having a comorbidity if they had at least one of the following: hypertension, diabetes, hypercholesterolemia, or obesity (body mass index [BMI] ≥25 kg/m^2).

Statistical analysis

All statistical analyses accounted for the complex KNHANES sampling design, including stratification, clustering, and sample weights. Participant characteristics and mental health outcomes were first compared according to vitamin D status (deficient vs. non-deficient). Continuous variables were presented as means±standard errors, and categorical variables were presented as unweighted counts with survey-weighted percentages. Between-group comparisons used the t-test for continuous variables and the Rao–Scott chi-square test for categorical variables. Variables that differed significantly between vitamin D groups in the univariate analyses (P<0.05) were selected as covariates for the multivariable models. Multivariable logistic regression models adjusted for these selected covariates were then used to evaluate the associations between vitamin D deficiency and the prevalence of psychological distress, depression, and anxiety. These models were fitted using complete-case analysis; 77 participants (1.6%) with missing covariate data were excluded from the adjusted models (n=4,635).

Although perceived stress differed significantly between vitamin D groups (P=0.030), it was deliberately excluded from the multivariable models. Because perceived stress conceptually and physiologically overlaps with the outcome variables of depression and anxiety, including it as a covariate could have introduced overadjustment bias if perceived stress lay on the causal pathway rather than acting as a true confounder.

Results are reported as adjusted odds ratios (AORs) with 95% confidence intervals (CIs). Statistical significance was defined as P<0.05. All analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing).

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Results

Participant characteristics

A total of 4,712 participants were included in the final analysis. The weighted prevalence of vitamin D deficiency was 45.6% (unweighted count: 1,911 in the deficient group vs. 2,801 in the non-deficient group). Participant characteristics stratified by vitamin D status are presented in Table 1. Several demographic characteristics differed between the groups. Compared with the non-deficient group, the vitamin D-deficient group was younger (mean age, 43.58 years vs. 52.68 years; P<0.001) and included a higher proportion of men (53.9% vs. 46.4%; P<0.001). Residential area also differed, with a higher proportion of urban residents in the deficient group (89.8% vs. 81.7%; P<0.001). Current alcohol use and current smoking were more common in the deficient group (P<0.001 for both). The prevalence of obesity (P=0.046) and high perceived stress (P=0.030) was also higher in the vitamin D-deficient group than in the non-deficient group.

Table 1. Participant characteristics according to vitamin D status (n=4,712)

Parameter	Vitamin D non-deficient (n=2,801)	Vitamin D deficient (n=1,911)	P-value
Sex			<0.001
Men	1,155 (46.4)	888 (53.9)	
Women	1,646 (53.6)	1,023 (46.1)	
Age (yr)	52.68±0.56	43.58±0.57	<0.001
Age group			<0.001
19–29 yr	167 (8.9)	408 (27.6)	
30–39 yr	312 (14.7)	286 (16.7)	
40–49 yr	396 (17.4)	387 (19.9)	
50–59 yr	514 (21.5)	303 (16.4)	
60–69 yr	755 (21.5)	264 (10.9)	
≥70 yr	657 (16.0)	263 (8.6)	
Household income			0.075
Q1 (lowest)	605 (16.4)	327 (14.2)	
Q2–Q4 (higher)	2,195 (83.6)	1,583 (85.8)	
Residence			<0.001
Rural	715 (18.3)	274 (10.2)	
Urban	2,086 (81.7)	1,637 (89.8)	
Sleep duration			0.007
≤5 hr	460 (15.6)	243 (11.8)	
6–8 hr	2,184 (79.6)	1,553 (83.1)	
≥9 hr	155 (4.8)	113 (5.1)	
Current alcohol use (yes)	1,341 (51.1)	1,053 (58.4)	<0.001
Current smoking (yes)	357 (13.9)	338 (20.0)	<0.001
Regular aerobic exercise	1,241 (48.8)	930 (51.7)	0.083
Perceived stress			0.030
Low	2,194 (76.1)	1,388 (72.6)	
High	605 (23.9)	523 (27.4)	
Comorbidities			
Hypertension	1,035 (31.9)	538 (24.6)	<0.001
Diabetes mellitus	417 (13.6)	247 (10.7)	0.006
Hypercholesterolemia	939 (30.9)	467 (22.6)	<0.001
Obesity	950 (35.6)	714 (39.1)	0.046
Anemia	277 (8.2)	216 (9.3)	0.221

Values are presented as unweighted counts (weighted %) or mean±standard error.

Vitamin D status and psychological distress

Psychological distress was more prevalent in the vitamin D-deficient group than in the non-deficient group (11.2% vs. 8.5%; P=0.004) (Table 2). Among specific conditions, anxiety showed significant between-group differences: the deficient group had a higher prevalence of anxiety (9.2% vs. 6.5%; P=0.005) and higher mean GAD-7 scores (2.44±0.10 vs. 2.08±0.07) (P=0.002). For depression assessed with the PHQ-9, both prevalence and mean scores were numerically higher in the deficient group, but the differences were not statistically significant.

Multivariable association between vitamin D deficiency and psychological distress

Multivariable logistic regression was used to estimate adjusted associations between vitamin D deficiency and the prevalence of psychological distress, depression, and anxiety. Fig. 2 presents the AORs after adjustment for sex, age, residential area, sleep duration, current alcohol consumption, current smoking, and comorbidities. Compared with the non-deficient reference group, the vitamin D-deficient group had an AOR of 1.20 (95% CI, 0.93–1.54) for psychological distress. The AOR for anxiety was 1.22 (95% CI, 0.91–1.63), suggesting a trend toward higher prevalence, whereas the

Table 2. Comparison of the prevalence of mental health outcomes according to vitamin D status

Variable	Vitamin D non-deficient (n=2,801)	Vitamin D deficient (n=1,911)	P-value
Psychological distress			
Prevalence	238 (8.5)	223 (11.2)	0.004
Depression (PHQ-9)			
Prevalence (score ≥10)	117 (4.3)	99 (4.9)	0.463
Score	2.33±0.07	2.53±0.09	0.079
Anxiety (GAD-7)			
Prevalence (score ≥8)	181 (6.5)	179 (9.2)	0.005
Score	2.08±0.07	2.44±0.10	0.002

Values are presented as unweighted counts (weighted %) or mean±SE.
PHQ-9, Patient Health Questionnaire-9; SE, standard error; GAD-7, Generalized Anxiety Disorder-7.

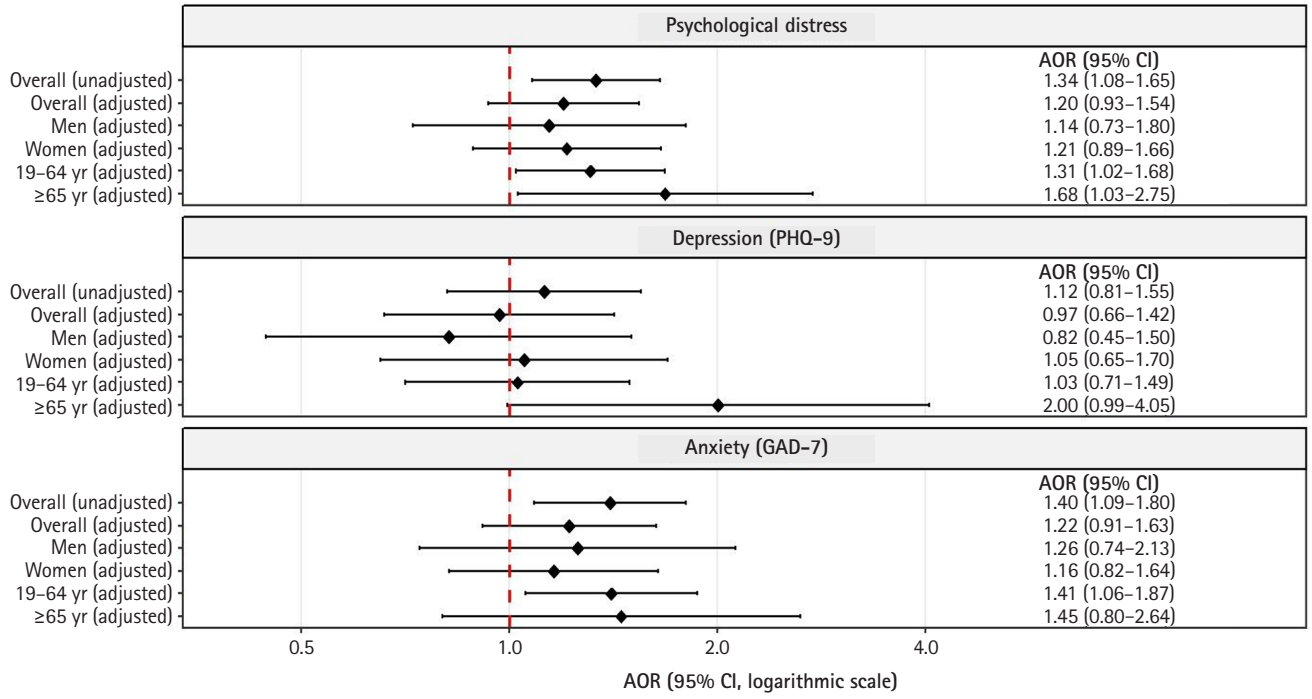

Fig. 2. ORs/AORs and 95% CIs for mental health outcomes according to vitamin D status. Results are shown for the total population (unadjusted and multivariable-adjusted) and for subgroups stratified by sex and age. Adjusted models included age, sex, residential area, smoking status, alcohol consumption, sleep duration, and comorbidities (hypertension, diabetes, hypercholesterolemia, or obesity), as applicable. Adjusted models included 4,635 participants owing to missing data on covariates. The x-axis is shown on a logarithmic scale, and the vertical dashed line indicates the reference value (OR=1.0). OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7.

AOR for depression was 0.97 (95% CI, 0.66–1.42). None of these associations reached statistical significance in the fully adjusted models.

Subgroup analyses

The prevalence of vitamin D deficiency differed significantly by sex (49.3% in men vs. 41.9% in women; P<0.001). In sex-stratified analyses, women in the deficient group had higher prevalences of psychological distress (13.8% vs. 9.7%; P=0.007) and anxiety (11.2% vs. 7.7%; P=0.012) than women in the non-deficient group, as summarized in Table 3. In contrast, no significant differences were observed among men for psychological distress (9.1% vs. 7.1%), depression (3.6% vs. 3.6%), or anxiety (7.4% vs. 5.2%). After covariate adjustment in multivariable logistic regression models, no statistically significant associations were observed in either sex.

By age, vitamin D deficiency was less prevalent in older adults (≥65 years) than in adults aged 19–64 years (30.4% vs. 49.3%; P<0.001). In unadjusted analyses, significant differences were limited to adults aged 19–64 years. In this group, psychological distress (11.5% vs. 9.1%; P=0.028) and anxiety (9.6% vs. 7.2%; P=0.023) were more prevalent in the vitamin D-deficient group than in the non-deficient group. By contrast, among older adults, the prevalence of psychological distress, depression, and anxiety did not differ significantly by vitamin D status. However, in fully adjusted models, vitamin D deficiency remained significantly associated with psychological distress in both age groups (AOR, 1.31; 95% CI, 1.02–1.68 for 19–64 years; AOR, 1.68; 95% CI, 1.03–2.75 for ≥65 years) and with anxiety among adults aged 19–64 years (AOR, 1.41; 95% CI, 1.06–1.87).

Additional subgroup analyses by lifestyle and health-related factors, including alcohol consumption, smoking, obesity, and perceived stress, showed no statistically significant associations in adjusted models, although a marginal trend was observed among participants who consumed alcohol (Supplement 1). A sensitivity analysis using a higher BMI threshold for obesity (≥30 kg/m^2) produced results consistent with the primary analysis (Supplement 2).

Discussion

Key results

This study examined the association between vitamin D deficiency and mental health outcomes, including psychological distress, depression, and anxiety, using nationally

Table 3. Subgroup analyses of mental health outcomes according to vitamin D status

Subgroups	Vitamin D status	Psychological distress	Depression	Anxiety
Sex				
Men	Non-deficient (n=1,155)	72 (7.1)	34 (3.6)	55 (5.2)
	Deficient (n=888)	77 (9.1)	31 (3.6)	61 (7.4)
	P-value	0.180	0.941	0.119
Women	Non-deficient (n=1,646)	166 (9.7)	83 (4.9)	126 (7.7)
	Deficient (n=1,023)	146 (13.8)	68 (6.4)	118 (11.2)
	P-value	0.007	0.182	0.012
Age group				
19–64 yr	Non-deficient (n=1,774)	163 (9.1)	81 (4.8)	130 (7.2)
	Deficient (n=1,522)	187 (11.5)	81 (4.9)	155 (9.6)
	P-value	0.028	0.905	0.023
≥65 yr	Non-deficient (n=1,027)	75 (6.5)	36 (3.0)	51 (4.5)
	Deficient (n=389)	36 (9.4)	18 (4.7)	24 (6.1)
	P-value	0.111	0.162	0.310

Values are presented as unweighted counts (weighted %).

representative data from the 2022 KNHANES. In unadjusted analyses, psychological distress and anxiety were more prevalent in the vitamin D-deficient group. After adjustment for potential confounders, including sex, age, and lifestyle factors, these associations were attenuated and were not statistically significant in the general population or in sex-stratified analyses. Nevertheless, unadjusted sex-stratified analyses showed higher prevalences of psychological distress and anxiety among women with vitamin D deficiency. In age-stratified adjusted analyses, vitamin D deficiency remained significantly associated with psychological distress in adults aged 19–64 years and those aged ≥65 years and with anxiety in adults aged 19–64 years.

Interpretation/comparison with previous studies

The finding that vitamin D deficiency was not significantly associated with depression in the fully adjusted model for the total population is consistent with a previous study by Ma and Li [13], which analyzed U.S. National Health and Nutrition Examination Survey data from 2007 to 2018. That study also reported that the association between vitamin D levels and depressive symptoms was no longer significant after covariate adjustment. In contrast, the present results differ from those of Rhee et al. [14], who reported a significant association between vitamin D deficiency and depressive symptoms in men using 2014 KNHANES data. These discrepancies may reflect methodological differences, particularly in outcome definition. Rhee et al. [14] analyzed symptom severity as a continuous PHQ-9 score using negative binomial regression, whereas the present study focused on clinically relevant symptom prevalence as a categorical outcome based on established cutoff scores.

Several biological mechanisms could plausibly link vitamin D deficiency with adverse mental health outcomes. The VDR is widely distributed in mood-regulating brain regions, including the prefrontal cortex, cingulate cortex, amygdala, and hippocampus. Functionally, vitamin D may protect against serotonin depletion, regulate enzymes involved in catecholamine synthesis, reduce hypothalamic–pituitary–adrenal (HPA) axis overactivity, and suppress systemic and central inflammatory cytokines [15-17].

The stronger unadjusted association observed among women may reflect interactions between estrogen and vitamin D. Estrogen regulates the expression of VDR and vitamin D-metabolizing enzymes, specifically 25-hydroxyvitamin D 1alpha-hydroxylase and 25-hydroxyvitamin D 24-hydroxylase, as well as the serotonergic system. This biological interplay supports a potential sex-specific hypothesis: because women experience hormonal fluctuations, such as those related to menstrual cycles or menopause, they may be more susceptible than men to disruptions in VDR signaling and HPA axis regulation associated with vitamin D deficiency [18-20]. This mechanism could help explain why the unadjusted prevalence rates of psychological distress and anxiety were higher in vitamin D-deficient women than in their non-deficient counterparts.

The age-stratified results suggested associations between vitamin D deficiency and mental health outcomes in both adults aged 19–64 years and older adults aged ≥65 years, although the robustness of the findings differed. Adults aged 19–64 years are often in socially and economically active stages of life and may experience occupational stress and

predominantly indoor work environments that limit sunlight exposure. For this group, adequate vitamin D status may be relevant to psychological well-being under daily stressors. In contrast, the significant adjusted association observed among older adults should be interpreted with caution. The number of prevalent psychological distress cases among older adults was small, likely contributing to the wide 95% CI and suggesting statistical instability. Future studies with larger cohorts of older adults are therefore needed to generate more precise and stable estimates.

Strengths

This study has several strengths. First, it used a large, nationally representative sample of Korean adults from the 2022 KNHANES. Because the analyses accounted for the complex sample design, the estimates are applicable to the Korean adult population. Standardized KNHANES protocols for measuring serum vitamin D concentrations and administering the PHQ-9 and GAD-7 also reduce information bias and support data reliability [9]. Second, vitamin D deficiency was defined using the Endocrine Society clinical practice guideline threshold (<20 ng/mL) [10] rather than the lower threshold proposed by the Institute of Medicine (<12 ng/mL) [21]. This stricter criterion may be more relevant for assessing non-skeletal outcomes such as mental health because it captures a broader range of individuals with low vitamin D status. Finally, by using both the PHQ-9 and GAD-7, this study assessed depression and anxiety rather than depression alone [22,23].

Limitations

This study also has several limitations. First, its cross-sectional design precludes causal inference about the relationship between serum vitamin D levels and psychological distress. Reverse causality remains possible, because depression or anxiety may reduce outdoor activity and sunlight exposure. Second, the PHQ-9 and GAD-7 are screening tools, not diagnostic instruments. Although these instruments are valid and reliable, high scores indicate symptom severity rather than a confirmed clinical diagnosis and should therefore be interpreted with caution. Third, seasonal variation in serum vitamin D levels could not be adjusted for. Although vitamin D synthesis is highly dependent on seasonal sunlight exposure, the publicly available KNHANES dataset excludes the specific month of examination to protect participant anonymity. The inability to control for the season of blood collection may therefore have introduced residual confounding. Finally, the analysis was restricted to the 2022 dataset because it was the only recent cycle that simultaneously provided data on both mental health instruments and serum vitamin D. Although this restriction ensured high data completeness, it precluded multi-year pooled analyses and limited the assessment of long-term trends and larger subgroup analyses. This reliance on a single-year dataset also resulted in a small number of psychological distress cases among older adults, limiting the precision of the age-stratified estimates.

Implications/future research

Despite these limitations, the findings may help inform public health strategies related to mental health. In particular, higher unadjusted prevalences of psychological distress and anxiety were observed among women and adults aged 19–64 years, groups in which vitamin D deficiency is common. Maintaining adequate vitamin D status could be considered as one supportive component of comprehensive mental health management, although these cross-sectional findings do not establish causality. Future longitudinal studies are needed to clarify temporality and the potential causal relationship between vitamin D deficiency and mental health outcomes. Pooling multiple KNHANES cycles would also help secure adequate sample sizes across stratified groups, including older adults. This approach would clarify subgroup-specific associations and support the assessment of long-term trends.

Conclusion

In conclusion, this study identified a high prevalence of vitamin D deficiency among Korean adults, particularly in younger age groups. Although the association was attenuated in fully adjusted models, the unadjusted prevalence of psychological distress was higher among women with vitamin D deficiency. This pattern suggests a higher clinical burden in this subgroup despite the absence of a significant formal interaction. In age-stratified models, the association with psychological distress remained statistically significant after adjustment in adults aged 19–64 years and older adults aged ≥65 years, although the estimate for older adults was imprecise. These findings may support preventive strategies in clinical and public health settings. Given the higher burden observed in these subgroups, maintaining adequate vitamin D levels could be considered as an adjunctive component of mental health support.

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Conceptualization: MB, Hyunah Kim. Investigation: MB, JJ, Hyojung Kang, Hyunah Kim. Methodology: MB, JJ, Hyojung Kang, Hyunah Kim. Supervision: Hyunah Kim. Writing–original draft: MB, JJ, Hyojung Kang. Writing–review & editing: JJ, Hyunah Kim, Hyojung Kang. All authors read and approved the final manuscript.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

The raw data supporting the conclusions presented in this article will be made available by the authors upon request.

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None.

Supplementary materials

Supplementary materials can be found via https://doi.org/10.15747/ACNM.26.0047

Supplement 1. Subgroup analyses of the adjusted association between vitamin D deficiency and psychological distress by lifestyle and health-related factors. Adjusted odds ratios and 95% confidence intervals are shown on a logarithmic scale.

Supplement 2. Sensitivity analysis of the adjusted association between vitamin D deficiency and mental health outcomes using an obesity threshold of body mass index ≥30 kg/m^2.

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Original Article

Association between dysphagia diet intake at acute-care discharge and activities of daily living at discharge from a convalescent rehabilitation ward: a single-center retrospective cohort study in Japan

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Abstract

Purpose: This study examined whether intake of a dysphagia diet at acute-care discharge was associated with activities of daily living (ADL) at discharge from a convalescent rehabilitation ward among older orthopedic patients.
Methods: This retrospective study included patients aged ≥65 years admitted to a convalescent rehabilitation ward between January 2019 and April 2024. Patients with pharyngeal or esophageal dysphagia were excluded. The exposure was dysphagia diet intake at acute-care discharge. Motor Functional Independence Measure (FIM) score at rehabilitation discharge was analyzed using multivariable linear regression adjusted for age, admission motor FIM score, and cognitive function. Nutritional indicators at rehabilitation admission were compared between groups, and reasons for diet modification during acute care were summarized.
Results: Among 300 patients, 74 (24.7%) received a dysphagia diet at acute-care discharge. At rehabilitation admission, the dysphagia diet group had poorer nutritional and muscle-related status than the regular diet group. After adjustment, dysphagia diet intake was associated with a 3.41-point lower motor FIM score at discharge. Ill-fitting dentures were the most common reason for diet modification (33.8%); however, the reason was unclear in 27.0% of cases.
Conclusion: Among older orthopedic patients without pharyngeal or esophageal dysphagia, intake of a dysphagia diet at acute-care discharge was associated with lower ADL at discharge from a convalescent rehabilitation ward after adjustment for selected covariates. This finding should be interpreted as a clinical risk marker rather than evidence that clinically indicated dysphagia diets should be avoided. Early reassessment of diet modifications and correction of reversible oral conditions may help improve rehabilitation care.

Keywords: Activities of daily living; Diet; Malnutrition; Aged; Rehabilitation

Introduction

Background

As the global population ages, oral and nutritional health in older adults have become important public health issues [1]. According to the World Health Organization, compromised oral health, whether due to disease or other factors, can adversely affect overall health. Older adults are also at high risk of malnutrition and oral problems, underscoring the need for integrated oral and nutritional management [2].

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A dysphagia diet is designed for individuals with swallowing difficulties caused by impairments in the oral cavity, pharynx, or esophagus. Such diets typically involve modifications in texture and cohesiveness to support safe and efficient swallowing [3]. In a study of older inpatients in an acute-care hospital, approximately 38% required a dysphagia diet [4]. Although dysphagia diets may improve swallowing safety, they often have lower nutritional content because water is added and may be visually less appealing, which can reduce appetite and increase the risk of malnutrition [5,6].

In rehabilitation inpatients, malnutrition is associated with adverse outcomes, including declines in activities of daily living (ADL) [7]. Because dysphagia diets may exacerbate malnutrition, nutritional management is an important component of care for patients receiving such diets [8]. Healthcare professionals should also strive to create conditions that allow patients to maintain oral intake without relying on dysphagia diets. However, many patients in acute care remain hospitalized without appropriate oral management, even when they have oral problems [9]. Consequently, some patients receive dysphagia diets despite lacking absolute indications, such as pharyngeal dysphagia, that would limit their ability to consume regular food safely.

The effect of dysphagia diet intake at acute-care discharge on subsequent ADL during convalescent rehabilitation remains unclear among patients who lack absolute indications, such as pharyngeal dysphagia.

Objectives

This study aimed to examine the association between dysphagia diet intake at acute-care discharge and ADL at discharge among convalescent rehabilitation patients, excluding those with absolute indications for dysphagia diets during the acute-care hospital stay, such as pharyngeal dysphagia. We also investigated why patients received a dysphagia diet during the acute-care hospital stay despite lacking an absolute indication. Our findings may inform nutritional strategies, ADL improvement at discharge, and continuity of care across the transition from acute care to rehabilitation.

Methods

Study design and participants

This retrospective cohort study included patients aged ≥65 years who were admitted to a convalescent rehabilitation ward for musculoskeletal disorders between January 2019 and April 2024. We focused on musculoskeletal disorders because recovery in these patients is considered more strongly influenced by nutritional status than recovery in patients with cerebrovascular or neuromuscular diseases, which depends primarily on neurological function. The exclusion criteria were inability to obtain nutrition exclusively through oral intake at admission, admission motor Functional Independence Measure (FIM) score ≥65, Mini-Mental State Examination (MMSE) score <20 at admission, diagnosis of depression at admission, activity restrictions due to medical management, pharyngeal or esophageal dysphagia, dysphagia diets prescribed for gastrointestinal disorders, transfer or death due to clinical deterioration or other complications, and length of stay ≤14 days or ≥91 days [10]. Patients with a motor FIM score ≥65 at admission were excluded to account for potential ceiling effects [11]. Although some of these patients might still have poor nutritional status, their baseline functional independence was already high, which limited the ability to accurately assess the effect of dietary modifications on motor FIM score at rehabilitation discharge. MMSE score and depression status were included because of their substantial influence on motor FIM score at discharge. A key feature of the study design was the exclusion of patients with pharyngeal, esophageal, or gastrointestinal indications for a dysphagia diet.

Exposure

The exposure was defined as intake of a dysphagia diet at discharge from the acute-care hospital. A dysphagia diet was classified as levels 2–4 of the 2021 Japanese Society of Dysphagia Rehabilitation Classification of Dysphagia Diets [12]. Levels 0 and 1, which generally require alternative nutrition, were excluded. Diet type at acute-care discharge was confirmed from the acute-care hospital discharge summary or, if undocumented, by direct telephone inquiry.

Outcome

The primary outcome was the motor FIM score at discharge from the convalescent rehabilitation ward. The motor FIM score comprises 13 items covering self-care, sphincter control, transfers, and locomotion, each scored on a 7-point scale, with higher scores indicating greater independence [13]. FIM scores were determined by consensus among the attending physician, physical therapist, occupational therapist, speech-language pathologist, nurse, and care worker.

Other variables

Other variables assessed at admission to the convalescent rehabilitation ward included acute-care hospital length of stay, age, sex, primary diagnosis, MMSE score, grip strength, skeletal muscle mass index (SMI), motor FIM score, body mass index (BMI), Mini Nutritional Assessment–Short Form

(MNA-SF) score [14], and sarcopenia. SMI was measured in the supine position using bioelectrical impedance analysis (InBody S10, InBody Japan Inc.). Sarcopenia was diagnosed according to the 2019 Asian Working Group for Sarcopenia consensus criteria [15].

Ethics

This study was approved by the Ethics Committee of the Heisei Medical Welfare Group Research Institute (Approval No. 2023-01). The committee waived the requirement for individual informed consent and approved an opt-out method, whereby study information was disclosed publicly and participants had the opportunity to decline participation.

Statistical analysis

Descriptive statistics were used to summarize the data. Continuous variables were expressed as medians with interquartile ranges (IQRs) because of their non-normal distribution. Categorical variables were presented as numbers and percentages. Missing data were handled using available-case analysis; patients were excluded only from analyses for which their data were missing. Patients were classified into dysphagia diet and regular diet groups according to diet type at acute-care hospital discharge. Group comparisons were performed using the Mann-Whitney U test for continuous variables and the Fisher exact test for categorical variables.

Multivariable linear regression analysis was performed to examine whether dysphagia diet intake at acute-care discharge was independently associated with motor FIM score at discharge. The dependent variable was motor FIM score at discharge, and the covariates—age, motor FIM score at admission, and MMSE score at admission—were selected based on a directed acyclic graph representing plausible causal relationships (Model 1) (Fig. 1). As sensitivity analyses for unmeasured baseline confounding, additional models (Models 2–4) were developed by progressively adjusting for MNA-SF score and handgrip strength. Multicollinearity was assessed using variance inflation factors (VIFs). All VIF values were below 5.0, indicating no evidence of serious multicollinearity. Descriptive comparisons of nutritional status at admission, reasons for dysphagia diet use during the acute-care hospital stay, and clinical course during the convalescent period were performed between groups. EZR (version 4.2.3; Jichi Medical University, Tochigi, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used for the analyses [16]. EZR is a modified version of R Commander with additional statistical functions commonly used in biostatistics. Two-sided P <0.05 was considered statistically significant.

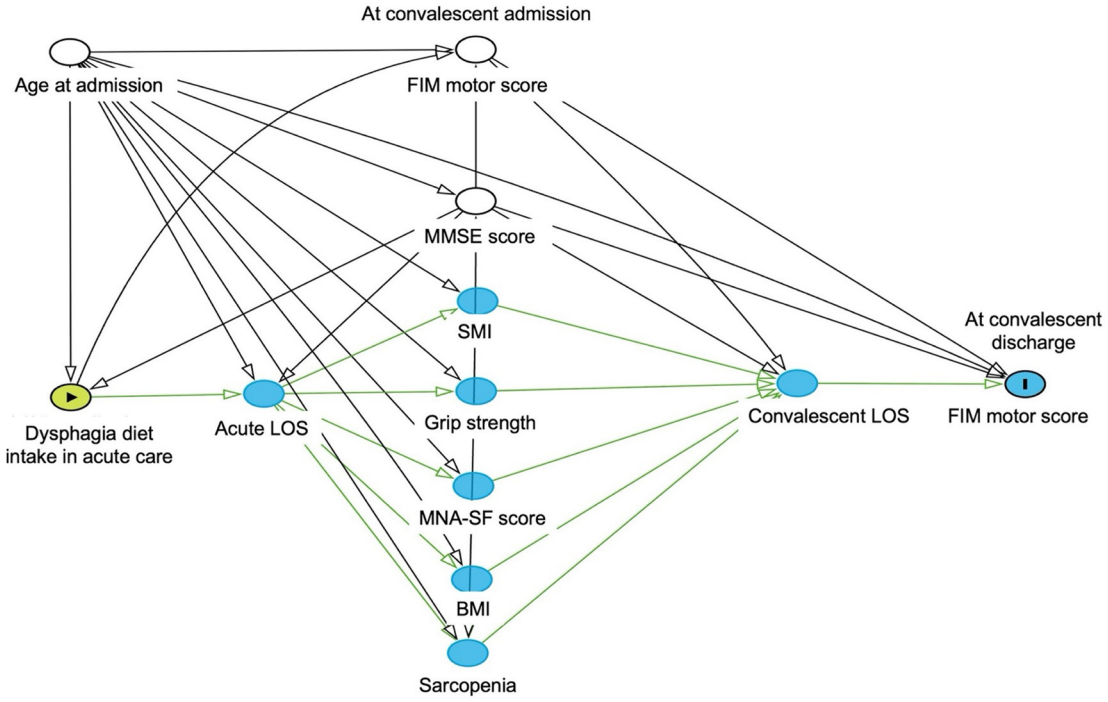

Fig. 1. Directed acyclic graph illustrating the presumed relationships among acute-care dysphagia diet intake, baseline characteristics, nutritional status, and functional outcome at discharge. FIM, Functional Independence Measure; MMSE, Mini-Mental State Examination; SMI, skeletal muscle mass index; MNA-SF, Mini Nutritional Assessment–Short Form; BMI, body mass index; LOS, length of stay.

Results

During the study period, 859 patients met the inclusion criteria. Of these, 559 were excluded based on the predefined criteria, leaving 300 patients (68 [22.7%] males and 232 [77.3%] females) for the final analysis (Fig. 2). The median age of the participants was 86.0 years (IQR, 81.0–89.0 years). The primary diagnoses were femoral fracture (n=163, 54.3%), thoracolumbar vertebral fracture (n=85, 28.3%), and other musculoskeletal disorders (n=52, 17.3%). Among the patients, 74 (24.7%) received a dysphagia diet at acute-care discharge, whereas 226 (75.3%) received a regular diet. The median acute-care hospital length of stay was 31.5 days (IQR, 23.8–41.3 days) in the dysphagia diet group and 28.0 days (IQR, 20.0–39.0 days) in the regular diet group. Table 1 presents the patient characteristics at admission to the convalescent rehabilitation ward.

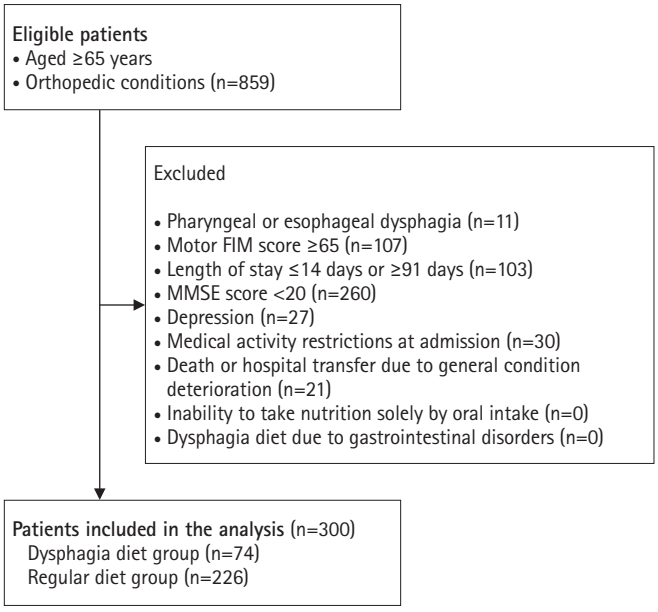

Fig. 2. Flowchart of the patient selection process. A total of 859 eligible patients aged ≥65 years with orthopedic conditions were screened. After applying the exclusion criteria, 300 patients were included in the final analysis (74 in the dysphagia diet group and 226 in the regular diet group). FIM, Functional Independence Measure; MMSE, Mini-Mental State Examination.

Comparison of nutritional status

At admission, participants in the dysphagia diet group had a significantly lower BMI (median, 19.01 kg/m^2; IQR, 17.07–21.59 kg/m^2) than those in the regular diet group (median, 20.55 kg/m^2; IQR, 18.05–22.63 kg/m^2; P=0.002), as well as a lower MNA-SF score (median: 4.0 [IQR, 3.0–6.0] vs. 5.0 [IQR, 4.0–7.0]; P=0.019). Handgrip strength was also lower in the dysphagia diet group (median, 14.20 kg; IQR, 12.20–18.80 kg) than in the regular diet group (median, 16.50 kg; IQR, 13.50–20.40 kg; P=0.019). Similarly, SMI was lower in the dysphagia diet group (median, 5.40 kg/m^2; IQR, 4.75–6.10 kg/m^2) than in the regular diet group (median, 5.70 kg/m^2; IQR, 5.10–6.70 kg/m^2; P=0.005). The prevalence of sarcopenia was higher in the dysphagia diet group (67.2%) than in the regular diet group (55.2%), although the difference was not statistically significant (P=0.089) (Table 2).

Association between dysphagia diet intake and motor FIM score

In univariable analyses, dysphagia diet intake at acute-care discharge was significantly associated with lower motor

Table 1. Patient characteristics at admission to the convalescent ward

Variable	Overall (n=300)	Dysphagia diet group (n=74)	Regular diet group (n=226)	P-value
Age (yr)	86.0 (81.0–89.0)	88.0 (82.3–90.0)	86.0 (81.0–89.0)	0.034
Sex				0.874
Male	68 (22.7)	16 (21.6)	52 (23.0)	
Female	232 (77.3)	58 (78.4)	174 (77.0)	
Disease				0.842
Hip fracture	163 (54.3)	41 (55.4)	122 (54.0)	
Thoracic or lumbar fracture	85 (28.3)	22 (29.7)	63 (27.9)	
Others	52 (17.3)	11 (14.9)	41 (18.1)	
CCI (point)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.799
Acute care LOS (day)	29.0 (21.0–40.0)	31.5 (23.8–41.3)	28.0 (20.0–39.0)	0.086
FIM motor score (point)	48.5 (39.0–56.0)	45.0 (36.3–53.8)	49.0 (40.3–57.0)	0.014
MMSE score (point)	26.0 (23.0–28.0)	25.0 (23.0–28.0)	26.0 (23.0–28.0)	0.464

Values are presented as median (interquartile range) or number (%).
CCI, Charlson Comorbidity Index; LOS, length of stay; FIM, Functional Independence Measure; MMSE, Mini-Mental State Examination.
P<0.05 was considered statistically significant.

FIM scores at discharge (Table 3). In multivariable linear regression analysis, dysphagia diet intake at acute-care discharge remained associated with lower motor FIM scores at discharge from the convalescent rehabilitation ward after adjustment for age, motor FIM score at admission, and MMSE score (β, –3.41; 95% confidence interval [CI], –5.55 to –1.28; P=0.002) (Model 1). This association persisted in sensitivity analyses that further adjusted for MNA-SF score and handgrip strength (Models 2–4) (Table 4).

Reasons for dysphagia diet intake at the acute-care hospital and clinical course during convalescent rehabilitation

The most common reason for dysphagia diet intake at acute-care discharge was ill-fitting dentures (n=25, 33.8%), followed by unclear reasons (n=20, 27.0%), patient preference (n=12, 16.2%), non-dental intraoral problems (e.g., mucosal abnormalities) (n=11, 14.9%), and poor general condition (n=6, 8.1%). During the convalescent rehabilitation, nine of 25 patients (36.0%) who received a dysphagia diet because of ill-fitting dentures were able to transition to a regular diet after dental intervention. The remaining patients continued to have denture-related problems and were unable to resume a regular diet. Of the 11 patients with other intraoral problems, six (54.5%) transitioned to a regular diet during the convalescent period. Among the 20 patients for whom the reason for dysphagia diet provision was unclear, 18 (90.0%) resumed a regular diet within 1 week of admission, whereas the remaining two continued receiving a dysphagia diet because of personal preference.

Discussion

Key results

Among patients without absolute indications for a dysphagia diet, such as pharyngeal or esophageal dysphagia, dysphagia diet intake at acute-care discharge was significantly associated with lower motor FIM scores at discharge from the convalescent rehabilitation ward. These patients also had poorer nutritional status at admission to the convalescent rehabilitation ward than those receiving a regular diet. The most common reason for dysphagia diet provision

Table 2. Comparison of nutritional indices between groups at admission to the convalescent ward

Variable	Overall (n=300)	Dysphagia diet group (n=74)	Regular diet group (n=226)	P-value
BMI (kg/m^2)	20.10 (17.71–22.50)	19.01 (17.07–21.59)	20.55 (18.05–22.63)	0.002
MNA-SF score	5.0 (3.0–7.0)	4.0 (3.0–6.0)	5.0 (4.0–7.0)	0.019
Grip strength (kg)	16.30 (13.1–20.0)	14.20 (12.20–18.80)	16.50 (13.50–20.40)	0.019
SMI (kg/m^2)	5.60 (5.00–6.60)	5.40 (4.75–6.10)	5.70 (5.10–6.70)	0.005
Sarcopenia	157 (58.1)	45 (67.2)	112 (55.2)	0.089

Values are presented as median (interquartile range) or number (%). Data availability differed across variables due to missing data: BMI (n=299), MNA-SF (n=300), grip strength (n=284), SMI (n=267), sarcopenia (n=270).
BMI, body mass index; MNA-SF, Mini Nutritional Assessment–Short Form; SMI, skeletal muscle mass index.
P<0.05 was considered statistically significant.

Table 3. Univariable regression analyses for FIM motor score at discharge

	No.	β (95% CI)	P-value
Dysphagia diet at acute-care discharge	300	–5.52 (–8.16 to –2.88)	<0.001
Age	300	–0.30 (–0.47 to –0.12)	<0.001
Sex	300	1.10 (–1.69 to 3.90)	0.440
FIM motor score	300	0.58 (0.49 to 0.66)	<0.001
MMSE score	300	1.14 (0.77 to 1.51)	<0.001
SMI	267	0.60 (–0.49 to 1.69)	0.280
Grip strength	284	0.52 (0.32 to 0.73)	<0.001
MNA-SF score	300	0.52 (–0.07 to 1.11)	0.086
BMI	299	0.07 (–0.26 to 0.39)	0.690
Sarcopenia	270	–1.18 (–3.71 to 1.35)	0.360
Acute care LOS	249	–0.07 (–0.14 to 0.01)	0.086

FIM, Functional Independence Measure; β, unstandardized regression coefficient; CI, confidence interval; MMSE, Mini-Mental State Examination; SMI, skeletal muscle mass index; MNA-SF, Mini Nutritional Assessment–Short Form; BMI, body mass index; LOS, length of stay.
P<0.05 was considered statistically significant.

Table 4. Multivariable regression models for FIM motor score at discharge

	Model 1 (n=300)		Model 2 (n=300)		Model 3 (n=284)		Model 4 (n=284)	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Dysphagia diet at acute-care discharge	−3.41 (−5.55 to −1.28)	0.002	−3.43 (−5.58 to −1.28)	0.002	−3.22 (−5.38 to −1.06)	0.004	−3.28 (−5.46 to −1.11)	0.003
Age	−0.10 (−0.24 to 0.04)	0.140	−0.10 (−0.24 to 0.04)	0.145	−0.10 (−0.25 to 0.04)	0.171	−0.10 (−0.25 to 0.05)	0.180
FIM motor score	0.51 (0.42 to 0.60)	<0.001	0.51 (0.42 to 0.60)	<0.001	0.49 (0.40 to 0.59)	<0.001	0.49 (0.40 to 0.59)	<0.001
MMSE score	0.36 (0.02 to 0.69)	0.040	0.36 (0.02 to 0.70)	0.038	0.32 (−0.02 to 0.66)	0.067	0.34 (−0.01 to 0.69)	0.057
MNA-SF score	NA	NA	−0.03 (−0.51 to 0.45)	0.896	NA	NA	−0.13 (−0.63 to 0.36)	0.600
Grip strength	NA	NA	NA	NA	0.12 (−0.06 to 0.30)	0.185	0.13 (−0.05 to 0.31)	0.168

The models were adjusted as follows: Model 1: Adjusted for dysphagia diet, age, admission FIM motor score, and MMSE score; Model 2: Adjusted for the variables in Model 1 plus the MNA-SF score; Model 3: Adjusted for the variables in Model 1 plus grip strength; Model 4: Adjusted for all variables listed in the table.
FIM, Functional Independence Measure; β, unstandardized regression coefficient; CI, confidence interval; MMSE, Mini-Mental State Examination; MNA-SF, Mini Nutritional Assessment–Short Form; NA, not applicable.
P<0.05 was considered statistically significant.

was ill-fitting dentures. In 27.0% of cases, the rationale for dysphagia diet provision during the acute-care hospital stay was unclear. Many of these patients transitioned to a regular diet immediately after admission to rehabilitation, suggesting that some restrictive diets may have been implemented as a precautionary measure or may have been avoidable with comprehensive nutritional assessment, including assessment of oral health status. Although the adjusted difference in discharge motor FIM score was modest, even small differences in functional independence at discharge may affect subsequent care needs, rehabilitation planning, and long-term outcomes in older adults.

Interpretation/comparison with previous studies

Our findings are consistent with the hypothesis that malnutrition may partly explain the association between dysphagia diet intake and reduced ADL at discharge. Malnutrition during acute hospitalization increases the risk of hospitalization-associated disability, defined as newly developed or worsened ADL impairment during hospitalization [17,18]. Previous studies in rehabilitation inpatients have reported associations between malnutrition and lower FIM scores at 21 days [19] and between low energy intake and poorer efficiency in motor FIM improvement [20]. Although nutritional status at admission to the convalescent rehabilitation ward was modeled as a mediator in the directed acyclic graph between the exposure and discharge FIM scores in our study, our findings are consistent with previous reports linking malnutrition to lower ADL among patients undergoing inpatient rehabilitation [7,19]. In the present study, dysphagia diets were generally lower in energy content than regular diets and were therefore considered the exposure variable rather than direct indicators of malnutrition. This study differs from previous studies because intake of a dysphagia diet, a potential contributor to malnutrition, was defined as the exposure rather than malnutrition indicators themselves. By excluding patients with pharyngeal or esophageal dysphagia, we focused on cases in which dysphagia diets might be avoidable through preventive or supportive measures, such as denture adjustment, potentially broadening opportunities for intervention. Several mechanisms may explain the association between dysphagia diets and lower motor FIM scores at discharge through malnutrition. These diets often have higher water content to soften food and improve bolus cohesion [5,6,8], resulting in lower nutrient density and larger intake volumes to meet energy needs, which can be challenging for older adults [21]. In addition, the reduced visual appeal of such diets may reduce appetite, further increasing the risk of malnutrition [5,8,22-25]. Dysphagia diets are a form of dietary restriction and should therefore be avoided when possible and carefully monitored when implemented. These recommendations are included in the hospital nutrition guidelines published by the European Society for Clinical Nutrition and Metabolism [21]. Malnutrition is also a known contributor to loss of muscle mass and strength [26]. In our study, patients receiving dysphagia diets had lower grip strength and SMI at admission to the convalescent rehabilitation ward, supporting the hypothesis that such diets may contribute to nutritional deterioration and subsequent functional decline.

Clinical significance

Although the adjusted difference in discharge motor FIM score was modest (3.41 points) and did not reach the established minimal clinically important difference of 19–22 points for older orthopedic patients [27,28], even small differences in functional independence at discharge may affect subsequent care needs, rehabilitation planning, and long-term outcomes in older adults by increasing the level of assistance required.

Limitations

This study has several limitations. First, dysphagia diet provision at acute-care discharge was determined from referral documents or verified by telephone, and the exact duration of dysphagia diet intake was unknown. Short durations may have had minimal effects, yet the observed negative association persisted even when such cases were included. Second, unmeasured confounding, such as overall physical condition during acute care, may have influenced the results. Nonetheless, given that many patients receiving dysphagia diets had oral problems, the association remains clinically plausible. These findings suggest that the observed association was not fully explained by measured nutritional and physical status. Nevertheless, residual confounding by pre-existing frailty, malnutrition, oral health status, and acute illness severity cannot be excluded. Furthermore, the lack of standardized swallowing and oral assessments during acute care limited our ability to determine the precise indications for diet modifications. Finally, the single-center design limits generalizability to other rehabilitation settings. In addition, excluding patients with an MMSE score <20 and depression limits the generalizability of our findings to broader clinical populations, as cognitive impairment and mood disorders are prevalent in rehabilitation settings. Because this was an observational study, the findings demonstrate an association rather than causation.

Clinical implications

We do not imply that clinically necessary dysphagia diets for swallowing safety should be avoided; rather, their prescription in this specific population should serve as a trigger for comprehensive dental and nutritional reassessment.

Conclusion

This study showed that dysphagia diet intake during the acute-care hospital stay among older orthopedic patients was associated with poorer ADL at discharge from the convalescent rehabilitation ward. This association may reflect dysphagia diets prompted by modifiable factors, such as poor oral health, or by other transient clinical factors that do not require long-term dietary restriction. Therefore, prescription of a dysphagia diet in this population should be interpreted as a marker of underlying, often modifiable vulnerability that warrants comprehensive assessment. Prospective studies are needed to determine whether proactive oral care and systematic nutritional assessment can prevent potentially avoidable dietary restrictions and improve ADL at discharge in older acute-care patients. Accordingly, addressing underlying causes through comprehensive assessment rather than relying solely on dietary modification is essential for improving ADL at discharge.

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Authors' contribution

Conceptualization: MA, KS, NS. Data curation: MA. Formal analysis: MA, KS. Investigation: MA. Methodology: MA, KS. Supervision: NS. Writing–original draft: MA. Writing–review & editing: KS, NS. All authors read and approved the final manuscript.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request but are not publicly available because of privacy and ethical restrictions.

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Supplementary materials

None.

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Original Article

Association of early parenteral energy provision with serum phosphorus decline and phosphorus-based refeeding syndrome in critically ill patients with liver cirrhosis: a Korean retrospective observational study

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Abstract

Purpose: Critically ill patients with liver cirrhosis are vulnerable to malnutrition and refeeding-related electrolyte disturbances, particularly with rapid caloric advancement. As hypophosphatemia is a key feature of refeeding syndrome (RFS) and phosphorus homeostasis may be impaired in cirrhosis, the association of early parenteral energy provision with serum phosphorus decline and RFS was evaluated in cirrhotic ICU patients.

Methods: This retrospective study included 72 adults with liver cirrhosis admitted to a tertiary intensive care unit (ICU) between January 2021 and August 2024. Parenteral energy intake was assessed at emergency department (ED) and on ICU days 1 and 2. Serum phosphorus reduction was defined as the percentage decrease from baseline to the nadir within 5 ICU days. Phosphorus-based RFS was defined per the 2020 ASPEN consensus as a ≥10% phosphorus decrease after reinitiating or increasing energy provision, graded as mild, moderate, or severe.

Results: Phosphorus-based RFS occurred in 53 patients (73.6%), including severe RFS in 35 (48.6%). ICU day 2 caloric intake per body weight correlated with phosphorus reduction (r=0.346, P=0.003) and was independently associated with greater decline (P=0.011) and with meeting RFS criteria (odds ratio, 1.19; 95% CI, 1.06–1.36; P=0.007), along with ED glucose load (P=0.001). Receiver operating characteristic analysis showed modest discrimination (area under the curve, 0.7061; cutoff, 10.92 kcal/kg/day).

Conclusion: Higher caloric delivery on ICU day 2 was associated with greater phosphorus decline and RFS in cirrhotic ICU patients. These exploratory associations do not establish causality, and the cutoff requires external validation. Monitoring caloric delivery and serial electrolytes may support safer parenteral nutrition.

Keywords: Refeeding syndrome; Hypophosphatemia; Nutritional support; Parenteral nutrition; Liver cirrhosis

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Introduction

Background

Refeeding syndrome (RFS) is a serious and potentially life-threatening complication that occurs when nutrition is reintroduced after a period of malnutrition, particularly when feeding is initiated rapidly or inappropriately [1,2]. The hallmark of RFS is an abrupt decline in serum phosphorus, accompanied by shifts in potassium, magnesium, and glucose levels, which can lead to cardiac, respiratory, and neurological complications [3-5].

Malnutrition and electrolyte disturbances are common in critically ill patients with liver cirrhosis. Cirrhosis is associated with impaired metabolic homeostasis and nutrient absorption, which may contribute to nutritional imbalance during critical illness [1,2]. In patients with advanced cirrhosis, depleted hepatic glycogen stores and persistent hypermetabolism may create an accelerated starvation state, providing biological plausibility for abrupt metabolic shifts when nutrition is reintroduced [6]. In addition, cirrhosis-related sarcopenia, characterized by impaired muscle protein synthesis and altered energy metabolism, may reduce peripheral nutrient utilization capacity, whereas chronic inflammation and endotoxemia may accelerate muscle catabolism and contribute to progressive micronutrient depletion [2,4]. These cirrhosis-related metabolic derangements are presented as background rationale and biological plausibility, not as findings of the present study. Because this study did not include a noncirrhotic critically ill comparator group, it was not designed to determine whether patients with cirrhosis are more susceptible to RFS than other intensive care unit (ICU) populations.

In the ICU, total parenteral nutrition (TPN) is commonly used in patients with liver cirrhosis when enteral feeding is not feasible [7,8]. However, aggressive caloric administration through TPN, particularly early after ICU admission, has been associated with refeeding-related electrolyte disturbances in previous studies [9,10]. Although RFS is recognized as a clinical entity, empirical evidence specifically evaluating the temporal relationship between caloric intake and phosphorus-based RFS in patients with cirrhosis admitted to the ICU remains limited [4,7]. Previous investigations of refeeding complications in ICU settings have primarily examined heterogeneous critically ill cohorts, in which cirrhosis subgroups were underrepresented or evaluated only secondarily [11]. Furthermore, the optimal rate and timing of energy provision to reduce refeeding-related electrolyte disturbances in patients with cirrhosis remain unclear [4,7,8]. Recent American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend cautious caloric advancement in patients with malnutrition or refeeding risk [4,7,8]; however, practical applications and supporting data for patients with liver cirrhosis remain sparse.

The early refeeding period is clinically important because phosphorus nadirs associated with refeeding-related metabolic shifts typically occur within the first 24–72 hours of refeeding. Evaluating early caloric load and its temporal association with phosphorus decline may therefore provide preliminary information to support safer nutritional management in patients with cirrhosis admitted to the ICU and receiving TPN.

Objectives

This study aimed to evaluate the association of early parenteral caloric intake with serum phosphorus changes, phosphorus-based RFS occurrence, and RFS severity in patients with liver cirrhosis admitted to the ICU.

Methods

Study design and population

This retrospective observational study included 72 adult patients with liver cirrhosis who were admitted to the medical ICU of a tertiary referral hospital between January 2021 and August 2024. All patients were admitted to the ICU via the emergency department (ED) because of acute decompensation; the main reasons for ICU admission were upper gastrointestinal bleeding, such as hematemesis; altered mental status, including hepatic encephalopathy or coma; and clinically significant ascites. Eligible patients were adults with liver cirrhosis who had early parenteral energy exposure through intravenous glucose-containing fluids and/or parenteral nutrition (PN)/TPN during the early phase of ICU admission and had available serial serum phosphorus measurements and nutritional intake records. Patients were excluded if they had baseline electrolyte imbalance involving phosphorus, potassium, or magnesium; missing electrolyte data; death within 48 hours after ICU admission; or transfer to hospice.

Patients were screened retrospectively from the electronic medical records of adults with liver cirrhosis who were admitted to the medical ICU via the ED during the study period. The final analytic cohort consisted of patients who met the eligibility criteria and had available serial serum phosphorus measurements and early nutritional intake records. In total, 114 adults with decompensated liver cirrhosis who were admitted to the ICU via the ED during the study period were

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screened for eligibility. Of these, 42 were excluded because of initial electrolyte imbalance involving phosphorus, potassium, or magnesium (n=18), missing electrolyte data for phosphorus, potassium, or magnesium (n=21), death within 48 hours (n=1), or transfer to hospice (n=2), leaving 72 patients in the final analysis. The patient selection process is summarized in the study flow diagram (Fig. 1).

Data collection

Electronic medical records were retrospectively reviewed to obtain demographic and clinical data, including age, sex, height, weight, body mass index (BMI), serum laboratory parameters, and nutrition-related variables.

For exposure classification, intravenous glucose was defined as any glucose-containing intravenous fluid, including 5% dextrose solution, 10% dextrose solution, Hartmann's solution with dextrose, and the glucose component of TPN. PN was defined as parenteral nutrient delivery provided through intravenous formulations containing macronutrients. TPN was defined as a formal PN formulation prescribed as the main nutritional support and containing glucose, amino acids, and/or lipid. In this study, early parenteral energy exposure included intravenous glucose-containing fluids and/or PN/TPN.

Energy intake was calculated as kcal/day and kcal/kg and was assessed at three time points: the day of ED presentation, ICU day 1, and ICU day 2. Nutrition-related variables included the timing of glucose administration, timing of formal TPN initiation, total caloric intake on ICU day 1, percentage of the estimated energy requirement delivered on ICU day 1, total caloric intake on ICU day 2, percentage of the estimated energy requirement delivered on ICU day 2, and thiamine administration.

Potential nonrefeeding determinants of serum phosphorus levels, including renal replacement therapy, diuretic use, and phosphate supplementation during the first 5 ICU days, were also reviewed from the electronic medical records. However, because the timing, cumulative dose, indications, and temporal relationship of these interventions to serum phosphorus measurements were not consistently structured in the retrospective records, they could not be incorporated as fully adjusted covariates in the primary multivariable models.

Baseline nutritional assessment variables included BMI, the Nutrition Risk Screening 2002 (NRS-2002)-based initial nutritional risk assessment, and reduced dietary intake within 2 weeks before admission when available. However, comprehensive nutritional assessment tools, such as the Subjective Global Assessment (SGA) and Global Leadership Initiative on Malnutrition (GLIM) criteria, recent weight loss, and formal malnutrition diagnoses were not systematically documented in the electronic medical records and therefore could not be consistently incorporated into the primary analyses.

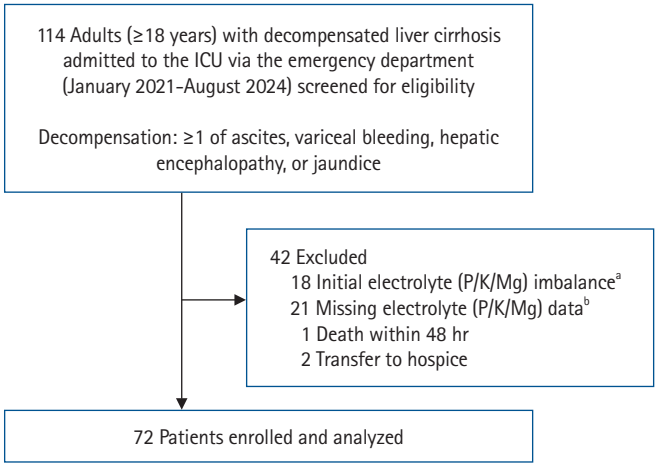

Fig. 1. Flow diagram of patient selection. A total of 114 adults with decompensated liver cirrhosis who were admitted to the ICU via the emergency department between January 2021 and August 2024 were screened. After 42 patients were excluded, 72 patients were included in the final analysis. ICU, intensive care unit. [a]Initial hyperphosphatemia or hypophosphatemia, hyperkalemia or hypokalemia, or hypermagnesemia or hypomagnesemia; [b]Missing initial test, or missing follow-up test within 5 days of ICU admission.

Definition of outcomes

The primary outcome was serum phosphorus reduction, defined as the percentage decrease from the baseline phosphorus level at ED presentation to the lowest value recorded within the first 5 days of ICU admission. The secondary outcome was whether patients met the phosphorus-based RFS criterion. According to the 2020 ASPEN consensus recommendations, RFS is defined as a decrease in serum phosphorus, potassium, and/or magnesium of 10%–20%, 20%–30%, or >30% within 5 days after reinitiating or substantially increasing energy provision, corresponding to mild, moderate, or severe RFS, respectively. Severe RFS may also be supported by organ dysfunction attributable to electrolyte decreases or by thiamine deficiency. In the present retrospective study, phosphorus-based RFS was operationalized using only the serum phosphorus component of the ASPEN criteria because the study aim focused on phosphate decline and phosphorus was the only electrolyte measured serially and consistently across all patients during the predefined 5-day observation window. Therefore, phosphorus-based RFS occurrence was

defined as a ≥10% decrease in serum phosphorus from the ED baseline to the nadir within 5 ICU days, and severity was classified as mild (10%–20% decrease), moderate (20%–30% decrease), or severe (>30% decrease). Potassium and magnesium values were reviewed as part of routine clinical care when available, but they were not used as independent diagnostic triggers in the primary RFS classification because serial availability was incomplete. Clinical manifestations and organ dysfunction were not used as mandatory diagnostic criteria because attribution to RFS could not be reliably determined from retrospective records in this critically ill population. Thus, the phosphorus-based RFS outcome in this study should be interpreted as an operational definition derived from the serum phosphorus component of the ASPEN framework, rather than as a full ASPEN classification using all three electrolytes and clinical criteria.

Statistical analysis

Continuous variables were presented as means±standard deviations or medians with interquartile ranges (IQRs), as appropriate, and categorical variables were presented as counts and percentages. Linear regression analysis was performed to evaluate the association between candidate predictors and serum phosphorus reduction (%). Logistic regression analysis was used to assess factors associated with meeting the phosphorus-based RFS criterion.

To reduce the risk of model overfitting, variables included in the multivariable models were selected a priori based on clinical relevance and the study hypothesis rather than through data-driven stepwise selection. The selected variables focused on early glucose exposure, timing of formal TPN initiation, and ICU day 1 and ICU day 2 caloric delivery, which were considered clinically relevant to early refeeding-related electrolyte changes. Because only 19 patients did not meet the phosphorus-based RFS criterion, the logistic regression model was considered susceptible to overfitting. Therefore, the multivariable logistic regression results were interpreted as exploratory and hypothesis-generating rather than confirmatory.

Renal replacement therapy, diuretic exposure, and phosphate supplementation were treated as clinically important determinants of serum phosphorus levels and were reviewed descriptively. However, these variables were not included as fully adjusted covariates in the primary regression models because their timing, cumulative dose, indications, and temporal relationship with the phosphorus nadir were inconsistently documented in the retrospective records. Accordingly, the observed associations should not be interpreted as causal effects of caloric delivery on serum phosphorus decline or phosphorus-based RFS status.

Thiamine administration was collected descriptively but was not included in the primary adjusted models because it was not protocol-driven, may have been influenced by clinician-perceived RFS risk, and could have introduced confounding by indication. Statistical significance was set at a two-sided $P < 0.05$. Statistical analyses were performed using R software (version 4.5.3; R Foundation for Statistical Computing).

Ethical considerations

The study protocol was reviewed and approved by the Institutional Review Board of Kosin University Gospel Hospital (IRB No. KUGH 2026-02-010). The requirement for informed consent was waived because of the retrospective design and use of deidentified data. All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. This manuscript follows the recommendations of the International Committee of Medical Journal Editors, the Committee on Publication Ethics, and the Guidelines on Good Publication Practice issued by the Korean Association of Medical Journal Editors.

Results

Baseline characteristics

A total of 114 adults with decompensated liver cirrhosis who were admitted to the ICU via the ED were screened. After 42 patients were excluded, 72 patients were included in the final analysis (Fig. 1). The median age was 61.0 years (IQR, 54.0–71.0 years), and 49 patients (68.1%) were men. The median BMI was 23.12 kg/m^2 (IQR, 20.76–25.69 kg/m^2), with nine patients (12.5%) having a BMI <18.5 kg/m^2 and two patients (2.8%) having a BMI <16 kg/m^2. The median Model for End-Stage Liver Disease (MELD) score was 21.0 (IQR, 14.0–24.25), and the median time from ED arrival to ICU admission was 6.98 hours (IQR, 4.41–15.68) (Table 1).

Regarding liver disease etiology, alcohol-related cirrhosis was the most common cause and was observed in 40 patients (55.6%). Hepatocellular carcinoma was present in 28 patients (38.9%), and 58 patients (80.6%) had comorbidities. The median percentage reduction in serum phosphorus was 29.68% (IQR, 8.45%–48.35%), and 53 patients (73.6%) met the phosphorus-based RFS criterion, including eight (11.1%) with mild, 10 (13.9%) with moderate, and 35 (48.6%) with severe cases based on serum phosphorus decline.

Regarding nutritional support variables, glucose was administered in the ED in 61 patients (84.7%), with a median ED

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glucose load of 0.40 g/kg (IQR, 0.00–0.61 g/kg) and 85.00 kcal (IQR, 0.00–106.25 kcal). TPN was initiated within 24 hours of ICU admission in 33 patients (45.8%) and after 24 hours in 36 patients (50.0%), whereas three patients (4.2%) received no formal TPN during the early ICU period. Thiamine supplementation was administered to 35 patients (48.6%). During the study period, thiamine administration was not governed by a standardized institutional protocol and was provided prophylactically or therapeutically at the discretion of the treating clinicians or nutrition support team according to perceived nutritional risk, clinical instability, alcohol-related liver disease, poor oral intake, or concern for refeeding-related electrolyte disturbance. The median total caloric intake was 835.00 kcal/day (IQR, 538.75–1,268.00 kcal/day) on ICU day 1 and 832.50 kcal/day (IQR, 734.25–1,197.75 kcal/day) on ICU day 2, whereas the median proportion of the estimated energy requirement delivered on ICU day 2 was 70.19% (IQR, 49.85%–89.94%). The median length of hospital stay was 12.0 days (IQR, 8.0–18.0 days), and in-hospital mortality occurred in 21 patients (29.2%).

Association between serum phosphorus reduction and early nutritional support

A significant positive correlation was observed between ICU day 2 caloric intake per body weight and the percentage reduction in serum phosphorus (Fig. 2). In the scatter plot analysis, the correlation coefficient was r=0.346, with an explanatory power of $R^2 = 0.120$, and the association was statistically significant (P=0.003, n=72).

ICU day 2 caloric intake per body weight differed signifi-

Table 1. Clinical and laboratory characteristics of the study population

Characteristics	Overall (n=72)
Demographics	
Age (yr)	61.00 (54.00–71.00)
Male sex	49 (68.1)
Height (cm)	167.00 (160.00–173.12)
Body weight (kg)	60.50 (55.60–74.00)
BMI (kg/m^2)	23.12 (20.76–25.69)
BMI <16.0 kg/m^2	2 (2.8)
BMI <18.5 kg/m^2	9 (12.5)
MELD score	21.00 (14.00–24.25)
Time from ED arrival to ICU admission (hr)	6.98 (4.41–15.68)
Etiology and comorbidities	
Alcohol-related liver cirrhosis	40 (55.6)
Hepatocellular carcinoma	28 (38.9)
Any comorbidity	58 (80.6)
Phosphorus-based RFS-related outcomes[a]	
Serum phosphorus decrease rate (%)	29.68 (8.45–48.35)
Phosphorus-based RFS criterion met	53 (73.6)
Mild phosphorus-based RFS	8 (11.1)
Moderate phosphorus-based RFS	10 (13.9)
Severe phosphorus-based RFS	35 (48.6)
Phosphorus-based RFS criterion not met	19 (26.4)
Nutritional assessment	
Initial nutritional screening	
Good nutritional status	22 (30.6)
At risk	41 (56.9)
High risk	9 (12.5)
Dietary intake in the preceding 2 wk	
≤30% of usual intake	60 (83.3)
30%–60% of usual intake	4 (5.6)
≥60% of usual intake	8 (11.1)
Nutritional support	
Timing of glucose initiation	
Timing of glucose administration (within 24 hr)	61 (84.7)
Timing of glucose administration (after 24 hr)	11 (15.3)
ED-1 glucose (g/kg)	0.40 (0.00–0.61)
ED-1 glucose (kcal)	85.00 (0.00–106.25)
Timing of TPN initiation	
Timing of formal TPN initiation (within 24 hr)	33 (45.8)
Timing of formal TPN initiation (after 24 hr)	36 (50.0)
No formal TPN during early ICU period	3 (4.2)
Nutrition delivery	
ICU day 1 total energy (kcal/day)	835.00 (538.75–1,268.00)
ICU day 1 energy adequacy (% of requirement)	67.81 (42.16–100.67)
ICU day 1 TPN amino acids (g/day)	34.20 (19.40–46.00)
ICU day 2 total energy (kcal/day)	832.50 (734.25–1,197.75)
ICU day 2 energy adequacy (% of requirement)	70.19 (49.85–89.94)
ICU day 2 TPN amino acids (g/day)	34.20 (31.33–47.00)
Thiamine supplementation	35 (48.6)
Outcomes	
Length of hospital stay (day)	12.00 (8.00–18.00)
Discharged	42 (58.3)
Transferred	7 (9.7)
In-hospital death	21 (29.2)
Other	2 (2.8)

Values are presented as median (interquartile range) or number (%).
BMI, body mass index; MELD, Model for End-Stage Liver Disease; ED, emergency department; ICU, intensive care unit; RFS, refeeding syndrome; TPN, total parenteral nutrition.
[a]Phosphorus-based RFS was operationally defined as a ≥10% decrease in serum phosphorus from baseline to nadir within 5 ICU days. Severity was classified according to the percentage decrease in serum phosphorus: mild, 10%–20%; moderate, 20%–30%; and severe, >30%.

cantly according to phosphorus-based RFS status (Table 2, Fig. 3). Patients who met the phosphorus-based RFS criterion received higher ICU day 2 energy delivery than those who did not meet the criterion (15.37±6.62 kcal/kg/day vs. 10.50±5.89 kcal/kg/day; P=0.005). This finding suggests that greater caloric delivery by ICU day 2 was associated with a higher likelihood of meeting the phosphorus-based RFS criterion.

Subsequent multivariable linear regression analysis identified ED glucose load (g/kg) and ICU day 2 kcal/kg/day as independent factors associated with the percentage reduction in serum phosphorus (Table 3). A higher ED glucose load was significantly associated with a greater reduction in serum phosphorus (β, 19.71; 95% confidence interval [CI], 7.94–31.47; P=0.001), and higher ICU day 2 kcal/kg/day was also significantly associated with greater serum phosphorus reduction (β, 1.32; 95% CI, 0.31–2.34; P=0.011). In contrast, the timing of ED glucose administration, TPN initiation, and ICU day 1 kcal/kg/day were not significantly associated with serum phosphorus reduction.

Because serum phosphorus concentrations in critically ill patients can be influenced by concurrent ICU interventions, the observed serum phosphorus decline should be interpreted in the context of potential nonrefeeding determinants. Renal replacement therapy, diuretic exposure, and phosphate supplementation were reviewed when available in the medical records; however, the timing and dose of these interventions relative to the phosphorus nadir were not consistently documented. Therefore, the observed association between early caloric delivery and serum phosphorus reduction should be interpreted as exploratory rather than as evidence of a direct causal effect.

Association between phosphorus-based RFS occurrence and early nutritional support

Comparison of ICU day 2 kcal/kg between patients who did and did not meet the phosphorus-based RFS criterion showed that caloric intake on ICU day 2 was significantly higher in the phosphorus-based RFS group than in the non-phosphorus-based RFS group (15.37±6.62 kcal/kg/day vs. 10.50±5.89 kcal/kg/day, respectively) (Table 2, Fig. 3). This difference was statistically significant in Welch's t-test (t=2.994, df=35.47, P=0.005), with a 95% CI for the mean difference of 1.57–8.18.

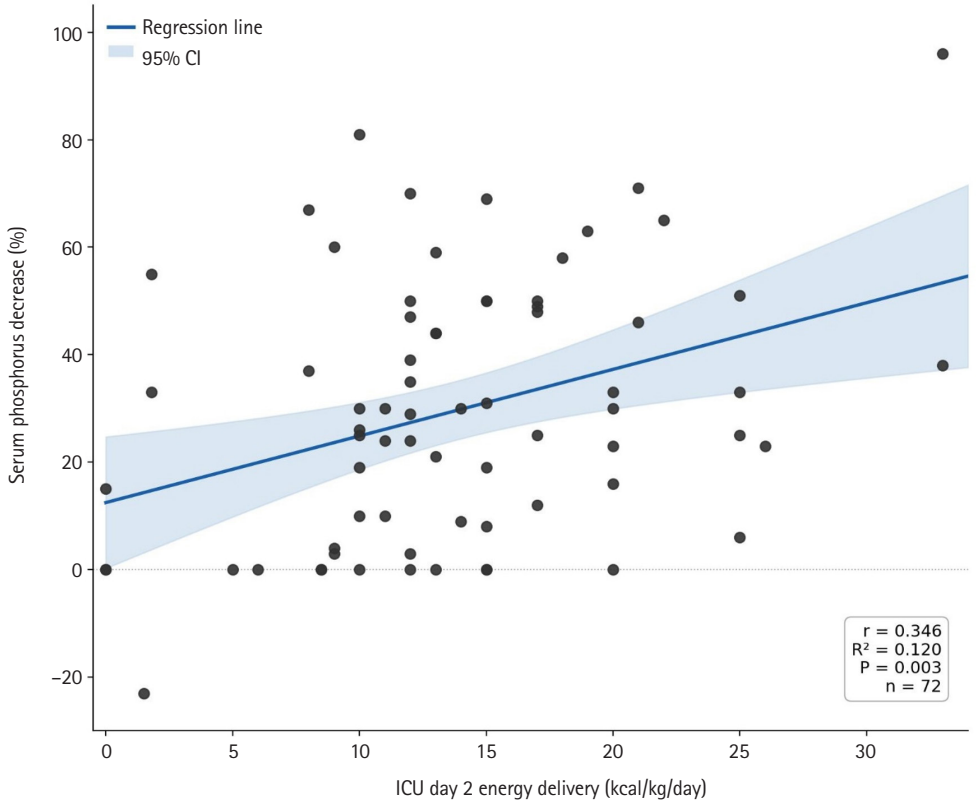

Fig. 2. Correlation between ICU day 2 energy delivery and serum phosphorus reduction. Scatter plot showing the relationship between caloric intake per body weight on ICU day 2 (kcal/kg/day) and the percentage reduction in serum phosphorus among critically ill patients with liver cirrhosis. The solid line represents the linear regression line, and the shaded area indicates the 95% CI. ICU day 2 energy delivery was positively correlated with serum phosphorus reduction. ICU, intensive care unit; CI, confidence interval.

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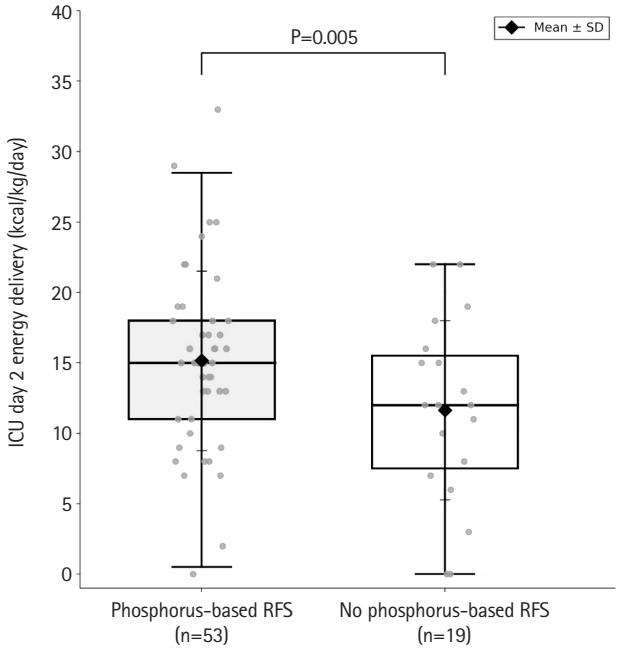

Fig. 3. ICU day 2 energy delivery according to phosphorus-based RFS criterion. Box-and-whisker plot comparing ICU day 2 energy delivery between patients who did and did not meet the phosphorus-based RFS criterion. Individual dots represent observed values. The box indicates the interquartile range, the horizontal line within the box represents the median, and the whiskers indicate the data range. The diamond marker and vertical error bar represent the mean±SD. Patients meeting the phosphorus-based RFS criterion received significantly higher ICU day 2 energy delivery than those not meeting the criterion. ICU, intensive care unit; RFS, refeeding syndrome; SD, standard deviation.

In multivariable logistic regression analysis (Table 4), ICU day 2 kcal/kg was the only independent factor significantly associated with meeting the phosphorus-based RFS criterion. Specifically, each 1 kcal/kg/day increase in ICU day 2 kcal/kg was associated with 19% higher odds of meeting the phosphorus-based RFS criterion (odds ratio [OR], 1.19; 95% CI, 1.06–1.36; P=0.007). In contrast, timing of glucose administration within 24 hours (OR, 4.62; 95% CI, 0.65–45.47; P=0.147), ED glucose load (g/kg) (OR, 3.52; 95% CI, 0.74–27.53; P=0.170), formal TPN initiation after 24 hours compared with within 24 hours (OR, 0.32; 95% CI, 0.08–1.24; P=0.108), no formal TPN during the early ICU period compared with formal TPN initiation within 24 hours (OR, 0.34; 95% CI, 0.01–5.26; P=0.451), and ICU day 1 kcal/kg (OR, 0.92; 95% CI, 0.84–1.00; P=0.076) were not significantly associated with phosphorus-based RFS status.

To further evaluate the discriminative performance of ICU day 2 kcal/kg for the phosphorus-based RFS criterion, receiver operating characteristic (ROC) curve analysis was performed (Fig. 4). The area under the curve (AUC) was 0.7061, indicating fair but modest discriminative ability. The optimal cutoff value determined by Youden's index was 10.92 kcal/kg/day, with a sensitivity of 77.4% and a specificity of 57.9%. Because this cutoff was derived from a single-center cohort and has not been externally validated, it should be considered an exploratory threshold rather than a clinically actionable target.

Table 2. ICU day 2 energy delivery by phosphorus-based RFS criterion

Variable	No.	Mean±SD	95% CI	t	df	P-value
ICU day 2 kcal/kg			1.57–8.18	2.994	35.47	0.005
Phosphorus-based RFS yes	53	15.37±6.62				
Phosphorus-based RFS no	19	10.50±5.89				

ICU, intensive care unit; RFS, refeeding syndrome; SD, standard deviation; CI, confidence interval; df, degrees of freedom.

Table 3. Multivariable linear regression analysis for factors associated with serum phosphorus reduction

Variable	β	SE	95% CI	P-value
Timing of glucose administration (within 24 hr)	15.64	9.02	−2.37 to 33.65	0.088
ED-1 glucose	19.71	5.89	7.94 to 31.47	0.001*
Formal TPN initiation after 24 hr vs. within 24 hr	−4.08	6.05	−16.16 to 8.01	0.503
No formal TPN during early ICU period vs. within 24 hr	−7.39	14.20	−35.76 to 20.97	0.604
ICU 1 kcal/kg	−0.51	0.36	−1.23 to 0.20	0.156
ICU 2 kcal/kg	1.32	0.51	0.31 to 2.34	0.011*

Formal TPN initiation was entered as a three-category variable, with formal TPN initiation within 24 hours as the reference category.
β, unstandardized regression coefficient; SE, standard error; CI, confidence interval; ED, emergency department; TPN, total parenteral nutrition; ICU, intensive care unit.
*P<0.05.

Table 4. Multivariable logistic regression analysis for factors associated with phosphorus-based refeeding syndrome status

Variable	OR	SE	95% CI	P-value
Timing of glucose administration (within 24 hr)	4.62	1.06	0.65 to 45.47	0.147
ED-1 glucose	3.52	0.92	0.74 to 27.53	0.170
Formal TPN initiation after 24 hr vs. within 24 hr	0.32	0.70	0.08 to 1.24	0.108
No formal TPN during early ICU period vs. within 24 hr	0.34	1.43	0.01 to 5.26	0.451
ICU 1 kcal/kg	0.92	0.04	0.84 to 1.00	0.076
ICU 2 kcal/kg	1.19	0.06	1.06 to 1.36	0.007*

Formal TPN initiation was entered as a three-category variable, with formal TPN initiation within 24 hours as the reference category.
OR, odds ratio; SE, standard error; CI, confidence interval; ED, emergency department; TPN, total parenteral nutrition; ICU, intensive care unit.
*P<0.05.

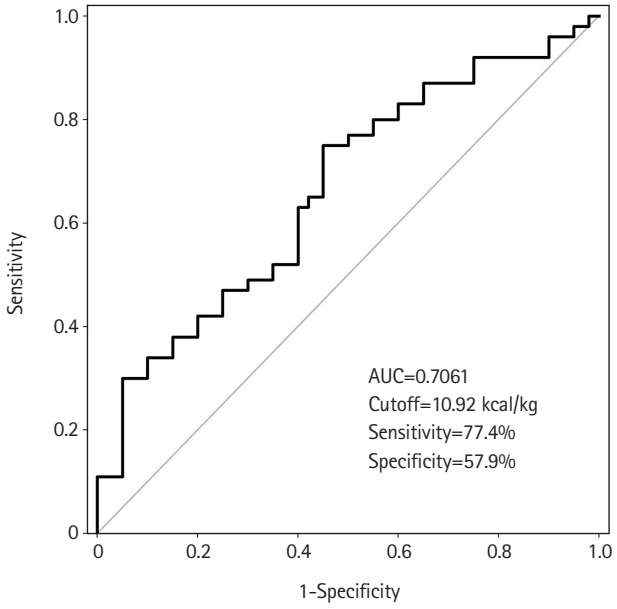

Fig. 4. ROC curve of ICU day 2 energy delivery for phosphorus-based RFS criterion. ROC curve showing the discriminative performance of ICU day 2 energy delivery for the phosphorus-based RFS criterion. The area under the ROC curve was 0.7061, indicating fair but modest discriminative ability. The optimal cutoff value was determined using Youden's index, with a cutoff of 10.92 kcal/kg/day, sensitivity of 77.4%, and specificity of 57.9%. This cutoff should be interpreted as an exploratory threshold rather than a clinically actionable target. AUC, area under the curve; ROC, receiver operating characteristic; ICU, intensive care unit; RFS, refeeding syndrome.

Discussion

Key results

In this retrospective cohort of critically ill patients with liver cirrhosis, greater caloric delivery on ICU day 2 was associated with a larger decrease in serum phosphorus and a higher likelihood of meeting the phosphorus-based RFS criterion. This finding is broadly consistent with the ASPEN 2020 and ESPEN 2019 and 2023 guidelines, which advocate gradual energy escalation in patients with malnutrition or refeeding risk. However, these guidelines do not provide numerical thresholds specific to patients with cirrhosis, and the underlying evidence derives largely from heterogeneous ICU or oncology cohorts with limited representation of patients with cirrhosis [4,7,12]. The 10.92 kcal/kg/day cutoff identified in this study may therefore provide a preliminary signal within this cohort, but it should be interpreted as a hypothesis-generating reference rather than as a definitive feeding threshold.

Interpretation/comparison with previous studies

Several methodological considerations should be emphasized when interpreting these findings. First, the outcome was based on a phosphorus-based operational definition derived from the ASPEN framework, not on the full ASPEN three-electrolyte classification incorporating phosphorus, potassium, magnesium, and clinical manifestations. Therefore, the observed proportion of patients meeting the phosphorus-based RFS criterion (73.6%) likely reflects biochemical phosphorus decline rather than clinically adjudicated RFS in every case. Second, serum phosphorus concentrations in critically ill patients may be affected by factors other than refeeding physiology, including sepsis, renal replacement therapy, diuretic exposure, respiratory alkalosis, dilutional effects from fluid resuscitation, and phosphate supplementation. Third, because this study was retrospective and did not include a noncirrhotic critically ill comparator group, the findings should be interpreted as associations observed within a cirrhosis cohort, not as evidence of causality or cirrhosis-specific susceptibility to RFS.

Previous observational studies have reported associations between lower initial caloric delivery and fewer refeeding-related electrolyte disturbances, which is consistent with the direction of our findings. This concern is further supported by studies using alternative methodologies, including percentage of estimated requirements and indirect calorimetry, which similarly showed that rapid energy delivery during

early critical illness was associated with metabolic complications [13-15]. In patients with cirrhosis, a recent study reported that refeeding hypophosphatemia occurred in approximately one-quarter of patients and was more common in malnourished patients receiving PN, although it was not significantly associated with Child–Pugh or MELD-defined disease severity [16]. This prior evidence provides biological plausibility for the associations observed in the present cohort.

Some studies in general ICU or surgical populations have reported that early aggressive caloric delivery may improve outcomes by reducing catabolism and promoting recovery [17,18]. A systematic review and meta-analysis reported that permissive underfeeding may confer clinical benefits, although without a definitive effect on mortality [19]. Taken together, these discrepancies support cautious, patient-specific nutritional management, particularly during the early phase of critical illness, when metabolic instability and electrolyte shifts are common.

A notable finding was the differential association between ICU day 1 and ICU day 2 kcal/kg. Although ICU day 1 kcal/kg was not significantly associated with serum phosphorus reduction or phosphorus-based RFS status, ICU day 2 kcal/kg was associated with both outcomes. This discrepancy may reflect the inherent variability in nutritional delivery on the first ICU day, when hemodynamic instability, procedures, fluid resuscitation, and fasting frequently interrupt feeding. By ICU day 2, nutritional support is generally more consistently established, making cumulative caloric delivery over the first 48 hours a more reliable indicator of metabolic refeeding burden. Thus, the rate of caloric advancement during this early window warrants close attention.

ICU day 2 kcal/kg was associated with phosphorus-based RFS status in the multivariable analysis, underscoring the tension between adequate and safe nutritional support in this population. Patients with cirrhosis admitted to the ICU frequently present with baseline malnutrition, depleted glycogen stores, protein-energy wasting, and impaired organ function, all of which create substantial nutritional demand. At the same time, rapid carbohydrate or caloric loading may precipitate electrolyte shifts that exceed metabolic adaptive capacity. In high-risk patients, careful initial caloric delivery with stepwise advancement and vigilant electrolyte monitoring, particularly serum phosphate monitoring, remains clinically prudent.

Neither the glucose infusion rate (≥2 mg/kg/min vs. <2 mg/kg/min) nor the timing of formal TPN initiation was significantly associated with outcomes in this study. Thus, cumulative caloric delivery per body weight may be more closely related to phosphorus-based biochemical changes than the rate of carbohydrate infusion or the nominal timing of formal TPN initiation. The lack of association with TPN timing may partly reflect confounding by clinical context, because the decision to initiate TPN is influenced by hemodynamic status, enteral feeding feasibility, and physician discretion. Overall, the total amount of energy delivered may be a more clinically meaningful parameter than route or timing alone.

These findings suggest several considerations for nutritional management in critically ill patients with cirrhosis. These patients often have poor chronic oral intake, malabsorption, systemic inflammation, ascites, and acute decompensation events, such as infection, gastrointestinal bleeding, or renal dysfunction, which may provide a plausible background for refeeding-related electrolyte disturbances. Refeeding-related electrolyte surveillance should ideally begin in the ED before ICU admission, particularly when glucose exposure and early parenteral energy delivery are anticipated. Early nutritional planning should consider total caloric intake, carbohydrate burden, baseline nutritional status, disease severity, organ dysfunction, and electrolyte trends. Serum phosphorus trends should also be interpreted alongside concurrent ICU interventions, including renal replacement therapy, diuretic use, and phosphate supplementation. ICU day 2 kcal/kg may serve as a practical bedside parameter for heightened surveillance during caloric advancement; however, the 10.92 kcal/kg/day cutoff should be regarded only as an exploratory, risk-informed reference rather than a rigid universal target.

Limitations

This study has several limitations. First, it was a single-center retrospective study with a relatively small sample size (n=72), which may limit generalizability and raises the possibility of selection bias and model overfitting. Although variables for the multivariable models were selected a priori based on clinical relevance and the number of covariates was limited, the regression estimates should be interpreted as exploratory and require validation in larger cohorts. Second, the RFS outcome was based on a phosphorus-based operational definition derived from the ASPEN criteria rather than on a full three-electrolyte classification including phosphate, potassium, and magnesium. Potassium and magnesium were not used as independent diagnostic criteria because serial values were not consistently available, and clinical manifestations or organ dysfunction were not incorporated as mandatory diagnostic criteria because reliable attribution to RFS was not feasible using retrospective records. Therefore, the apparent proportion of patients meeting the phosphorus-based RFS criterion may have been overestimated, and

outcome misclassification cannot be excluded. Third, major determinants of serum phosphorus levels were not fully captured or adjusted for in the primary models. In particular, renal replacement therapy, diuretic use, and phosphate supplementation may directly affect serum phosphorus concentrations and, consequently, both the primary outcome of serum phosphorus reduction and the classification of phosphorus-based RFS. Although these variables were reviewed from the electronic medical records when available, their timing, cumulative dose, indication, and temporal relationship to the phosphorus nadir were not consistently structured. Other factors, including sepsis severity, respiratory alkalosis, and dilutional effects from fluid resuscitation, may also have contributed to hypophosphatemia independently of refeeding physiology. Fourth, although NRS-2002-based initial nutritional screening and reduced dietary intake within 2 weeks before admission were available and summarized, comprehensive baseline nutritional assessment was limited. Detailed nutritional assessment tools, such as SGA and GLIM criteria, recent weight loss, muscle mass assessment, and formal malnutrition diagnoses were not systematically documented in the electronic medical records and therefore could not be consistently incorporated into the primary analyses. Fifth, thiamine administration was not standardized and was not included in the primary adjusted models; therefore, its potential modifying or confounding effect could not be fully evaluated. Finally, this study did not include a noncirrhotic critically ill comparator group; therefore, the findings should be interpreted as associations observed within this cirrhosis cohort and should not be considered evidence that cirrhosis itself increases RFS risk compared with other ICU populations. Overall, the findings should be interpreted as exploratory associations between early caloric delivery and phosphorus-based biochemical outcomes rather than as evidence of a causal effect of nutritional support on RFS development.

Future directions

Prospective multicenter studies with larger cohorts are warranted to validate the 10.92 kcal/kg/day threshold identified in this study and to determine whether its application within structured feeding protocols improves patient outcomes. Future studies should incorporate standardized baseline nutritional assessment; serial phosphate, potassium, and magnesium monitoring; systematic documentation of phosphate replacement, renal replacement therapy, diuretic exposure, and acid-base status; and protocolized thiamine administration. Studies including both cirrhotic and noncirrhotic critically ill comparator groups are needed to determine whether the observed associations are specific to cirrhosis or reflect broader ICU-related refeeding physiology. Developing prediction models for phosphorus-based refeeding-related electrolyte disturbance and integrating nutritional surveillance into electronic medical records may further support patient-specific feeding strategies.

Conclusion

In critically ill patients with liver cirrhosis, higher early caloric delivery through PN, particularly on ICU day 2, was associated with greater serum phosphorus decline and a higher likelihood of meeting the phosphorus-based RFS criterion. However, given the retrospective observational design, phosphorus-based operational definition of RFS, and potential influence of concurrent ICU interventions such as renal replacement therapy, diuretic use, and phosphate supplementation, these findings should be interpreted as associations rather than causal effects. The ICU day 2 caloric threshold identified in this study should be considered exploratory and hypothesis-generating, not a definitive clinical target. Further prospective studies with standardized electrolyte monitoring and baseline nutritional assessment are needed to validate these findings.

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Authors' contribution

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Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

Contact the corresponding author for research data availability.

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Supplementary materials

None.

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Original Article

Effects of oral deprivation and continuous gastrostomy feeding on masticatory function in rats

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Abstract

Purpose: Tube feeding is frequently used in older adults and patients with dysphagia. However, when oral intake cannot be resumed, masticatory function may decline. Eating provides nutrition and helps maintain oral function, but the effects of different nutritional routes on masticatory muscles remain unclear. This study investigated the effects of a feeding model that combined differences in feeding route, diet form, and oral deprivation on masticatory-related muscles and masticatory function.

Methods: Seven-week-old male Sprague–Dawley rats were assigned to receive a solid diet (solid group), a liquid diet (liquid group), or continuous gastric feeding via gastrostomy (gastrostomy group) for 3 weeks. The time required to complete feed intake, masseter electromyographic activity, and masticatory muscle weights were evaluated.

Results: Energy intake and body weight changes did not differ significantly among the groups during the feeding period. Masseter muscle weight was significantly lower in the liquid group than in the other groups, whereas temporalis muscle weight tended to be higher in the solid group. The time required to complete feed intake was significantly longer in the gastrostomy group (389.7±210.4 sec/g) than in the solid and liquid groups (140.0±21.4 and 207.8±82.2 sec/g, respectively; $P<0.01$). When solid food was consumed after the 3-week feeding period, muscle activity during eating was higher in both the liquid and gastrostomy groups than in the solid group.

Conclusion: Feeding models involving oral deprivation or gastrostomy feeding altered masticatory-related muscle characteristics and chewing performance in rats. Reduced feeding activity may contribute to impaired chewing and changes in tongue weight.

Keywords: Deglutition; Enteral nutrition; Sprague-Dawley rats; Masseter muscle; Gastrostomy

Introduction

Tube feeding is widely used for nutritional management in older adults and patients with reduced swallowing function. Among tube feeding methods, nasogastric tube feeding and percutaneous endoscopic gastrostomy are commonly used to administer enteral nutrition [1]. Tube feeding is therefore a useful option for nutritional management. However, some individuals have difficulty transitioning from tube feeding to oral intake, and declines in masticatory and feeding function are major concerns [2].

Diet provides energy and nutrients and also helps maintain oral functions, including mastication and swallowing. Even when diets have the same energy content, intake through the oral cavity may have distinct physiological and psychological significance [3]. Masticatory movement is achieved through coordinated activity of the masseter and temporalis muscles and the tongue, and activity generated during food consumption is essential for maintaining masticatory function. During mastication, the masseter muscle primarily controls jaw-closing force, whereas the temporalis muscle helps control occlusal force and mandibular movement [4]. The tongue also plays an essential role in feeding, including bolus formation and food transport [5]. Because these masticatory-relat-

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ed muscles contribute directly to oral function, their weight is closely related to masticatory function, and decreased frequency and intensity of masticatory activity can lead to muscle atrophy and functional decline [6]. These findings suggest that reduced oral motor activity and oral stimulation during prolonged tube feeding may be associated with alterations in masticatory muscle function.

Previous animal studies have evaluated the effects of different food forms on masticatory function and intake behavior [7-10]. For example, rodent studies have compared solid feed with powder or liquid feed, which induces less mastication [11-13]. These studies have demonstrated the role of adequate mastication in maintaining masticatory muscle function, even when nutrition is sufficient. However, tube feeding–induced declines in masticatory muscle function have not been adequately reproduced in experimental animals, and no studies have examined the role of oral nutritional intake, compared with tube feeding, in preserving masticatory function.

In the present study, some rats received continuous intragastric infusion of liquid feed that bypassed oral intake, whereas others received solid or liquid feed orally with the same nutritional composition. This design allowed comparison of feeding models involving oral solid feeding, oral liquid feeding, and continuous gastrostomy feeding. We hypothesized that the absence of oral intake would lead to functional decline in rat masticatory muscles. To test this hypothesis, we examined the significance of oral intake in tube-fed rats using objective indicators, including the time required to complete solid-feed intake and the weight of the masticatory muscles.

Methods

Ethics statement

All procedures were approved by Otsuka Pharmaceutical Factory, Inc. (approval number: OPFCAE-2023184), and were conducted in accordance with the animal experimentation guidelines of Otsuka Pharmaceutical Factory, Inc., which comply with relevant Japanese regulations and guidelines for the care and use of laboratory animals, including the Act on Welfare and Management of Animals and the Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities. This study is reported in accordance with the ARRIVE guidelines.

A harm–benefit analysis was performed to justify the experimental design, including 3R measures: reduced sample size, pilot studies, intervention criteria, and environmental enrichment. The endpoint fate of all animals was documented. Animals were monitored daily throughout the study for general health status, body weight, food intake, catheter condition, wound healing, and signs of pain or distress. Humane endpoints were established before study initiation. Animals showing severe deterioration in health status or complications associated with the gastrostomy catheter were removed from the study and euthanized according to the predefined humane endpoint criteria. The sample size was determined on the basis of previous experience with similar exploratory animal studies and practical considerations rather than a formal statistical power calculation.

Test feed

The purchased animals were allowed to acclimate, during which AIN-93G solid feed (Oriental Yeast Co., Ltd.) was provided *ad libitum*. After the acclimation period, AIN-93G feed was replaced with the test feed. To prepare the test feed, a liquid food (HINEX E-Gel, Otsuka Pharmaceutical Factory, Inc.) was freeze-dried into powder and then solidified using a feed manufacturing machine (Oriental Yeast Co., Ltd.). The composition of the test feed is shown in Table 1.

Experimental animals

Thirty 7-week-old male Crl:CD Sprague–Dawley rats (Jackson Laboratory Japan, Inc., Kanagawa, Japan) were used. The rats were housed at 23±3 °C and 55%±15% humidity under a 12-hour light/dark cycle, with lights on from 7:00 to 19:00.

Experimental procedures

Feeding with the test feed was initiated after the 5-day acclimation period. Animals were then allocated to three experimental groups using body weight–based allocation to ensure comparable baseline body weights among groups: the solid group, which received oral intake of feed prepared by solidifying a liquid food; the liquid group, which received oral intake of a liquid food; and the gastrostomy group, which received liquid food through a gastrostomy catheter. Rats in the

Table 1. Nutritional composition of the test feed

Group	Solid (n=10)	Liquid (n=10)	Gastrostomy (n=7)
Form	Solid	Liquid	Liquid
Energy (kcal/100 g)	396[a]	80	80
Water (g/100 g)	5.8	81.1	81.1
Protein (g/100 g)	15.8	4.0	4.0
Fat (g/100 g)	8.7	2.2	2.2

[a]The energy content in the solid feed is a theoretical value derived from the content of energy-producing nutrients (protein, fat, and carbohydrates).

gastrostomy group were fasted from the day before group allocation. Laparotomy was subsequently performed under isoflurane anesthesia, and a catheter was placed in the stomach, as described previously [14]. After surgery, the rats received intramuscular ampicillin preparation and were monitored daily for general condition, body weight, food intake, wound healing, and catheter patency. Humane endpoints had been predefined before study initiation, and animals with severe complications associated with the gastrostomy catheter or other signs of substantial distress were removed from the study and euthanized according to institutional guidelines.

The rats were housed individually from the day of group allocation, and the test-feed intake period was set at 3 weeks. The solid group was offered test feed providing 80 kcal/day, and actual intake was determined by subtracting the amount of unconsumed feed collected daily. The liquid and gastrostomy groups were pair-fed on the basis of the actual intake of the solid group measured on the previous day. For the liquid group, the test feed was poured into a glass feeding dish, placed inside the cage, and changed daily. For the gastrostomy group, the test feed was loaded into a syringe (J-Feed injector, JMS Co., Ltd.), connected to the upper end of the animal-specific gastrostomy catheter, and infused continuously over 24 hours using a syringe pump. In the liquid and gastrostomy groups, access to drinking water was discontinued after test-feed intake began, and the rats received only water contained in the test feed.

After 3 weeks of test-feed intake, the rats underwent surgery to place a transmitter for measuring muscle potential. The transmitter, receiving board, and data acquisition system were components of the long-term automatic telemetry measurement system (Data Sciences International [DSI]). Under isoflurane anesthesia, laparotomy was performed in five rats per group, and the transmitter was placed in the peritoneal cavity. Because telemetry devices were limited, five animals from each group were selected for electromyographic measurements. Animals were selected on the basis of body weight to ensure representative body-weight distributions within each group. After the abdominal procedure, an incision was made on the right side of the face, and a recording needle electrode was inserted into the superficial layer of the right masseter muscle and fixed with sutures. After the facial surgical procedure, the rats received intramuscular ampicillin preparation and were awakened from anesthesia. During recovery, the animals were monitored daily for postoperative health status, wound healing, body condition, and signs of pain or distress. After the surgical procedures, a 2-day recovery period was established, during which the rats were fasted.

After the recovery period, each group was administered 2.5 g of the specified test feed, and muscle activity generated until feed intake was completed was measured. The time required to complete feed intake was also measured. If no feeding behavior was observed within the maximum measurement time of 1.5 hours, measurement was discontinued, and the remaining feed was weighed to calculate the time required to consume 1 g of feed. After muscle activity was measured, all rats underwent tissue collection as follows. Laparotomy was performed under deep isoflurane anesthesia, and the rats were euthanized by exsanguination via incision of the abdominal vena cava. After death was confirmed, the masseter and temporalis muscles and tongue were removed from the left side of the face. The gastrocnemius and anterior tibial muscles were removed from the left lower limb and weighed using a precision electronic balance. The masseter muscle was treated as a single sample without separating the superficial and deep layers.

Outcome assessments were conducted without blinding to group allocation.

Analysis of muscle potential

Masseter muscle potential during feeding was analyzed using PONEMAH software (DSI), which was designed for a long-term automatic telemetry measurement system. Muscle-potential data were aggregated only during periods of mastication activity, and data were excluded using a peak threshold of 0.05 mV·s. The sum of muscle potentials during mastication was calculated as the amount of muscle activity.

Statistical analysis

All results are expressed as mean±standard deviation. Before analysis of variance (ANOVA), normality was assessed using the Shapiro–Wilk test, and homogeneity of variance was assessed using Levene's test. All outcome measures satisfied the assumptions of normality and homogeneity of variance (all $P>0.05$). Statistical analyses were conducted using one-way ANOVA. When a significant overall group effect was observed, Fisher's least significant difference test was used for post hoc pairwise comparisons. Fisher's least significant difference test was selected because this study was exploratory and involved only three predefined comparison groups. The significance level was set at 5%. All analyses were performed using Excel Statistics, version 3.20 (Social Survey Research Information Co., Ltd.).

Results

Characteristics

The flow of animals through the study, including exclu-

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sions and analysis populations, is summarized (Fig. 1). The three groups did not differ significantly in total energy intake or body weight at autopsy (Table 2). Throughout the test-feed intake period, the general condition of rats in the solid and liquid groups was favorable. Three rats in the gastrostomy group met the predefined humane endpoint criteria because of gastrostomy catheter obstruction or catheter dislodgement from the stomach; these rats were euthanized and excluded from further analyses. In addition, one rat each in the solid and liquid groups was excluded from the feeding-time analysis because feeding behavior could not be reliably recorded. No substantial violations of normality or homogeneity of variance were detected.

Masticatory-related muscle characteristics

Masseter muscle weight was significantly lower in the liquid group than in the solid and gastrostomy groups (Fig. 2A). Temporalis muscle weight tended to be lower in the liquid and gastrostomy groups than in the solid group, although the overall group effect did not reach statistical significance (ANOVA: $F(2,24)=3.09$, $P=0.064$) (Fig. 2B). Consistent with this finding, Tukey-adjusted post hoc analyses did not identify statistically significant differences among groups. Tongue weight was significantly lower in the gastrostomy group than in the other groups (Fig. 2C). In contrast, gastrocnemius and anterior tibial muscle weights did not differ significantly among the three groups (Fig. 2D and E).

Masticatory function

The time required to complete intake of masticatory solid feed was significantly longer in the gastrostomy group than in the other groups (Fig. 3). Masseter muscle potential during intake of masticatory solid feed was significantly higher in the liquid and gastrostomy groups than in the solid group (Fig. 4).

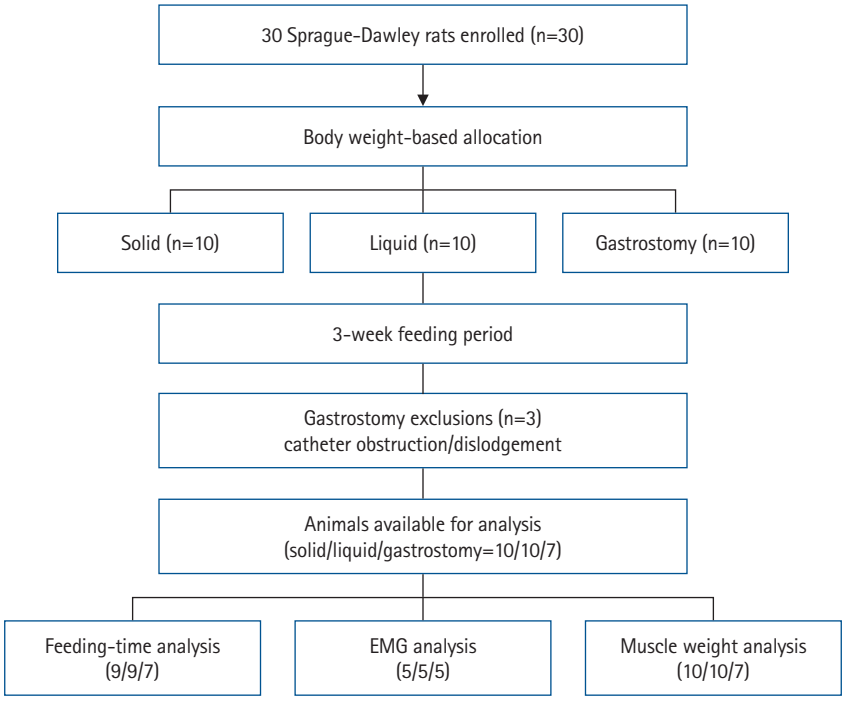

Fig. 1. Animal flow diagram prepared according to the ARRIVE 2.0 guidelines. Thirty rats were allocated to experimental groups using body weight–based allocation. Three rats in the gastrostomy group met predefined humane endpoint criteria because of catheter obstruction or dislodgement and were excluded from further analyses. One rat each in the solid and liquid groups was excluded from the feeding-time analysis because feeding behavior could not be reliably recorded. Five animals per group were selected for electromyographic analysis because of the limited availability of telemetry devices. EMG, electromyography.

Table 2. Body weight at autopsy and total energy intake

Group	Solid (n=10)	Liquid (n=10)	Gastrostomy (n=7)	P-value
Final body weight (g)	305.4±17.8	305.1±6.3	292.6±10.4	0.097
Total energy intake (kcal)	1,305.1±195.4	1,256.7±62.7	1,255.3±7.9	0.626

Values are presented as mean±standard deviation.
For P-values, results from one-way analysis of variance are shown.

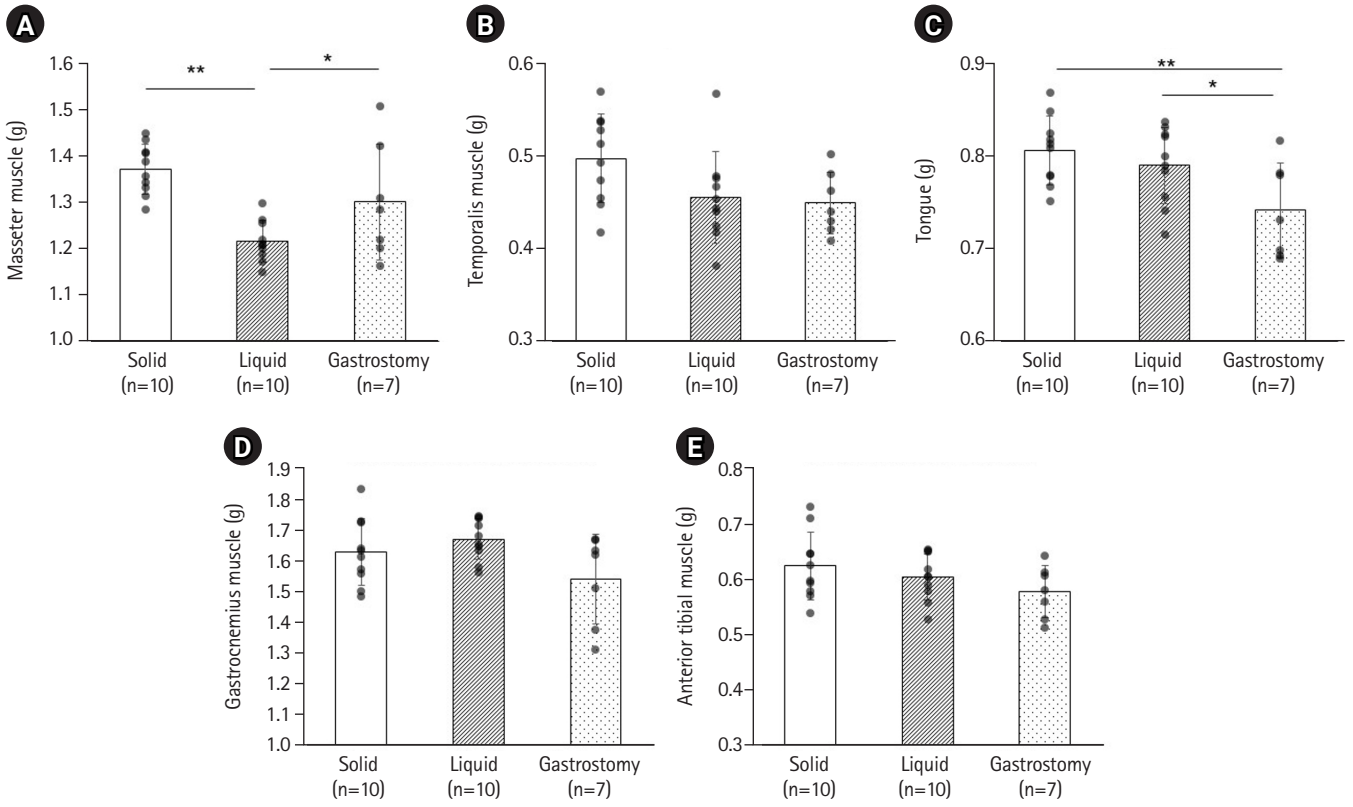

Fig. 2. Weights of masticatory muscles and lower-limb skeletal muscles. (A) Masseter muscle, (B) temporalis muscle, (C) tongue, (D) gastrocnemius muscle, and (E) anterior tibial muscle. Data are presented as mean±standard deviation. *P<0.05, **P<0.01 (Fisher's least significant difference test).

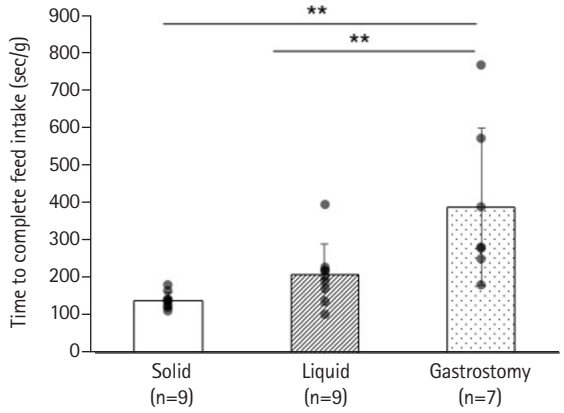

Fig. 3. Time required to complete intake of the provided solid feed. One animal each in the solid and liquid groups was excluded from this analysis because feeding behavior could not be reliably recorded. Data are presented as mean±standard deviation. **P<0.01 (Fisher's least significant difference test).

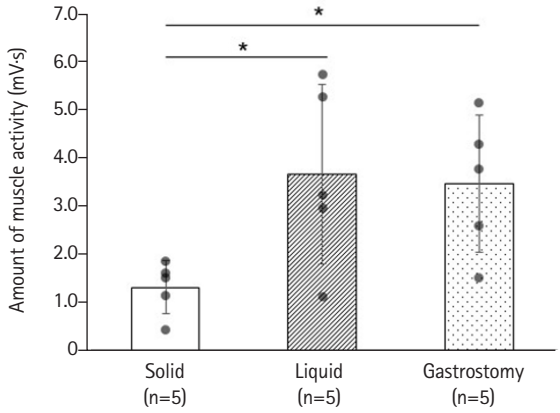

Fig. 4. Masseter muscle activity during intake of solid feed. Data are presented as mean±standard deviation. *P<0.05 (Fisher's least significant difference test).

Discussion

Key results

Mastication, the first major step in digestion, requires coordination of the tongue, facial muscles, jaw, and teeth. Long-term administration of enteral nutrition may be associated with poor systemic health and gradual development of masticatory and swallowing dysfunction, indicating that

maintaining the masticatory system is important for tube-fed patients [2]. Therefore, experimental animals that simulate the clinical conditions of tube-fed patients should be investigated. Previous animal studies have compared the effects of different feed forms [11-13,15], but no studies have comparatively evaluated the effects of tube feeding. In the present study, rats received nutrition through continuous intragastric infusion of liquid feed without mastication and were compared with rats receiving oral intake of solid or liquid feed with the same nutritional composition.

Interpretation/comparison with previous studies

Masticatory muscle activity is influenced by the physical properties of food. In rabbits, soft feed has been shown to decrease the number of daily bursts and the activity time of the masseter muscle [12], and similar results have been reported in rats fed powder feed [11]. On the basis of these findings, we hypothesized that restricted masticatory movement may impair masticatory function. To test this hypothesis, we compared the amount of muscle activity (mV·s) in rats, as determined from the waveform of the masseter muscle potential. The amount of muscle activity generated until completion of solid-feed intake was significantly higher in the liquid and gastrostomy groups than in the solid group. Increased masticatory muscle activity during consumption of food with the same physical properties may reflect reduced mastication efficiency; therefore, the higher total muscle activity observed in the liquid and gastrostomy groups was likely attributable to restricted masticatory movement in the present study. The time required to complete feed intake was also longest in the gastrostomy group, suggesting that feeding behavior was affected by disuse of oral function. Because the gastrostomy group received no oral intake during nutrition administration, the longer feeding time may reflect changes in the coordinated use of oral structures involved in mastication and swallowing, requiring compensatory muscle activity when solid-feed intake resumed. In addition, tongue weight was significantly decreased only in the gastrostomy group, which may reflect reduced tongue muscle mass associated with prolonged absence of oral feeding activity.

This reduction may have contributed to decreased ability to form and transport a bolus. A study examining the relationship between tongue pressure and masticatory function reported that reduced tongue pressure decreased the ability to form a bolus and delayed food clearance from the oral cavity [16]. These findings suggest that decreased tongue weight may hinder bolus formation and swallowing movement and, in the present study, may have contributed to the prolonged time required to complete solid-feed intake in the gastrostomy group. In the liquid group, continuous oral stimulation likely contributed to partial maintenance of basic oral-movement functions, such as the swallowing reflex and bolus transport, although no mastication load was present during the feeding period. The liquid group did not differ significantly from the solid group in the time required to complete solid-feed intake, despite exhibiting greater muscle activity. This finding suggests that increased muscle activity in the liquid group may have compensated for slightly reduced masticatory efficiency during solid-feed consumption, thereby maintaining the time required to complete feed intake. Overall, these observations suggest an association between reduced oral feeding activity and changes in chewing performance and masticatory-related muscles.

Inefficient feeding movement may therefore increase muscle activity and slow the rate of food intake.

Next, we focused on the weight of masticatory muscles in rats receiving no oral feed intake, hypothesizing that the most prominent weight changes would occur in muscles with major roles in mastication. To test this hypothesis, we measured the weights of tissues involved in mastication: the masseter muscle, temporalis muscle, and tongue. Masseter muscle weight was significantly lower in the liquid group than in the other groups, with no significant difference between the gastrostomy and solid groups. Temporalis muscle weight tended to be lower in the liquid and gastrostomy groups. Previous studies have reported functional alterations in masticatory muscles in animals fed diets requiring reduced mastication [11,13]. Because masticatory efficiency is improved by coordinated activity of the masseter and temporalis muscles, decreased weight of either muscle may contribute to reduced masticatory efficiency [4]. Decreased masticatory muscle weight may also affect masticatory rhythm and muscle coordination. The temporalis muscle, which works with the masseter muscle to increase masticatory efficiency, has an important role in the power phase [4]. Although temporalis muscle weight tended to be lower in the liquid and gastrostomy groups, the overall group effect did not reach statistical significance (ANOVA: $F(2,24)=3.09$, $P=0.064$). Therefore, any contribution of temporalis muscle changes to the observed differences in chewing performance remains speculative. However, masseter muscle weight in the gastrostomy group was comparable to that in the solid group (Fig. 2A). Botulinum toxin A (BoNTA) injection into the unilateral masseter muscle induced molecular and morphological changes related to muscle atrophy and affected the entire ipsilateral masticatory musculature [17]. These reports suggest that functional impairment of some masticatory muscles may broadly affect other masticatory muscles.

A possible explanation for the absence of decreased masseter muscle weight in the gastrostomy group is compensatory change associated with muscle degeneration. Previous studies using a model of long-term disuse induced by BoNTA have reported increases in connective tissue, collagen content, and fatty infiltration in the masseter muscle [18]. However, because no histological analyses were performed in the present study, the involvement of such tissue changes remains speculative and should be interpreted with caution. Further studies including histological evaluation are needed to clarify this mechanism. In contrast, in the liquid group, muscle degeneration may have progressed more gradually because the rats maintained some level of oral intake, albeit limited, which may have reduced muscle weight without compensatory tissue changes. Notably, despite preserved muscle weight in the gastrostomy group, functional impairment was suggested by increased muscle activity and prolonged feeding time. Disuse of the gastrocnemius muscle, which shares fast-twitch characteristics with the masseter muscle, has been reported to increase the proportion of connective tissue [19], supporting this proposed mechanism. Further studies are warranted to better characterize the underlying mechanism.

The results of this study suggest that prolonged non-oral feeding may be associated with reduced function of the masticatory muscles and tongue. Our findings also suggest that daily masticatory movement and oral stimulation are important for maintaining function. In contrast, continued oral intake in the liquid group, although the feed was liquid, may have suppressed declines in masticatory muscle weight and function to some extent. These findings provide preliminary insight into potential changes in oral function associated with prolonged non-oral feeding. However, direct extrapolation to older adults, patients with dysphagia, or long-term enterally fed patients should be made cautiously.

Limitations

The present study had several limitations. First, rats in the gastrostomy group differed from those in the solid and liquid groups, which were exposed to feed for a certain period. Therefore, the possibility that differences in acclimation to feed, in addition to decreased masticatory muscle function, contributed to the prolonged time required to complete feed intake cannot be completely ruled out. Second, the time required to complete feed intake was assessed at only a single time point, and the subsequent recovery process was not investigated. Third, the 48-hour fasting period after transmitter implantation may have affected muscle volume and function in these rats through metabolic changes and weight loss. This fasting period was used to allow adequate recovery by avoiding potential effects of feeding on the wound site during the early postoperative period. However, the possibility that fasting affected the results of the feeding intervention cannot be completely ruled out. Fourth, although the gastrostomy group underwent laparotomy and catheter placement, sham surgery was not performed in the other groups. Therefore, the possibility that surgical invasiveness affected some of the observed changes cannot be excluded. Fifth, this study focused on masticatory function and did not include functional evaluation of swallowing coordination. Swallowing-related muscle activity was not measured because of technical complexity and low reproducibility. The absence of evaluations of swallowing reflex and bolus transport efficiency is a key limitation of this study. In light of these limitations, future research should include comprehensive evaluation with histological analysis and swallowing-function assessment.

Conclusion

The present findings suggest that prolonged reduction or absence of oral feeding activity may affect masticatory-related muscles and chewing performance. Continuous oral stimulation, even with a liquid diet, appeared to partially preserve oral function compared with complete bypass of oral feeding through gastrostomy. Further studies are needed to clarify the underlying mechanisms and their relevance to clinical populations requiring long-term enteral nutrition.

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Authors' contribution

Conceptualization: IY. Methodology: AH, IY. Formal analysis: AH, IY. Validation: AH, IY. Project administration: IY. Writing–original draft: AH. Writing–review and editing: AH, IY. All authors read and approved of the final manuscript.

Conflict of interest

Airi Honjo and Ippei Yamaoka are employees of Otsuka Pharmaceutical Factory, Inc. Otherwise, no other potential conflict of interest relevant to this article was reported.

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Data availability

Contact the corresponding author for research data availability.

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Supplementary materials

None.

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Case Report

Metabolic deterioration in a patient with refractory status epilepticus complicated by refeeding syndrome: a case report

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Abstract

A 50-year-old moderately built woman with hypothyroidism presented with acute-onset headache, neck pain, vomiting, and transient confusion. She developed seizures in the emergency department requiring intubation. She was subsequently reintubated for refractory status epilepticus, requiring propofol infusion to achieve burst suppression. During her initial intensive care unit course, she had hypoalbuminemia and persistent hypokalemia. Following the initiation of enteral feeding and propofol infusion, she developed metabolic abnormalities suggestive of refeeding syndrome, including severe hypophosphatemia, feed intolerance, and glucose intolerance. A detailed dietary history suggested chronic malnutrition, possibly related to anorexia nervosa. She also exhibited features consistent with propofol infusion syndrome, including hypothermia, elevated lactate, and hemodynamic instability. The interplay between propofol use and refeeding syndrome appeared to trigger a cascade of complications, including worsening hypotension, hyperlactatemia, rhabdomyolysis, hepatic and renal failure, and ultimately fatal cardiac arrest. Refractory status epilepticus requiring propofol infusion, in the context of carbohydrate deprivation and critical illness, may have contributed to catastrophic metabolic deterioration. This case highlights the complexity of metabolic disturbances in critically ill patients and underscores the importance of considering multiple overlapping mechanisms when evaluating clinical deterioration in this setting.

Keywords: Case reports; Critical illness; Hypophosphatemia; Propofol infusion syndrome; Refeeding syndrome

Introduction

Background

Refeeding syndrome is a serious metabolic disturbance that occurs when nutrition is reintroduced after prolonged undernutrition. It is characterized by fluid retention and reductions in serum phosphate, potassium, and magnesium levels due to insulin-mediated intracellular electrolyte shifts. The American Society for Parenteral and Enteral Nutrition (ASPEN) 2020 criteria outline major risk factors for refeeding syndrome [1]. Refeeding syndrome is estimated to occur in up to 34% of critically ill patients with chronic starvation related to disease-associated malnutrition, anorexia nervosa, malignancy, inflammatory bowel disease, short bowel syndrome, alcoholism, or poverty [1,2]. Despite routine nutrition screening, refeeding syndrome remains underrecognized in the intensive care unit (ICU). Early identification, cautious caloric initiation, electrolyte repletion, and thiamine supplementation can prevent most complications. However, recognition in critically ill patients is often challenging due to overlapping clinical conditions and altered metabolic responses. Evidence guiding recognition in these settings remains limited [1].

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One such clinical scenario is status epilepticus requiring propofol infusion, in which metabolic deterioration may be attributed to propofol infusion syndrome (PRIS). PRIS is a rare but serious complication associated with prolonged or high-dose propofol administration in the ICU, with increased susceptibility in patients with status epilepticus. Pathophysiologically, PRIS and refeeding syndrome are distinct entities. PRIS primarily results from impaired mitochondrial fatty acid oxidation leading to cellular energy failure, whereas refeeding syndrome arises from rapid electrolyte and micronutrient shifts following nutritional repletion. Despite these differing mechanisms, both conditions, along with status epilepticus itself, may impair cellular energetics and share overlapping clinical features, including metabolic acidosis, rhabdomyolysis, and cardiovascular instability.

Objectives

This report describes a malnourished woman with suspected anorexia nervosa who developed severe metabolic deterioration while receiving propofol infusion for refractory status epilepticus, highlighting the potential for catastrophic metabolic consequences arising from multiple interacting factors (Fig. 1).

Case report

Ethics statement

Written informed consent for publication of this case was obtained from the patient's family.

Patient information/clinical findings

A 50-year-old moderately built woman with hypothyroidism, treated with levothyroxine, presented with a 1-day history of headache, neck pain, vomiting, and altered mentation. In the emergency department, she developed generalized tonic-clonic seizures requiring intubation.

Diagnostic assessment/therapeutic intervention

Magnetic resonance imaging demonstrated leptomeningeal enhancement, and cerebrospinal fluid analysis revealed lymphocyte-predominant pleocytosis with mildly elevated protein levels. Viral meningitis, partially treated bacterial meningitis, and aseptic meningitis were considered. Empiric therapy with ceftriaxone, acyclovir, and corticosteroids was initiated.

Baseline laboratory evaluation, including hematology, blood glucose, liver, and renal function tests, was within normal limits, except for hypoalbuminemia (3 g/dL; normal

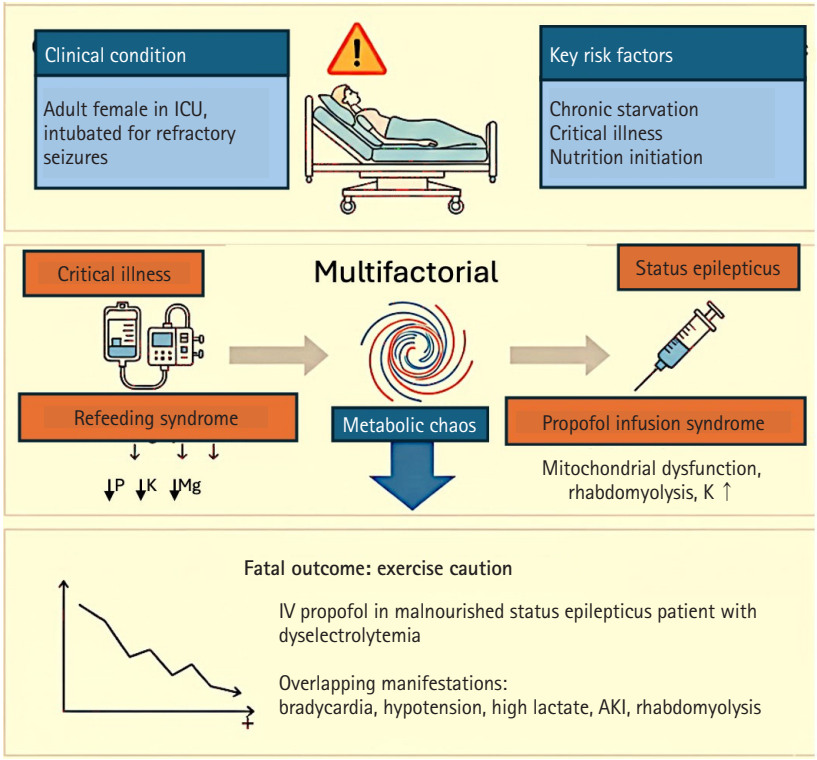

Fig. 1. Metabolic factors contributing to clinical deterioration. ICU, intensive care unit; P, serum phosphorus; K, serum potassium; Mg, serum magnesium; IV, intravenous; AKI, acute kidney injury.

range, 3.5–4.5 g/dL), low-normal serum phosphorus (2.5 mg/dL; normal range, 2.5–4.5 mg/dL), and hypomagnesemia (1.4 mg/dL; normal range, 1.6–2.5 mg/dL). Enteral nutrition was initiated using a blended diet administered via a nasogastric tube. During the first week, she developed persistent hypokalemia (2.5–3.0 mEq/L) despite intravenous potassium supplementation. Her neurological status improved, and she was extubated after 72 hours. However, within 24 hours, she required reintubation due to recurrent seizures (Table 1).

Enteral feeding was restarted after reintubation with a commercial formula on day 6 of admission at 25 kcal/kg and 1 g/kg of protein. She remained in refractory status epilepticus despite midazolam infusion. Although the clinical seizures ceased, electroencephalography (EEG) demonstrated persistent epileptiform activity. Ketamine infusion resulted in minimal improvement, prompting the addition of propofol. Propofol infusion at 4 mg/kg/hr achieved burst suppression but required norepinephrine support because of hypotension. On the second day of propofol therapy, hypotension worsened and lactate increased to 4 mmol/L. Cardiac, renal, and pulmonary function remained stable, and urine output was preserved. Because EEG monitoring was unavailable, propofol was continued for a total of 36 hours. She became hypothermic, consistent with the known effects of propofol. She then developed intolerance to enteral feeds and was started on maintenance intravenous 5% dextrose at 100 mL/hr. Although she did not have diabetes, she developed marked glucose intolerance, with glucose levels rising to 300 mg/dL and requiring insulin infusion. This was followed by severe hypophosphatemia (0.6 mg/dL), persistent refractory hypokalemia (2.5–2.8 mEq/L), and low-normal corrected calcium. Her serum albumin had declined to 2 g/dL by day 7 of admission.

Since the clinical features raised suspicion for refeeding syndrome, a more detailed dietary history was obtained from the family. Although the family initially reiterated that she had been consuming a normal diet until 1 day before admission, further details raised concern. The history revealed prolonged severe caloric restriction, particularly avoidance of carbohydrates because of fear of weight gain, which the family described as her "normal diet." Given the low albumin level at admission, chronic malnutrition, and severe electrolyte abnormalities, refeeding syndrome was considered. Once refeeding syndrome was suspected, thiamine supplementation and aggressive electrolyte replacement were initiated, and glucose administration was reduced. Intravenous thiamine was administered as a 200 mg loading dose, followed by 100 mg every 8 hours.

After 36 hours of propofol infusion, her temperature was low (33.9 °C), her heart rate had decreased from 80 to 60 beats/min, and lactate remained elevated at 5 mmol/L, raising concern for propofol-related toxicity. The propofol infusion rate was reduced to 3 mg/kg/hr for the next 4 hours until EEG assessment could be performed and serum creatine phosphokinase (CPK) and triglyceride levels could be measured. Midazolam and ketamine were also tapered. Serum triglyceride was 230 mg/dL, and CPK was 8,000 IU/L (normal range, <200 IU/L). Because intravenous levothyroxine was not readily available, levothyroxine tablets were administered via nasogastric tube, and the free T4 level was measured. After 40 hours of propofol infusion, EEG showed complete suppression. Propofol and midazolam were therefore discontinued over the subsequent 4 hours. Normothermia returned and lactate improved to 2.5 mmol/L, although norepinephrine requirements did not decrease and she became progressively oliguric. Nutrition was withheld for that day.

Caloric intake was planned at approximately 25 kcal/kg/day at the time of ICU admission. During the first 2 days of ICU admission, enteral nutrition was provided as a blended kitchen diet administered via nasogastric tube. However, absorption during this period was unpredictable and was likely lower than intended because of the nature of blended

Table 1. Temporal progression of key metabolic parameters during ICU course

Hospital day	Key clinical events	K (mEq/L)	P (mg/dL)	Mg (mg/dL)	Lactate (mmol/L)	CPK (IU/L)
Day 0 (Admission)	Seizure and intubation	3.4	2.5	1.4	1.2	NR
Day 1–3	ICU stay, NG feeds (blended diet), extubation	2.5–3.0	NR	NR	NR	NR
Day 6	Reintubation, commercial feeds started	2.6	2.2	1.5	1.8	NR
Day 7	Propofol infusion (4 mg/kg/hr), hypotension, hypothermia, feed intolerance	2.5	0.6	1.4	5.0	8,000
Day 8[a]	Propofol stopped at 1:00 PM	2.8	2.0	1.3	2.5	NR
	Sudden collapse, AKI, cardiac arrest	6.2	2.5	NR	>14	80,000

ICU, intensive care unit; K, serum potassium; P, serum phosphorus; Mg, serum magnesium; CPK, creatine phosphokinase; NR, not recorded; NG, nasogastric; AKI, acute kidney injury.
[a]Day 8 initial laboratory values were obtained at 4:00 AM. Propofol was stopped at 1:00 PM. Rhabdomyolysis, anuria, hyperkalemia, and cardiac arrest occurred at 10:00 PM.

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feeds and frequent interruptions related to extubation and subsequent reintubation, precluding accurate caloric estimation. Following reintubation, commercial formula feeds were administered at 25 kcal/kg/day for approximately 24 hours. During this period, the patient also received an estimated additional 530 kcal/day from propofol infusion. Because refeeding syndrome was not initially suspected, planned caloric restriction was not implemented. After refeeding syndrome was considered, enteral feeds were discontinued because of intolerance. Intravenous dextrose was briefly initiated but discontinued within 2 hours because of abrupt hyperglycemia requiring insulin therapy, before full correction of the electrolyte abnormalities (Fig. 2).

Follow-up and outcomes

Approximately 52 hours after initiation of propofol infusion, and 8 hours after its discontinuation, she developed sudden profound hypotension, anuria, severe hyperkalemia, elevated liver enzyme levels, and worsening hyperlactatemia. Serum CPK increased from the previous value to 80,000 IU/L. She subsequently progressed to cardiac arrest and died.

Discussion

In this patient, mild hypophosphatemia and refractory hypokalemia within the first 72 hours of admission suggested underlying malnutrition and evolving refeeding syndrome [2]. This later progressed to severe hypophosphatemia, further supporting the diagnosis of refeeding syndrome. An important consideration is the unintended caloric contribution from propofol, which is formulated as a 10% lipid emulsion providing 1.1 kcal/mL [3]. The transition to commercial formula feeds, in addition to the calories delivered through propofol infusion, would have substantially increased total energy provision and may have contributed to refeeding syndrome. The metabolic impact of high-dose propofol-derived calories as a direct precipitant of refeeding syndrome remains uncertain [4]. However, because caloric restriction is central to the management of refeeding syndrome, this mechanism is plausible.

The subsequent development of hypotension, hypothermia, rhabdomyolysis, and hyperlactatemia, followed by improvement in lactate after discontinuation of propofol, raised concern for possible propofol-related metabolic toxicity. However, the dose and duration of propofol in the present case did not meet the classical criteria associated with a higher risk of PRIS, which are typically described as doses exceeding 4 mg/kg/hr for more than 48 hours. Although PRIS has been reported at lower doses in critically ill patients, the diagnosis in this setting remains uncertain [3,4]. Risk factors

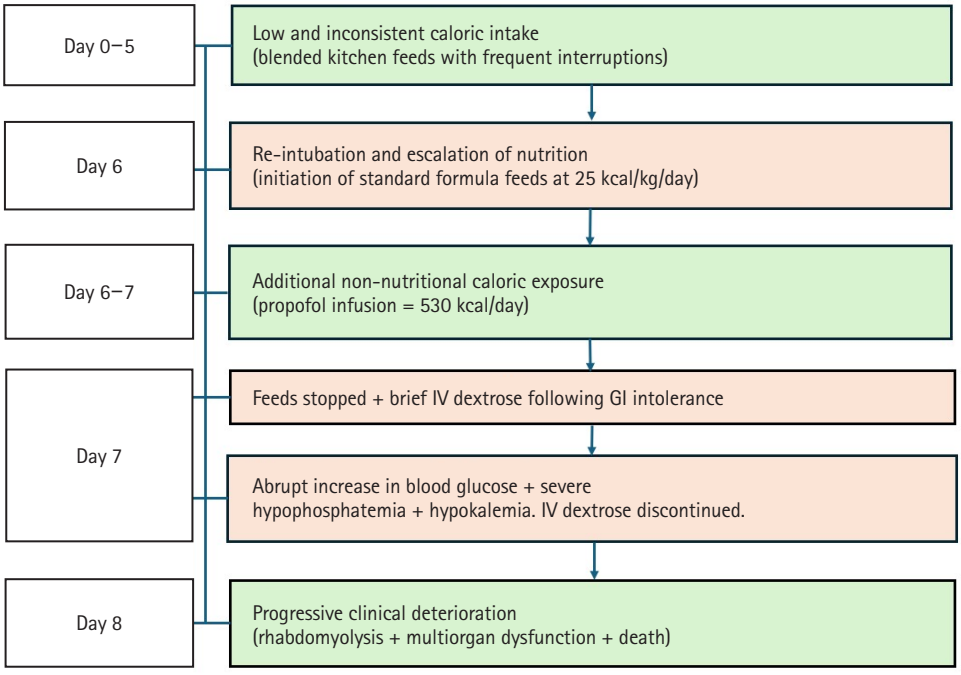

Fig. 2. Timeline of nutritional exposure and metabolic deterioration. This schematic illustrates the temporal relationship between changes in nutritional intake, additional caloric exposure from propofol and dextrose, the development of electrolyte abnormalities, and subsequent clinical deterioration, supporting the diagnosis of refeeding syndrome in the setting of critical illness. IV, intravenous; GI, gastrointestinal.

such as refractory status epilepticus, carbohydrate deprivation, catecholamine use, and critical illness may increase susceptibility to propofol-related metabolic toxicity [5]. PRIS typically presents with metabolic acidosis, rhabdomyolysis, and cardiovascular collapse, several of which overlap with refeeding syndrome, critical illness, and status epilepticus, thereby limiting diagnostic specificity.

Mitochondrial fatty acid oxidation impairment and cellular energy imbalance are believed to underlie PRIS [6]. In contrast, refeeding syndrome results from electrolyte and micronutrient shifts following nutritional repletion, particularly hypophosphatemia and thiamine deficiency, both of which can impair ATP generation. In critically ill patients, these metabolic disturbances may coexist or overlap, making diagnostic distinction difficult.

Refractory status epilepticus itself is a well-established cause of rhabdomyolysis because of sustained muscle activity, tissue hypoxia, and metabolic stress. Furthermore, critical illness-related factors, including hypotension, catecholamine exposure, and multiorgan dysfunction, may have amplified muscle injury and impaired clearance of muscle breakdown products. Previous reports of patients with status epilepticus receiving propofol infusion have suggested that several features attributed to PRIS, such as rhabdomyolysis and elevated liver enzymes, may instead arise from prolonged seizure activity itself [7-9].

Although refractory status epilepticus likely contributed to rhabdomyolysis, it does not fully explain the profound electrolyte disturbances observed. The combination of severe hypophosphatemia and persistent hypokalemia is more consistent with refeeding syndrome. Hypothermia and bradycardia suggest the possibility of additional metabolic stress related to propofol infusion. It is also important to note that severe hypophosphatemia itself can precipitate rhabdomyolysis.

Gut failure and poor levothyroxine absorption may explain the low free T4 level (8 pmol/L), although this value would not typically cause severe decompensation, and omission of 2–3 doses of levothyroxine would be insufficient to produce clinically significant hypothyroidism given its long half-life. Therefore, while a mild contribution to metabolic vulnerability cannot be fully excluded, hypothyroidism is unlikely to explain the acute and severe manifestations observed in this case, which were more consistent with refeeding syndrome and possible propofol-related toxicity.

Taken together, this case is best interpreted as multifactorial metabolic deterioration in a severely malnourished patient with refractory status epilepticus complicated by refeeding syndrome. Refeeding syndrome likely went unrecognized initially in this patient, subsequently triggering abrupt electrolyte shifts. Hypophosphatemia was the hallmark abnormality, although it may also occur for other reasons in critically ill patients [2,10,11]. Hypomagnesemia, hypokalemia, thiamine deficiency, insulin resistance, and gastrointestinal failure are also features of refeeding syndrome [12]. Thiamine requirements rise sharply with carbohydrate reintroduction, and deficiency may lead to acute neurological complications [13]. Additional complications include arrhythmias, seizures, confusion, and gastrointestinal failure, resulting in high mortality, all of which were seen in this case [10]. Phosphate depletion impairs ATP production, contributing to respiratory and cardiac dysfunction, as well as rhabdomyolysis [14].

In conclusion, this case highlights the complexity of metabolic disturbances in critically ill patients and underscores the importance of considering multiple mechanisms when evaluating clinical deterioration in this setting. Diagnosis is particularly challenging because the metabolic signatures of these conditions overlap. Clinicians must exercise extreme caution when initiating nutrition and intravenous propofol in malnourished patients with status epilepticus.

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Authors' contribution

Conceptualization: MM. Data curation: MM. Visualization: MM. Investigation: MM. Literature search: MM, KN. Supervision: MM. Writing–original draft: MM, KN. Writing–review & editing: MM, KN. All authors read and approved the final manuscript.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability

Not applicable.

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None.

Supplementary materials

None.

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Abbreviations should be avoided as much as possible. One word should not be expressed through an abbreviation, although more than two words may be expressed through an abbreviation. The full term for which the abbreviation stands should be used at its first occurrence in the text. Abbreviations should not be present in the title. Common abbreviations, however, may be used, such as DNA.

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The use of International Standardized (SI) units is encouraged. These are available at NIST (https://physics.nist.gov/cuu/Units/index.html). Arabic numbers should be used, and all units use SI units (International System of Units). Use a comma after thousands (e.g., 10,000).

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Statistical methods must be described, and the program used for data analysis and its source should be stated.

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The manuscripts for original articles should be organized in the following order: Title page, Abstract, Main text, References, Tables, Figure legends, and Figures.

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Type of article	Abstract (words)	Text (words)[a]	References	Tables and figures
Original article	Structured, 250	3,000	40	10
Review article	Structured, 250	5,000	50	10
Case report	200	1,500	20	10
Guidelines	Structured, 250	5,000	100	15
Interesting images	NR	800	10	5
Editorial	NR	1,500	10	5
Letter to the editor	NR	1,000	10	5

NR, not required.
[a]The length of each article is negotiable with the editor-in-chief.

Reporting guidelines

Authors should follow the relevant reporting guidelines for specific study designs, such as randomized controlled trials, diagnostic accuracy studies, meta-analyses, observational studies, and non-randomized studies. Recommended sources include the EQUATOR Network (https://www.equator-network.org/) and the National Library of Medicine (https://www.nlm.nih.gov/services/research_report_guide.html).

Annals of Clinical Nutrition and Metabolism requires compliance with the reporting guidelines summarized in Table 2 for the listed article types. For other study design and reporting guidelines, contact the editorial office at https://e-acnm.org/about/contact.php.

Table 2. Reporting guidelines for specific study designs

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	https://www.equator-network.org/reporting-guidelines/consort/
TREND	Non-randomized controlled study	https://www.cdc.gov/trendstatement/index.html
STROBE	Observational studies	https://www.equator-network.org/reporting-guidelines/strobe/
STARD	Diagnostic/prognostic studies	https://www.equator-network.org/reporting-guidelines/stard/
PRISMA	Systematic reviews and meta-analyses	https://www.equator-network.org/reporting-guidelines/prisma/
CARE	Case reports	https://www.equator-network.org/reporting-guidelines/care/
AGREE	Clinical practice guidelines	https://www.equator-network.org/reporting-guidelines/the-agree-reporting-checklist-a-tool-to-improve-reporting-of-clinical-practice-guidelines/

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